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## Open Public Hearing

## Open Committee Discussion
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Call to Order and Opening Remarks

Introductions, Susan Leitman, Acting Chair, BPAC

DR. LEITMAN: I am calling the 114th meeting of the FDA Blood Products Advisory Committee to order and to start. My name is Susan Leitman, of the NIH Clinical Center. Chris Stowell, our usual chair, could not be with us today and so I am substituting as chair.

We have a lot of topics to discuss today. Even if we are on time, we're not going to get out until 5:45, so I'll try and move things expeditiously, but there should be a lot of things that the committee will want to actively discuss today since the topics are important and have been brought to this committee before without resolution on some of the topics.

I would like to start by introducing the other members of the Blood Products Advisory Committee meeting. Why don't we introduce ourselves, and I'll start to our right. Please give us your name, your position, and your institution.

DR. ORTEL: Tom Ortel at Duke, I'm chief of hematology.

DR. LERNER: Norma Lerner, pediatric hematologist at Blood Division of NHLBI.

DR. SIMON: Toby Simon. I'm a senior medical director with CSL Behring and the acting industry representative.

DR. REES: Robert Rees. I am the director-manager of the Blood Bank Regulatory Program for the state of New Jersey.

DR. SANDBERG: I am Sonja Sandberg. I'm a professor of
DR. CHITLUR: Meera Chitlur. I am the director of the Hemophilia Treatment Center at Children's Hospital of Michigan.

DR. MURRAY-KOLB: Laura Murray-Kolb. I am an associate professor at Penn State in the Department of Nutritional Sciences.

DR. BRITTENHAM: Gary Brittenham. I'm a hematologist.

Columbia University.

DR. RABE: Ingrid Rabe. Medical epidemiologist with Arboviral Diseases Branch of CDC in Fort Collins, Colorado.

DR. DEMARIA: Al DeMaria. I'm the medical director of the Bureau of Infectious Disease and Laboratory Sciences, and the State Epidemiologist for the Massachusetts Department of Public Health.

DR. STAPLETON: Jack Stapleton, professor of Internal Medicine and Microbiology at the University of Iowa.

DR. RAGNI: Margaret Ragni, University of Pittsburgh, Department of Medicine, Division Hematology, director of the Hemophilia Center.

MR. TEMPLIN: Chris Templin person with hemophilia B,

consumer representative.

DR. ESCOBAR: Miguel Escobar. Hematologist and director of Hemophilia Center in the University of Texas in Houston.

DR. LEITMAN: Thank you very much. That's about a 50-50 split between experts in hemolytic disorders and experts in infectious disease disorders, which reflects the two main topics of today and tomorrow's discussions.

I would like to now introduce Dr. Peter Marks, director of CBER,
for opening remarks from the center director.

Opening Remarks, Peter Marks, MD, PhD, Director CBER

DR. MARKS: Thanks very much. They just took down some slides because we were confused -- I was going to tell you about a reorg but we did not move the center from the Center for Biologics to the Center for Devices and Radiologic Health, and that is being corrected right now.

Good morning. I wanted to take the opportunity at the beginning of this meeting to inform the members of the Blood Products Advisory Committee and those in attendance of an internal reorganization in the Center for Biologics Evaluation and Research that became effective October 16, 2016.

This reorganization will not affect the products or matters considered by the Blood Products Advisory Committee, but it will change what office brings some matters to the committee for consideration. In an effort to become more effective and operationally efficient, the Center underwent an internal restructuring in order to better engage and leverage the expertise of our review staff and harmonize our regulatory work across different platforms used to treat similar conditions.

The new CBER structure includes the Office of Blood Research and Review, the Offices of Vaccines Research and Review, and the Office of Tissues and Advanced Therapies. The formation of the Office of Tissues and Advanced Therapies involved the transfer of the Office of Blood Research and Review's division of Hematology Clinical Review and part of its division of Hematology Research and Review, along with appropriate support staff to what previously was the Office of Cell Tissue and Gene Therapies.

This reorganization will allow the Office of Blood Research and
Review to focus on transfusion medicine, which with its combination of new
technologies and emerging infectious diseases becoming an ever more complex
field, and the new Office for Tissues and Advanced Therapies will have
responsibility for all plasma-derived and recombinant versions of therapeutic
proteins for hematology as well as all cell tissue and gene therapies.

Dr. Jay Epstein, who has had a distinguished career at the agency,
will continue to lead the Office of Blood Research and Review, and in terms of
leadership for the new office of Tissues and Advanced Therapies, Dr. Wilson
Bryan has recently been appointed as its office director. Again, as you can see, the
reorganization means that matters now brought to the Blood Products Advisory
Committee will happen from two different offices within our center. However, the
charge of the committee will not change.

And with that, I just want to take this opportunity to welcome all
those in attendance today and to thank all of the members of the committee for
their service. We look forward to productive discussions. Thanks very much.

DR. LEITMAN: Thank you, Dr. Marks.

I would now like to introduce Lieutenant Commander Bryan
Emery, the designated federal officer for BPAC, to read the conflict of interest
statement.

Conflict of Interest Statement, Bryan Emery, LCDR,

Designated Federal Officer BPAC

LCDR EMERY: Good morning. The Food and Drug Administration
is convening this November 17 and 18 for the 114th meeting of the Blood Products
Advisory Committee under the authority of the Federal Advisory Committee Act
of 1972. Thank you all for attending this meeting and welcome to this two-day
Dr. Susan Leitman will serve as the acting chair in place of the current BPAC chair, Dr. Christopher Stowell, who is unable to attend this meeting due to an unavoidable family situation. Mr. Christopher Templin will serve as the acting voting consumer representative, representing all consumer interests. Dr. Toby Simon will serve as the acting industry representative.

Dr. Simon is employed by CSL Behring of King of Prussia, Pennsylvania. Industry representatives act on behalf of all related industry. Industry representatives are not special government employees and do not vote. Government employees who have financial conflicts when it has been determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. With the exception of the industry representative, all participants of the committee are either special government employees or regular federal employees from other agencies and are subject to the federal conflict of interest laws and regulations.

The following information on the status of this advisory committee's compliance with federal ethics and conflict of interest laws including, but not limited to, 18 U.S. Code 208, are being provided to participants at this meeting and to the public. Related to the meeting topics listed in the agenda of this meeting, members and consultants of this committee have been screened for potential conflict of interest of their own as well as those imputed to them, including those of their spouse and minor children, and for the purposes of 18 U.S. Code 208, their employers.

Their interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teachings, speaking, writing, patents,
royalties, and primary employment. Based on the agenda topics and the analysis of the financial interests reported, FDA has determined that all members of this advisory committee are in compliance with federal ethics and conflict of interest laws under 18 U.S. Code 208.

Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. Based on the agenda topics and the analysis of all the financial interests reported by members and consultants, no conflict of interest waivers were issued to any voting and nonvoting members of this committee under 18 U.S. Code 208.

There may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. These individuals were not screened by the FDA for conflicts of interest. However the FDA asks in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. The 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. This
conflict of interest statement will be available for review at the registration table.

Before we move forward, I would like to provide the following additional guidance with regards to the discussions relating to today’s meeting topics. For the November 17, 2016 BPAC meetings, topics IA, IB, and II are determined to be particular matters of general applicability. Based on these determinations, participants are also being provided with the following guidance to be followed.

Particular matters of general applicability as such should not focus their discussion on any particular products, but instead focuses on various strategies and methodologies, e.g., iron management, ferritin testing, blood collection from female donors and adverse events in teenage U.S. blood donors.

This BPAC meeting is not being convened to recommend any action against or for the approval of any specific iron supplement or iron testing products for U.S. blood donors. This BPAC is not being convened to make specific recommendations that may potentially impact any specific product, party, entity, or firm in a unique way. This BPAC meeting will not involve the approval, disapproval, labeling requirements, post-marketing requirements, or related issues regarding the legal status of any specific products.

Any discussion of individual products and methods will only be to serve as an example of the product class. This concludes the reading of the conflict of interest statement and topic discussion guidance for the record.

With this, let me hand the meeting back to the chair, Dr. Susan Leitman.

DR. LEITMAN: Thank you, Lieutenant Commander Emery.

Let’s advance to Topic IA, which is Considerations for Iron
Management in Blood Donors. We will hear the first four presenters and hold all
questions until those four presentations are completed and then open questions
from the BPAC or the speakers. The first speaker is Dr. Wendy Paul of the Office
of Blood Research and Review, FDA.

Dr. Paul?

**Topic IA: Introduction and Background, Wendy Paul, MD, OBRR, FDA**

Dr. PAUL: Good morning. My name is Wendy Paul, and I am a
medical officer in the Division of Blood Components and Devices, Office of Blood
Research and Review, CBER. I'm here today to present topic IA, which is
Considerations for Iron Management in Blood Donors. I am going to provide an
overview and an introduction to the topic, so the first thing I'll talk about is the
issue for consideration. I'll give you some background information including
regulatory history, previous public discussions, and AABB recommendations. I'll
also give you an overview of the agenda topics for today, as well as questions for
the committee.

The issue for consideration is that FDA is seeking advice from the
committee on acceptable procedures for iron management in blood donors.
Requirements for blood and blood components intended for transfusion or for
further manufacturing use, the final rule was effective May, 2016. In the rule 21
CFR 630.10 addresses donor eligibility requirements. It states that a donor is not
eligible if the donor is not in good health or if you identify any factor that may
cause the donation to adversely affect, one, the health of the donor, or two, the
safety, purity, and potency of the blood or blood component.

Additionally, additional donor eligibility requirements include
minimum hemoglobin cutoffs at 12.5 grams per deciliter in females and 13 grams per deciliter in males, and further that the donation frequency must be consistent with protecting the health of the donor, with a minimum inter-donation interval of 8 weeks for single whole blood red cells or apheresis red cell units, and 16 weeks for two units of apheresis red blood cells.

Despite hemoglobin screening and deferral practices to protect the health of donors, iron depletion is a well-known consequence of blood donation. Iron balance in blood donors is influenced by several factors. So following donation of a unit of whole blood, a healthy donor loses approximately 200 to 250 milligrams of iron, and there are other factors that influence the balance in donors which includes the volume of blood collected, the donation frequency, whether or not there is iron supplementation, the age and sex of the donor, with particular attention paid to premenopausal females.

Multiple studies have identified that female gender, especially premenopausal women, donation frequency is a major risk factor for iron deficiency in those donors. Early stages of iron depletion may have no apparent physiological consequences. However, as iron depletion progresses, a state of absent iron stores and iron deficient erythropoiesis may result. Some of the physical manifestations of iron deficiency are listed on this slide and include anemia, fatigue, as you can see, pica, restless leg syndrome, and decreased cognitive development or function.

In terms of the background, a BPAC was convened in September of 2008 to discuss the issue of iron deficiency in blood donors. There was a unanimous decision that iron depletion is a concern in blood donors, that there was also a lack of accurate, convenient, and rapid tests to assess iron stores. The
committee also discussed the risks and benefits of strategies for mitigation of iron depletion, and at the conclusion of the meeting, no recommendations were made to implement any specific strategies. Another BPAC was convened in July of 2010, where the committee discussed hemoglobin and hematocrit standards and the appropriate inter-donation interval.

They also heard the results of the REDS-II RISE study which evaluated the predictors of iron deficiency and low hemoglobin. The committee also discussed the risks and benefits of extending inter-donation intervals and at the conclusion, it was recommended that there be further analysis of the RISE data prior to making a decision on adjusting the inter-donation intervals.

This figure is taken from the REDS-II RISE study, the donor iron status evaluation study, published by Dr. Cable and his group. Preliminary results were published in March of 2011. This graph plots iron stores using plasma ferritin as a marker against the number of blood donations over the past 12 months.

The solid line on the top represents male donors. The dashed line in the middle represents female donors over the age of 50. The bottom dotted line represents women under the age of 50. As you can see, women presented with lower ferritin levels than men and as expected, premenopausal females presented with the lowest ferritin levels.

It is also notable that ferritin decreases with increasing donation frequency. I’d like to highlight that the decrease in ferritin levels is marked, much more marked in men, with males reaching low levels after as few as two to three donations per year, and being relatively close to the mean ferritin levels seen in women at the frequency of five donations or more.
This second figure, also taken from the RISE study, depicts the effect of donation frequency on venous hemoglobin levels. Male donors again with the solid line, women over 50 in the dashed, and women less than 50 on the dotted line. As you can see, there is a slight decrease in hemoglobin in male donors as the donation frequency increases. However, if you were to compare this figure to the previous figure, it highlights that venous hemoglobin does not accurately reflect iron stores.

In November of 2011, there was a public workshop organized by the FDA and other stakeholders to discuss blood donor safety and blood availability issues related to donor hemoglobin qualification standards in the United States, and to discuss possible measures to decrease the incidence of iron deficiency in blood donors. The discussion included laboratory testing methods to assess iron stores and methods to possibly mitigate iron loss. At the conclusion of that workshop, it was decided that further consideration was needed for donor education, ferritin testing, adjustment of the inter-donation interval, iron supplementation, and the effects of mitigation measures on the blood supply.

In December of 2012, the AABB issued a bulletin, bulletin number 12-03, called Strategies to Monitor, Limit, or Prevent Iron Deficiency in Blood Donors. That bulletin recommended options for reducing the risk of iron deficiency in blood donors. Those options included ferritin testing, iron replacement, and prolonging the inter-donation interval.

So just a little bit of what we know about ferritin and its relevance in the setting of blood donation. Ferritin represents a storage form of iron in humans. Under normal conditions, serum ferritin roughly reflects the body's iron content. Therefore, a low serum ferritin is a sensitive indicator of iron depletion.
We also know that ferritin concentration declines very early in the development of iron deficiency. So ferritin concentration decreases before you actually see changes in hemoglobin concentration, red cell size, or serum iron levels.

We should also note that ferritin is an acute phase reactant and as such, will be increased in acute or chronic diseases, even in the presence of an iron deficiency, and we also know that there are no available tests that are readily available at the point of care.

So what are other countries doing to mitigate the risk of iron deficiency in blood donors? The international forum regarding practices related to donor hemoglobin and iron was a survey published in Vox Sanguinis in 2016 by Dr. Goldman and colleagues. It was a survey conducted from blood centers inquiring about their practices. The survey consisted of seven questions, but for the purposes of today's discussion, I will provide a high-level summary of the responses to five of those questions as listed on this slide.

So when centers were asked about the maximum number of donations per year that were allowable as well as the inter-donation intervals, the maximum donations ranged from three to seven annually. The way the number of maximum donations was determined, in some centers it was determined by the inter-donation interval. In other centers, they actually allowed fewer donations than would have been allowed by inter-donation intervals. Some centers also reported gender-specific limits with fewer annual donations allowed for teenaged and female donors. Overall, inter-donation intervals ranged from 56 to 150 days for both male and female donors.

When asked about the type of educational materials provided, the majority of centers said that they include information on the association between
frequent donation and iron deficiency. Only a minority of those responding said
that they recommended supplemental iron. Some centers said that they did
provide additional guidance for donors considered to be at an increased risk for
iron deficiency, so those failing to meet hemoglobin requirements, young donors,
women of childbearing age, and frequent donors.

In regards to ferritin testing, 10 of 20 respondents actually
responded to that question and the answers varied widely. Interestingly, in Hong
Kong, they sample 100 random donors per month. In Switzerland, ferritin is
measured at every donation.

In Denmark, ferritin is measured at the first and every tenth
donation. In Canada, Hema-Quebec monitors ferritin in black females at specific
drives. Other centers say they provide ferritin testing for donors who fail the
hemoglobin screen and still others, no testing at all.

In response to the question on iron supplementation, some centers
said that they provide iron supplementation without ferritin testing, and the
population that received the supplementation ranged from all donors, some
centers said female donors of reproductive age, others said all donors donating
every fourth month or more frequently.

Those centers who responded that they provide iron
supplementation with ferritin testing provided it to donors with low hemoglobin
in some places, those who are repeat donors, other centers donors failing
hemoglobin screening, and other centers black females. The formulation of iron
provided and dosages of elemental iron varied widely.

So today, we're going to hear the new data that's been published
since our last committee meeting about donor iron deficiency in blood donors.
The first study we will hear about is the REDS-II donor iron status evaluation, or RISE study. The objectives of that study were to evaluate the effects of blood donation intensity on hemoglobin status and how predisposing donor variables modify this relationship. Some of those variables include demographics, reproductive, and behavioral factors. The second objective was to provide data for development of guidelines for the optimal frequency of donation.

The next study is the hemoglobin and iron recovery study, or the HEIRS study. The objective was to determine the effect of iron supplementation in iron-depleted and iron-replete donors on the time to recovery of 80 percent of the hemoglobin removed, and the recovery of ferritin to the baseline.

The strategies to reduce iron deficiency, or STRIDE study, the objectives were to determine if donors would take steps on their own to mitigate donation-related iron losses when provided with iron status information and written recommendations.

The second objective was to determine if providing iron supplements after each donation without information on iron status would replace donation-related iron losses.

We will then hear a study on iron deficiency in Canadian blood donors. The objectives of that study were to assess the prevalence and risk factors for iron deficiency, to identify areas for improvement both in donor and physician education, as well as blood center practices to address iron deficiency.

Finally, we will hear about the prevalence of blood donor iron deficiency and feasibility of ferritin-based iron replacement, a blood collection agency-based study. The objective of this study was to determine the operational feasibility of implementing ferritin testing and iron supplementation in two blood
I just want to, at this point, provide some information about the INTERVAL trial. We won't be hearing about that trial today, but the objective of that trial was to determine whether intervals between blood donations can be safely and acceptably decreased to optimize blood supply while maintaining the health of the donors. What I can say is that enrollment for that study took place between 2012 and 2014 and the data analysis began in August 2016, and I've provided a link to the study website.

So in summary, studies confirm that iron deficiency occurs in blood donors. Frequent donors and premenopausal females are at the greatest risk with as few as two donations per year. Potential mitigation measures include ferritin testing, iron supplementation, and prolonged inter-donation intervals.

So the questions for the committee today are, number one, does the available scientific evidence support the need for routine monitoring of iron stores in A, all blood donors, B, frequent blood donors both male and female, and C, premenopausal female donors?

Question number two, does the available scientific evidence confirm that iron supplementation in blood donors A, mitigates iron deficiency; B, improves hemoglobin recovery?

Question number three, please comment on the feasibility of iron supplementation in consideration of A, potential adverse events, and B, adherence.

Question number four, please comment on whether available scientific data support the effectiveness of the following methods for iron supplementation in blood donors, A, educational material provided to the donor,
and B, iron supplements provided to the donor by the blood center.

And the final question for the committee, please comment on whether there are adequate data at this time in support of a strategy for increasing the minimum inter-donation intervals for men and women to prevent iron deficiency from blood donation without monitoring of iron stores. Thank you.

DR. LEITMAN: Thank you very much, Dr. Paul.

Our next speaker is Dr. Ritchard Cable from the American Red Cross in Farmingham, Connecticut, who will be addressing us on the topic of iron deficiency and blood donors with results of the REDS-II donor iron status evaluation, or RISE study. Dr. Cable?

Iron Deficiency in Blood Donors, The REDS-II Donor Iron Status Evaluation (RISE) Study, Ritchard Cable, MD, American Red Cross

DR. CABLE: I took some liberties with the title. Having presented twice to this group, now six years ago, on REDS-II RISE study, I am going to present that, but I thought it would be helpful to describe other studies on the prevalence of iron deficiency, particularly ones that have been conducted since REDS-II, not specifically related to what we're not going to discuss, which is the implications of iron depletion or mitigation strategies, compare these studies over time and across geography since we now have some international comparisons to make, and present consensus conclusions across all the studies as well as areas where there seems to be important differences.

So I selected key studies both for historical purposes and also larger studies that did not select donors, but rather recruited somewhat a random donor
The first study was actually in 1977, which is nearly 40 years ago, with the newly available ferritin test. Clement Finch determined that blood donors were iron depleted with low ferritins and that the relationship between giving blood and, more frequently, having lower ferritins was established in a kind of a qualitative way.

In 1981, Toby Simon, who I had breakfast with, I worshipped at his altar, because that was, geez, Toby, how long ago was that? I'm not going to answer that. An excellent JAMA article that caught my interest when I was looking for research areas of interest several years after that assessed the effects of gender, age, menstruation, donation frequency in whole blood donors. I'll show you a little bit about that study.

The RISE study was published in 2010 to 2012, conducted in 2007 to 2009, and I'm going to show you a fair amount of data from that. Then subsequent to RISE, Salvin in 2014 determined the prevalence of iron deficiency in a representative donor sample in Australia.

Finally, unpublished data from the REDS-III group is data from the RBC Omics study which has just been completed. It's a genomics study with multiple objectives, but one of the things that we have available are 13,770 whole blood essentially unselected with ferritin available at the time of recruitment, and analyzing this I think will provide a fair amount of unselected donor data in the United States.

Finally, I wanted to bring up the fact that the AABB, Bryan Spencer working with Red Cross presented data that single donor platelets who are male and had low but acceptable hemoglobin levels have a rather remarkable
frequency of iron depletion, contrary to expectation. This was presented at the plenary abstract of AABB just a few weeks ago.

So this is a curve from Toby Simon's study showing lifetime blood donations by gender and showing hemoglobin and ferritin results from a cross-sectional study of about I think 700 blood donors or thereabouts. You can see the same, the slides that were shown by Dr. Paul from the REDS-II study were, if you will, incubated in my mind that this study and there were similar data available that shows that more recent blood donation activity had a higher influence than lifetime donations on ferritin, but it wasn't presented in such a nice graphic way. REDS-II data you saw does make that point.

A couple things to point out and I'm going to come back to this is, the time the study was done, men had to have a 13.5 hemoglobin level to donate. This was an AABB standard, although not an FDA requirement, and it was the requirement in these donors.

The study was conducted in Albuquerque which is just a few feet over 5,000 feet. So I think that points at the influence of altitude and/or smoking on driving the hemoglobin level higher. The theory was that it would drive ferritin levels lower. People who were anemic from a higher baseline level would be more likely to be taken as blood donors because if you were, they will pass the standard, even though they are quite iron deficient. The idea was that you would see more iron deficiency at higher elevations or in smokers. This was the thinking at the time of REDS-II. As you can see, hemoglobin was not affected in either gender over lifetime donations.

Now, I'm going to describe the RISE study in a few summary slides. There is a lot more to it, the two references are given in some of the material.
Basically, we recruited two cohorts of blood donors across six blood centers in REDS-II. We recruited a first-time and reactivated donor cohort.

The reason the reactivated donors were added to the first-time cohort was pragmatic. This is a two-year follow-up study and we didn’t believe we could get enough first time donors recruited that would agree to a two-year follow-up study at the time of their first blood donation. It turns out we were right. We needed the reactivated donors. So we have two sorts of donors in this cohort. Our thinking was that after two years, the iron status of donors would return to normal. I think we showed that in fact was the case.

The second cohort was a frequent donor cohort, which is defined as two or more donors in women or three or more donors in men in the last year. This has been used in several other studies as the definition of frequent donor. Donors were asked as a condition of enrollment to donate frequently for the 15- to 24-month study period, at the same level as defined as frequent donor, twice for women or three times for men, and we measured a whole bunch of stuff at baseline and longitudinally through the study, which I don’t have time to show you with great detail.

But at enrollment, this is a key slide that many other studies have verified and/or actually shown before RISE, which is, we defined two levels of iron deficiency concern. The first level we named absent iron stores and that was defined as a ferritin less than 12. Many other studies suggest that that’s a fairly good level of ferritin to predict that if you did the bone marrow, you wouldn’t see any iron in the bone marrow.

The other condition was a less serious condition on the way to iron deficiency called iron deficient erythropoiesis. We used a ratio that had been
shown to correlate well with iron deficient erythropoiesis by other measures. That
was the logarithm of soluble transferrin receptor divided by ferritin, and that
goes up in iron deficiency with a cutoff of 2.07.

We determined the cutoff as a 97.5 percentile of first-time males
and you can see in this block here the 2.5 percentile -- you can see that first-time
males are essentially not iron depleted, but first-time females are, but in both
genders, becoming a frequent donor causes you to be quite a bit markedly more
likely to be iron depleted, both at the more serious level of AIS and the less
restrictive level of IDE. These numbers are, I’m going to show you in other slides,
will compare to some of the other studies.

Looking at the factors that influence iron deficiency, we did a
multivariate analysis for a whole bunch of factors. We ended up, the significant
ones, we ran a multivariate model, correcting and adjusting for the various
factors.

Here, you have a model of age in two different -- we segregated out
by gender to show the following, which is that women who are younger are more
likely to be iron deficient than women who are older or than men. There is a
slight hint that younger men may be more iron deficient at the less restrictive
level, but it's not as big an impact.

What was very marked was the influence of donation frequency on
the prevalence of these two indicators. We used a two-year trailing red cell
donation frequency. In other words, donations other than the one we were taking
blood at, for 24 months prior, and in the United States, that can go up to 13 if you
do the math. So you can see it's segregated into different strata.

The first thing to show you is that we used first-time donors as the
reference group. You can see that the reactivated donors basically did not differ
from the first-time donors in the prevalence of iron depletion, so, if you will,
confirming our decision to combine them for the purpose of this study. But you
can see rather remarkable odds ratios. These are really higher than you usually
see in human studies. In the prevalence as related to blood donation history,
particularly at the higher levels, with odds ratios 19 and 50 for the two levels of
iron depletion. Down at the bottom in the footnote are the factors that we
corrected for in the model.

We also followed these donors for two years. Because of budget
restrictions, the interim visits were rather, were not sampled randomly but rather
in the higher risk strata. So we don't have great data on men. We have better data
on women because they were deemed at a higher risk and more often sampled at
the interim visits.

But looking at this model, using all visits including the interim visits
rather than just the enrollment visit, you can see that we see the same results
with perhaps less of a signal, as the relationship between blood donation and, this
is AIS but there's a similar slide for iron deficient erythropoiesis, you can see the
numbers are a little bit lower, this 8.6 at 10-plus donations was 19 in the
enrollment slide, for example.

You can see other factors coming in. We can see that iron
supplements are protective and rather meaningfully so, about halving the odds
ratio. Smoking is working in a counterintuitive format. We thought it might raise
the risk. It in fact lowered the risk. We still don't have a good explanation for that.
We think it might be an artifact of, well, we don't know why. Let's leave it at that.

Gender, you can see that the female male ratio is clear, but the odds
ratios are actually not as high as the odds ratios you see with donation intensity, which is what you would expect from the curves that Dr. Paul showed, for example, that men, when they donate frequently, start to look a lot like women, and the influence of multiple donations is greater on men than on women, but women start out more iron deficient.

This is a slide that a number of people have waxed eloquent on that has been used to discuss possible donation intervals. What this is is looking at the interval between the donation that was measured for ferritin and how long it was before the previous donation, and looking at the odds ratio using the group that donated more than 26 weeks later is the reference group. So the reference group is not shown here but it would be the far right and it would be at one, the red line.

You can see that the ratios at frequent donors, every eight weeks, is over four times the odds of that than people who wait 26 weeks. You can see the ratio slowly go down until you get down to about 14 weeks or so between donations, when it seems to kind of level off, but really, except for one little blip here, at the 19 right here, that just barely gets across one, so that at 19 weeks that is not significant, but the larger group, the bundled group from 20 to 25 weeks, is significant.

So my conclusion is, unlike the introductory materials you were given from FDA, this does not support an interval of 14 weeks to prevent iron depletion, but rather an interval of 26 weeks and over. This is my opinion.

The odds ratios are small. Well, they're not that small there. They're two on average. So I think you can't make much out of this. We were looking at the time for a solution that would be a palatable interval for the FDA. We did this analysis specifically to answer the question that the FDA posed and we came up
with 14 weeks as a candidate interval, but you can see, there's still plenty more risk at 14 weeks than at 26 weeks, and there's no magic cutoff anyway.

So conclusions. Frequent whole blood and red cell donors, males and female, have a high prevalence of iron deficiency. Ferritin decreases with increasing donation frequency, which is the most important factor in predicting iron deficiency in multivariable models.

Additional variables are female gender, menses and younger age in females, lower weight, and no iron supplements. There were others, but I list these as the most relevant and, if you will, subject to consideration by regulatory agencies. Smoking, for example, I don't think we're going to suggest that people to start smoking to prevent iron deficiency, as an example, probably not. The odds ratios for AIS, as I said, is elevated compared to -- is significant compared to donation intervals up to 26 weeks.

Now, I want to comment a little on the Australian donor study which was done in 2014 and was an unselected donor study, probably the first largescale. I'm not showing the Canadian data because you will see that later. That has some prevalence data. It's a significantly smaller study.

So I'll show you this one as a larger study and the downside is that the Australians do things differently than the United States. They have a 12-week required interval. Their hemoglobin is 12 for females and 13 for men, and at the time RISE was done, of course, it was 12.5 for both genders in the RISE study.

They also looked at pheresis donors, but mostly the plasmapheresis, not platelet pheresis as we do, and they have even different hemoglobin standards for that. They don't seem to do double red calls in Australia from what I could tell.
Finally, they define iron deficiency by the World Health Organization standard of 15 nanograms, which would tend to raise their frequency compared to a 12 cutoff. So it's not an ideal study from the American point of view, but is a completely unselected donor group.

Here, you can see they analyze it in all donors, new donors, basically first-time donors, exclusive whole blood donors that they define as donors that have never given pheresis, and apheresis donors, they define these as people who do give apheresis donations, although they also, I believe that's exclusive apheresis donors. They don't give red cells anymore.

You can see that there's a gender difference in the first three groups. It's quite marked. The prevalences look a little lower. This is for ferritin 15, they look a little lower than RISE. I'm going to show you head-on comparisons in a minute. They are lower.

The other thing is they don't seem that much in the way of apheresis iron deficiency, which I think as you see may reflect the fact that they're doing plasmapheresis and probably not doing it all that often. Data was not provided on that point, but it was an unselected donor group and I think it will be useful in the following sense to compare to the RBC Omics study which I do want to describe in some detail even though the results are preliminary because much more is coming from this in the next few months that might be helpful.

This was a study of 13,770 whole blood donors. They were over-recruited into minority groups and very high frequency donor strata. So we had 2,000 black donors, 2,000 Asian donors, 2,000 Hispanic donors, 2,000 donors who we call super donors, these are donors who gave depending on how we cut it, either 9 or 10 times over two years and had not been deferred for hemoglobin.
That's the definition of our super donors. Then 6,800 unselected Caucasians who were not super donors. These Caucasians are probably most comparable to the Australian study, I believe.

This is part of a much larger genomic analysis which is ongoing that includes such studies as pica, restless leg, ability to donate without becoming iron deficient, and also in vitro hemolysis data related to red cell storage.

But we have, as I said, ferritin, hemoglobin, and red cell indices as well as an additional donor questionnaire and a complete donation history available to us. This was completed also before the United States changed its donor standards to 12.5, so it's comparable to RISE anyways.

If you look at the Australian data versus the Omics data, you will see that there is not much going on at the lower levels of donation intensity, that they look the same, and these are the data from both that I haven't shown to you before. Nothing terribly surprising here, but you can see that in the Omics data, in the Caucasian donors, at five donations you start to see an uptick, you might even have seen a couple three and four donations a year, an uptick of a prevalence in the iron deficiency in men, not so much in women.

If you go to the highest tier of frequency, the Australians only report six plus donors in two years, six plus donations in two years, so there is only one number, but I showed you the Omics data for six, seven, eight, and nine donations in two years. I cut it off at that point because you can only give nine donations in Australia in two years if you follow the rules.

You can see a rather significant higher frequency of iron deficiency in Caucasians compared to, presumably, Caucasian Australians, for reasons that aren't entirely clear, and in this analysis at the higher level it looks like females
are also higher.

Finally, I want to show you some of the early data on the effect of blood donation and ferritin in different racial groups. These, hard to see, but each triplet is Caucasians on the left, African Americans in the middle, and Asians on the right. We're not showing Hispanics at this point. You can see that Caucasians appear to be much more likely to be iron depleted at higher donation levels. I don't believe anyone has seen this before. This is certainly true in men but also looks like it might be true in women.

We haven't completed the statistical analysis of this, but lumping these donors into buckets as first-time donors, one to four donations in the last year, and five to eight donations in the last year, you can see that the P value is clear at five to eight donations for men. It's less clear for the other groups and the influence at one to four donations appears to come from Asians have a higher prevalence than the other two groups, which is a little hard to understand, but that's what the data is showing at this time.

This is all very preliminary and I just thought you should see it for the purpose of considering discussion.

Finally, don't freak out, this slide is basically my effort to summarize all these studies as to the mean or median ferritin in blood donors in these studies. Male and female, that's the slash, and I tried to lump the frequencies going forward in meaningful ways. What I'm trying to show you is in the red, which is it looks like RISE and Omics are similar to each other, and they are, but they are much different than Australia, and interestingly enough, they are different from earlier studies done in the United States with different donor standards; Simon's 1981 data and Finch's original 1977 data, all suggest that
something’s happened in how we manage donors that makes donors more likely
to be iron depleted at higher donation intensities. I don't know why. I'll speculate
a little in a minute.

Finally, I just want to show you the results of the Spencer abstract,
which these are some of the reasons why we think you might get more iron
deficiency in donors than you think. One of them is that they selected on a high
platelet count and high platelets are a correlate of iron deficiency.

So we shouldn't be too surprised that they have iron deficiency, and
they come from a frequent donor red cell population. That's where we recruit
them from. But we looked at donors who were between 12.5 and 13.5 in
anticipation of trying to do something to prevent the implications of the new FDA
rule, which is going to decimate our almost entirely male pheresis donor
population.

You can see that the prevalences in these two groups are high, that
obviously it's more likely in the 12.5 to 12.9 group, which is no longer a blood
donor group, but that in any case, in this group, blood donation frequency,
pheresis donation frequency is quite significant as well. The prevalence of, this is
ferritin less than 12, in these male-selected low hemoglobin donors, is rather
startlingly high. That's what I wanted to show to you, that we can't ignore
pheresis donors in our thinking.

I just wanted to redux the RISE conclusions for you. I'm not going
to talk about them again, but just to remind you that I want to make conclusions
on the other studies in the alpha stage, that Australian donors show similar
findings to RISE but iron deficiency prevalence in frequent male donors appears
lower than the United States, possibly because of differing donor genetic
background. I'm thinking maybe the English, Celtic, the people who got sent to
Australia from England are rather a homogeneous population, different from the
United States and there may be some genetic components.

Also, that the comparison of all studies suggests that maybe
something we're doing in the United States is raising the frequency of iron
depletion and frequent donors compared to 40, 20, 30 years ago.

The REDS Omics study is going to be helpful for you. I'm not going
to make too much of it, but apheresis donors appear to also have a higher than
expected prevalence and as we talk about who's at risk, we have to understand
the prevalence of iron deficiency is going to be influenced by geography,
underlying donor requirements, and how the blood centers go around recruiting
donors.

Keep in mind that prevalence in blood donors are the donors that
come back. If you've driven people to iron depletion and they can't be a blood
donor, they're not coming back, and so the problem may be worse than the
prevalence indicates. We may be selecting out people who are better able to keep
their hemoglobin up despite being driven into dangerously low ferritin levels by
our ministrations.

So that last bullet is to point out that blood donors are not a general
population, they are selected for the ability to give blood and have hemoglobin at
the acceptance levels. Thank you.

DR. LEITMAN: Thank you, Dr. Cable.

Our next speaker is Dr. Joe Kiss from the Institute for Transfusion
Medicine in Pittsburg. Dr. Kiss will talk about his study, oral iron
supplementation after blood donation, a randomized clinical trial.
Oral Iron Supplementation and Blood Donation: A Randomized Clinical Trials, Joseph Kiss, MD, Institute for Transfusion Medicine

DR. KISS: Thank you, Dr. Leitman and members of the committee, for allowing me to present our work with the HEIRS study, which is operated out of the umbrella of the REDS-III program.

Okay, so my objectives will be to describe the design and key findings from HEIRS. HEIRS was basically designed and there is a progression from the RISE data which was in REDS-II to HEIRS and subsequent studies. It was designed to be a kinetic study of hemoglobin recovery and ferritin recovery, essentially a quantitative analysis, so it was highly controlled in selected donor populations based on their level, we knew their level of iron stores going into their donation history, as well as some other demographic variables that turned out to be not very significant so I won't say much about gender as well as age, but we did stratify the study along those lines.

Then I think there is sufficient data in this study to consider the impact, as Dr. Cable has alluded to, the inter-donation interval versus iron supplementation and the relative advantages of each.

So just to remind the group, and here we have on the lower panel here, Iron Man, most people know him, but the top panel there is for those of who you don't know her, Iron Woman. And of course, body iron is thought of as in various compartments and I want to make a few points here. These are the total amounts that are present in a normal individual, and the two main compartments, which are measurable, include of course the hemoglobin compartment, and we can develop a math equation to look at iron content there,
and that’s the bulk of it at 70 percent, and storage sites, which as we’ve learned
and as we know, ferritin is a fairly good measure of.

But at lower levels, it’s not very informative. It detects, it’s more
qualitative, and it can be beefed up with serum transferrin receptor, as was
reported earlier as well. So this also is a measurable site. The other sites are not
measurable but fortunately they’re very small in number. I’m going to allude to
the combination of these two later on in another analysis we did of total body
iron to look actually at iron levels in the body quantitatively.

Here’s the problem in a nutshell that, again, Dr. Cable alluded to.
This shows you the relatively low levels and one point I want to make here is
storage sites are relatively small. Most of the iron in the body is actually in a
functional role. The storage of iron is actually quite small, and I make an analogy
to a car engine. Most of your reserve is in the gas tank and very little of it is
actually in the engine, it’s just the opposite in the body. Most of it is functional,
it’s deployed for use, mainly in carrying oxygen and transferring oxygen, but in
other vital cellular processes including many enzymes.

But the problem here is that in relation to iron stores, females, of
course you see the difference there, females being low in comparison to males,
and then we take a unit of blood out, and these are figures from Dr. Cable’s paper
with a 500-cc blood draw with additional 25 mLs. This is the amount we actually
measured in the papers. So this is the real number, if you will, with the 500-mL
blood draw. You can see in reference to the females, the relative less reserve in
females than males, but it’s still a very sizeable amount.

So in blood donation, once this occurs, and this would be in
someone who is normal, coming in to donate for the first time, this iterates and it
really depends on how quickly you make up this difference, which turns out to be very slow.

I left one slide out of your packet. You can review it in terms of background information on HEIRS. I did it to save time. We studied in HEIRS, HEIRS was a randomized, non-blinded study looking at iron supplementation in various well-stratified groups of donors. We chose previous donors, not new donors, and they wanted to give them some baseline, some time to recover hemoglobin, and whatever else, so we gave them four months. We didn't take them immediately after their last 8-week donation.

We stratified them according to what we called at the time iron replete and iron depleted. We drew that at 26 and Dr. Cable has explained our rationale for this number. We also stratified by age and sex, and I don't have anything more to say about the last two variables in my talk.

The overall schema looks like this. We actually budgeted for 400. We were able to do the study with 334 donors. We got a rapid turnaround ferritin value to randomize them in these two groups. They're what we called iron depleted and iron replete, and in fact, with this schema, and then they were randomized and then a group randomly assigned to receive iron gluconate with a 38-milligram dose of iron versus nothing, no placebo, then followed for a period of 24 weeks with regular blood draws and analysis. Then we determined that our primary endpoint was hemoglobin recovery as the time to 80 percent of the hemoglobin drop.

A couple points on this slide. We chose this dose because largely we did a literature review, but we were very much influenced by the work of Dr. Radke who had a study with 20 versus 40 and basically in his multiple donor
study, 20 milligrams maintained ferritin in that study, and 40 began to see some rise in ferritin with time, and the toxicity was essentially equivalent.

So we thought that we wanted to see an effect and that was a good dose to pick. We also debated this number. We thought maybe IRBs would give us a problem with giving so-called iron replete individuals iron, and we're glad it wasn't really. We had enough controls in the study to allow this and we're glad we did it because we found some things about what we were calling iron replete donors at the time.

The overall baseline characteristics of the subjects, so we randomized 215, this study was actually, the analysis was based on 193. We thought we had enough follow-up visits to give us nice stable outcomes and curves so the statisticians were happy. You can see here in the groups there that the low ferritin group, males and females, the average ferritin in the low ferritin group was about 15. In the higher ferritin group, or so-called iron replete group, it was about 52 in women and 60 or so in men, so not much different.

Now, I'm going to show you the hemoglobin recovery. I'm showing this as a percent of their baseline. So of course the iron-depleted group did have a lower baseline hemoglobin, but this is just normalized for the percent recovery. The days to 80 percent recovery here of course were very rapid in the iron-supplemented groups, and just to orient you, the red is the iron-treated groups, the continuous lines are the ferritin less than 26, and the broken lines are the ferritin greater than 26.

So there is a lot of information here, but basically the numbers here are their recovery of 80 percent of their lost hemoglobin and the numbers of days to that, and you can see here that these groups are significantly different between
the iron-supplemented groups and their corresponding counterpart here.

We were not surprised at all of course that you take an iron deficient population, give them iron, and we see these differences both in terms of their rapidity of recovery as well as overshoot here. In other words, they were actually anemic coming into it. So they were able to get up to this level once they received the iron.

We're not surprised at all. In fact, we used that to power the study to determine the number of subjects we were studying. We were a little bit surprised though that in something we thought was iron replete, that they still recovered significantly faster than the other ferritin greater than 26 group, and that they did overshoot, although that's not statistically significant here in terms of the -- it's only about 1 or 2 percent above their baseline, but they did improve their hemoglobin recovery and overall hemoglobin levels.

To look at that phenomenon a little more closely, we did a recovery by ferritin quartiles, and what we saw was that the group that had a ferritin of less than 50, as you see here, the dots here indicate the median recoveries, and these are the confidence intervals. Where you see an interval there, we did not achieve, there was no upper limit confidence interval in these groups.

So you can see by the dots and by the lines here that this group was significantly slower than the iron-supplemented groups, whereas if your ferritin was above 50, there was no significant difference. So we actually identified for the first time, I think, the upper limit where iron supplementation was helpful, and that having a ferritin higher than that level was 50.

To look at the significance of that number, these are the ferritin recovery curves in the groups that were not supplemented with iron. What we see
here is in the group above 50, which you see in the upper curve, we see that this is the time course of ferritin after donation, with no other intervention, just left to their own. We see that the ferritin levels all remain above 30 here whereas in the other quartiles, ferritin dips into iron-deficient range. So this is all indeed iron deficiency erythropoiesis and this group was able to sustain going forward. We were able to identify the reason for this.

Now, if we look at more closely at ferritin recovery, and again, these are the four groups that you've seen, these are the average in those groups, we see a couple of things. One is, again, with iron, we see a very rapid recovery of ferritin, and I'm going to use this group.

So this is our so-called iron replete group after donating a unit of blood with about 250 milligrams of lost iron. We see over time a nadir in the ferritin as there is re-equilibration. The arrows here indicate recovery of hemoglobin. So we see this decline and we see a plateau, and then only when the iron essentially has been placed into the hemoglobin and that's recovered, we see recovery of stores. So this is a nadir over this period of time.

We can also ask questions from this, such as, we happen to have a 168-day total interval here, and it happens to be nice, you can divide this into three 8-week intervals. So we see 56, 112, and 168 days. If we ask the question if one takes iron, how long does it take to recover ferritin to baseline, if we look here, this is about 85 or 80 to 90 days, about 85 days to do it.

So it seemed that people taking it for this period of time were able to get back to their baseline and we see of course in the non-supplemented groups, it's a very delayed recovery of ferritin out over time. Really, no one except the iron group here, no one gets up, at least in the average, gets up to where their
baseline started, even by 168 days.

Now, we wanted to refine this because all the estimates about how long to take iron after donating a unit of blood were really based on some assumptions. One was that they would only absorb about 10 percent of the ingested iron. So you say 10 percent, they need about 2,400 milligrams of elemental iron, and these were really theoretical estimates, but we're actually able to show here how long it would take.

When we, however, did a comparison of the total body iron, and I don't have time to go through the actual data here very easily, but when we compared these by intervals, if they took iron this interval, that interval, the only interval that was significant in terms of the gain in ferritin was an interval of one, 56 days.

We were asked when we submitted the paper for review to look at a little bit more tighter intervals during this time. So this is Dr. Cable's paper just published in August. In the actual journal Transfusion; the prepublication online version was published earlier.

We can see that doing a total body iron analysis of the total gain in iron over this time, fully 88 percent of the iron that was gained in the treated groups was gained over the first eight weeks. There was a little bit of a lag here, but basically that's why it is really important in terms of, we actually could identify a period of time. You can see that the overall iron absorption, I'm basically translating this to absorption, because the gain in this iron is very early in the first few weeks, and then tails off, and by eight weeks it's not distinguishable from controls.

So that's in terms of iron supplementation, what groups benefit,
how long that benefit, how long supplementation needs to occur. I want to return back to the groups that were not supplemented and I want to come to this point, and that is that, and I’ve made this point already on the ferritin curves, and this is true of also when we measure this as total body iron or ferritin, just the storage iron. So for participants not taking iron in the study, the median recovery time was longer than 168 days, and fully two-thirds of the subjects did not get back to their baseline by the end of the study period, which was cut off at 24 weeks.

Now, this has obvious implications in terms of if the original eight weeks was really based on hemoglobin recovery, and we know that occurs more rapidly than ferritin and iron recovery, but we think of this blood donation, most people are repeat donors and interim process, this is a continued phenomenon with blood donation.

In RISE, as Dr. Cable mentioned, and again, I’m using some of the information here, the 16 weeks, we now know that it’s more of a broad range here more than a discrete number, but it looked like in RISE, again, I’m going to show you this that you’ve already seen, that with time, even if we can’t pick an exact, precise number here, with time there is a lower risk of AIS, so ferritin less than 12, and it does equate out here to greater than 20 to 25 weeks.

But over time, there seems to be this progression. I’m going to show you this slide again, which you’ve seen. If the endpoints are a little bit different, this is ferritin values, not portion of subjects with AIS, but this is very flat. So this only group here that actually had adequate iron storage at some point we can see and they don’t even get, even in the highest ferritin group, they do not recover all of their ferritin. So this is a very flat curve compared to perhaps what we were seeing here.
But the difference I believe between these curves, apparent benefit of waiting or increasing inter-donation interval, is the fact that at the end of study in RISE, 39 percent of the donors said they had ingested some form of iron supplements. So almost 40 percent were taking iron, whereas in the HEIRS study, wanting to be a proof of principle study, we told them if they weren't assigned to take iron, not to take it. So these are, basically, the difference I think is between there's a composite effect here between waiting and some of the people in this study taking iron supplements.

My conclusions for you are, the first one is the amount of iron removed in the 10 minutes or so it takes to donate a unit of blood requires over 24 weeks to replace on a standard diet without any added supplemental elemental iron. Iron supplements accelerate hemoglobin recovery and we know the group that would benefit in terms of improving their hemoglobins faster and to higher levels.

Nearly 90 percent of the net gain from iron supplementation is realized within 8 weeks after blood donation. One can argue about treating longer with more deficiency and that's a minor, relatively, that's a finesse point. Increasing inter-donation interval appears to be a less effective way to manage iron deficiency and I could word this a little more strongly, that saying to be effective as a mitigation against iron deficiency, it has to be fairly long, and we've heard from Dr. Cable and from those curves, it probably needs to be on the order of twice a year or every six months, but it can be mitigated population-wise because some of those people will be also taking them.

So I wanted to thank my many colleagues in the HEIRS working group and the REDS-III program, and I thank you for your attention.
DR. LEITMAN: Thank you very much, Dr. Kiss, for all of that important data, dense data for us to consider later when we consider the questions posed to us by the FDA.

Our final speaker for the first part of 1A is Dr. Bryan Spencer and he will talk about strategies to reduce iron deficiency in blood donors, a randomized trial. So more discussion, I think, on the same study, is that correct? Are you presenting more data on the same REDS study?

**Strategies to Reduce Iron Deficiency in Blood Donors: A Randomized Trial, Bryan Spencer, MPH, American Red Cross**

MR. SPENCER: So I was asked to present this morning a few slides on the CHILL study that will be discussed at greater length this afternoon, so whether that precedes or follows STRIDE is fine. Since these are up, we can start with STRIDE.

Good morning and thank you for the invitation to present results from the strategies to reduce iron deficiency study. This was a randomized trial. The eligibility for the STRIDE study used the same definitions of frequent donor that Dr. Cable described for the RISE study, females with two red cell donations in the prior year, and males with three. They had to be adults at the point of enrollment.

We needed them to be off of iron supplement for at least a month prior to enrollment and generally, almost exclusively, that meant that these were donors who were not routinely taking iron. They had to be willing to be randomized to one of five groups, including being assigned to take pills on a blinded basis for a 24-month follow-up.

The exclusions were relatively few and narrow. We did not want to
enroll someone who intended to become pregnant within the next two years and because we were giving iron, we didn't want people who suggested the possibility for iron overload. So if their enrollment ferritin was greater than 300, we didn't enroll them.

So these are the five groups to which we randomized the subjects in STRIDE. They represented an educational intervention, that's groups one and two, and then a pill intervention, which is groups three, four, and five.

In the intervention group, we wanted to see whether providing donors information about their iron status following each donation was sufficient for them to take steps to mitigate their low iron. So we provided information each time and on the basis of the results made recommendations either to continue donating or to take steps to mitigate a low ferritin result.

The control group for this intervention simply got a letter following their donation, did not provide their ferritin values, thanked them for donating, and asked them to continue to donating at their regular frequency.

In the pill groups, we had a dosage of iron, 38 milligrams, that's roughly equivalent to an over-the-counter iron supplement, 19 milligrams is equivalent roughly to an over-the-counter multivitamin with iron, and then we had a placebo pill. So the pills, the donors didn’t know what they were getting, the research staff, other than one person at one blood center that acted as the pharmacy, also didn't know what the donors were getting, just to avoid the possibility that they might be managed in any way differently.

But the point was to try to define what might be the minimum intervention that would be successful in helping prevent or reverse iron depletion in these donors. It might be bills or it might simply that providing information
with recommendations alone was sufficient, what we wanted to test, two broad
strategies.

So a little more detail on that first group, the iron status letter arm. So again, the messaging was differentiated on the basis of a ferritin greater than
or equal to 26, or less than 26. If it was greater than or equal to 26 nanograms per
mL, or micrograms per liter, their letter said thanks for donating and
recommended that they continue donating at that same frequency.

If their ferritin was low, less than 26, we recommended, we told
them that and recommended one of two interventions, that they take an iron
supplement and we provided a little information on that, that they could buy it
over the counter, they could speak with their pharmacist, we didn't recommend a
particular type or formulation, or that they consider delaying their next donation
for six months. Donors were allowed to choose either option or neither and we
assessed this at the end of the study.

So this table shows that we had a successful randomization, the
geometric mean ferritin was not statistically different across the five groups, the
iron status letter, control letter, and then the three pill arms, they're in the same
order as I showed previously and will be in that order throughout the rest of the
presentation.

We see a really large share, 20 percent or greater, with absent iron
stores and more than 63 percent with ferritin less than 26, so this is a group that's
very heavily iron-depleted and we see, again, a very tight correlation as we saw
from the earlier RISE data between ferritin less than 26 and this composite
measure, iron deficient erythropoiesis, that includes both soluble transferrin
receptor and ferritin.
So our activities during the study included administration of questionnaires at enrollment and study conclusion. We asked about symptoms associated with iron depletion, certain medications that might influence absorption of iron, we asked about multivitamin taking, and then at the end of the study, we asked about adherence to the group assignments and the response to the protocol.

Following the enrollment donation and the ferritin test, they got assigned to the study arm. They were asked to donate at the same rate as pre-enrollment and then we got these lab assays at each donation visit.

So the completion of STRIDE is represented in blue. Overall, 56 percent of our original cohort of 692, so 393 donors, completed a final visit in STRIDE at roughly 20 to 24 months follow-up. That was a little bit lower than we had projected.

The loss to follow-up of 116 donors is not unexpected and what you see in a regular blood donor population. They come and go, they don't always come back, so that's not surprising, but we had a certain amount of withdrawals that was much greater in the pill groups than in the two letter groups.

We think that this was not due to adverse events from taking iron. In fact, we see that the proportion of donors that reported adverse events associated with iron were relatively few, and they did not differ by iron dose. So those getting placebo pills reported as many adverse events as did the 19 milligrams and 30 milligrams.

So we don't think that was the difference, but we did hear from many donors that they decided they wanted to be taking iron or their clinician thought they should be taking iron, and so many people withdrew from the study.
As we learned through additional analysis afterwards, they actually continued as donors, but they appeared to be uninterested in continuing to donate taking pills without knowing what the iron content was.

So we will show a few different analyses of data from the study. We will compare group differences at the end of the study. That will be with the 393 subjects that completed stride. We will look at changes between enrollment values for iron status and final visit for those same subjects, so a paired analysis.

Then we will do a methodologically stronger, statistically stronger, repeated measures, longitudinal analysis of all visits associated with the 692 donors enrolled. So that actually represents, I believe it's about 2,500 donor visits. There are many more observations in this and it captures all of the available information.

Then, again, some of the human factors of interest from this study, which we got at the final visit questionnaire.

So group differences at final visit, we found very clear, and as expected, differences in geometric mean ferritin with the intervention groups, those getting the letter and those getting intermediate and a low dose iron, having higher levels of ferritin compared to the two control groups which did not really change.

The log measured the ratio of sTfR to ferritin likewise improved in the intervention groups, and either stayed the same or declined in the others in the proportion of subjects with ferritin less than 12 is dramatically different across these groups. Likewise, ferritin at a cutoff of 26. So the group differences are very apparent at the study's conclusion.

Our paired analysis shows that the drop in ferritin less than 26 was
very large, by half, in all three intervention groups. The drop of absent iron stores
was even greater, 70 percent or higher in all three of the intervention groups.
There was no change in the control groups.

So thus far, we see very big improvement in all three intervention
groups and they don’t look different, one from the other. There is a lot of
information plotted here, but the point is just to show graphically about a 10 to
18-point improvement in ferritin in the treatment groups, flat curves in the two
controls, with sTfR in the measure in the ratio of that with ferritin.

A decline represents improvement and in the two controls, we see a
worsening status. Likewise, here in the hemoglobin, curves are not so easy to see
here. You do see some decline in the control groups. We will show some more
information on that in a moment.

So with the repeated measures longitudinal analysis, we have both
continuous measures as well as binary outcomes. So the linear regression,
looking at the continuous measures, shows a clear improvement in those getting
pills, but it’s here, with the stronger statistical analysis, that some differentiation
between the groups getting iron pills and the group getting a letter with iron
information and recommendations begins to show up.

These two groups are not statistically different from each other.
Their improvement is statistically different from their enrollment, but these two
groups are in fact different from the iron status letters. So we do see that they
differentiate themselves a little bit with a longitudinal analysis and in contrast,
the control groups either stayed the same or got worse.

And that holds true for soluble transferrin receptor improvement,
lower values in these two groups, basically no change here, and higher values,
worsening iron status, in the two control groups. We see that in the bottom left, and again, the iron status letter has improved. That group has improved but not as much those getting pills.

With our binary outcomes, similar effects. Improvement in the risk for ferritin less than 26, that's dropped by 70 percent or more in those getting pills, and is dropped by a statistically significant amount, and a clinically meaningful amount in the iron status letter, but not quite as much as the two pill groups, and unchanged here. Ferritin less than 12 shows a similar pattern. Meanwhile, in the control groups, the risk for absent iron stores went up by roughly half to 75 percent.

**So this slide on hemoglobin shows the very meaningful difference between the control groups and the pill groups.** So here again, we see differentiation between those who got a letter with iron, with ferritin values and recommendations, and those who got pills, but the range between the two controls, basically a drop of 0.3 grams per deciliter and a 0.3-gram improvement in those who got pills. That's a very large and meaningful difference at any blood center.

So at the end of the study, we asked at that final visit on the questionnaire, what did donors who got a letter advising them what measure to take, advising them to take a measure on the basis of a low ferritin value, what did they actually do?

We found that 70 percent of the donors responded in some way. Some of them, a minority, only delayed their subsequent donation following receipt of that letter, but a large share, 40 percent, decided to take iron. Then 19 percent decided to do both. They reported delaying their donation and taking
iron.

So all told, 70 percent took some step to protect their iron status and 58 percent of them decided to take iron. It seemed like they were committed to maintaining the same donation frequency and chose not to delay.

So this shows a little bit of the operational outcome. Those who decided to take iron end up with more visits with the red cell donation and more red cell components donated, so there's some difference because some of their donations are double red cell apheresis visits, but we see a pretty meaningful difference between those who did take iron and those who didn't. Likewise, those who delayed donation end up unsurprisingly with fewer visits, given that they lengthen that interval by a meaningful amount.

We wanted to know what donors might do in the future if such a program were scaled up. Would donors take iron if the blood center advised them to do so? By a large majority, they indicated that they were likely to do that, or more or less likely to do that, neutral on the idea, and 10 or 20 percent at the most that said that they weren't likely to do that.

So by and large, there is a great willingness of donors, expressed willingness to go take iron, go buy and take iron if the blood center advises them to do so. A slightly larger proportion indicated that they would take iron if the blood center gave it to them, so there was some minor difference but it wasn't terribly large.

Meanwhile, we would love to know, what are donors actually doing with respect to iron supplementation? But that's not part of the donor intake. In the Connecticut region of the Red Cross, however, we have been systematically asking donors this since late in 2015. We reported on this at last month's AABB, it
was a top poster with Dr. Cable as the lead author, and what we see is overall, I
don't have an overall number here, but I can tell you that overall 21 percent of
donors report taking iron, either in the form of a multivitamin or as a separate
iron supplement.

The proportion taking iron as the multivitamin was much greater. It
was about 70-plus percent and about 20 percent taking a separate iron
supplement, and then 10 percent that reported taking both. Females were much
more likely to take iron supplements than males and you see a clear age gradient,
which matches data you see from CDC and NHANES reports that older people
are more likely to take nutritional supplements than younger people, but there is
essentially a fourfold difference in the youngest age group here compared to the
older age group. This is in logistics models controlling for age, sex, race, ethnicity,
donation procedure, and donation frequency.

A couple of other interesting nuggets from this are that we found
surprisingly that the single donor platelet donors were actually more likely to
report taking iron than red cell donors. Thirty percent of the SDP donors said
that they take iron. Eighteen percent, so fewer than the 21 percent overall, of our
double red cell apheresis donors, said they’re taking iron. So that makes it clear
that there is a lot more room for improved education from the blood center to
blood donors on the need for iron.

As far as why they take iron, we asked them what are they taking
and what form, how frequently, and why? This graph shows what are the
expressed motivations for those, the 70 percent who are only taking an iron
supplement, and those who take iron in the form of a multivitamin?

For this group, the largest group, general health and wellness is by
far the overwhelming motivation, and other reasons pale in comparison. We allowed them to mark multiple reasons for why they take iron, but this stood out. Just to be healthy.

Those who were taking a separate iron supplement, it looked more clearly geared to blood donation. The largest response was health and, well, it was actually, I donate blood. Health and wellness was also very large, but I donate blood and to avoid deferral were also very frequent, but it's notable that this is a very small group.

The conclusions from STRIDE, we see that providing regular blood donors, these are all frequent donors, with either a low or intermediate dose of iron for 8 weeks or with iron status information and recommendations were effective and mostly equivalent interventions for mitigating iron deficiency. We saw improvements in ferritin in all three groups. We saw a large hemoglobin change in the iron supplement groups compared to the two control groups, 6 grams per deciliter.

Donors without intervention had worsening iron status in longitudinal analysis. So remembering how frequent, how large the prevalence of iron deficiency was at enrollment, it's notable that it got even worse during follow-up.

The donors in the pill arms did de-enroll more frequently than those in the other groups, but the adverse events for iron were infrequent generally and they were unrelated to iron content. We saw the donors provided with their ferritin value and education will act on their own to prevent or treat iron deficiency. A large majority of donors say they're willing to take iron supplements if recommended to do so.
So we conclude that iron supplementation of frequent donors is feasible and it's effective with simple operational procedures. So we think that this gets a basis for blood centers to start to take measures.

What they are might be somewhat different, but we think that once that happens and comparative effectiveness research is performed, that will help us to define which is the optimal population for ferritin screening or for iron supplementation, what are the best methods for encouraging iron supplementation in blood donors, and what is the willingness or tolerance of blood donors for daily iron pills? Those might vary across different centers.

Thank you.

DR. LEITMAN: Thank you very much, Bryan. We are about ten minutes behind in our schedule and so I'm going to change the schedule a little bit. We're going to take a break now, but it's going to be a short break, a ten-minute break. We'll come back, hear the final two presenters on the same topic, and then we'll ask questions for all of the foregoing speakers.

So ten-minute break.

(Brief Recess.)

DR. LEITMAN: So let's go on to the next speaker. The next speaker is the same as the immediate prior speaker and is not on your schedule, but we are going to ask Bryan Spencer to come back, and he will give brief number of slides another extension of the REDS-RISE studies, the CHILL study.

So Bryan?

**Comparison of the History of Donation and Iron Levels in Teen Blood Donors – CHILL, Bryan Spencer, MPH, American Red Cross**
MR. SPENCER: My apologies. When I'm out of the office, I can't
use my caffeine IV drip. So I just have to suck up the regular way.

So I was asked to present a couple of slides on a study we have
recently concluded on iron status of teenage donors; because it's teens it's slated
for the afternoon session, but because of the topic being directly on point to their
iron status, I was asked to present a few summary slides right now. So I was
asked to hold it to five minutes or so.

So this graph here summarizes the ferritin results from 4,200
donors, 4,265 donors, who are followed over the course of a single school year,
and I will give details on the study design in the afternoon, but 85 percent of
these donations are from donors in the 16, 17, 18-year-old age range. So our
interest was in characterizing iron status in teenage blood donors and trying to
assess whether the impact of blood donation was different on teens compared to
adults. We really wanted to have large numbers, 16, 17, 18-year-olds, perhaps to
evaluate separately, or at least as a group compared to an adult control, and we
capped it at 49 so that we weren’t also controlling for women of childbearing
years and not.

What we see here, for all of these 6,000 ferritin results is that a
really large proportion of them are very low. Each band here represents 8 points
of ferritin. So it is somewhere in this second band where a ferritin less than 12,
absent iron stores, would fall, and then this fourth band, the cutoff of 26 with
ferritin less than 26 would fall, and this is 10 percent of the overall sample. So we
are looking at 20 percent or so with absent iron stores. Again, 85 percent of these
are teenagers, and roughly 40 percent that are 26 or less. We have truncated the
X-axis. There are 70 results greater than 200 that aren’t showing, just so that you
can see the spread.

So there's a lot of data graphed here. I will just hit a few points, but this separates out 4,265 donors at their first visit. Again, we followed them longitudinally over a school year. We have first-time donors up top, females and males, and each pair of bars on the X-axis represents an age group, and the dark bar is what proportion has ferritin less than 12 or ferritin less than 26, and we see for females that ferritin less than 26 sure looks higher in the younger donors compared to the 19- to 49-year-olds.

And also for ferritin less than 12, you may remember Dr. Cable's slide that showed no donors in the RISE study, no male first-time donors, that had absent iron stores. That study was limited to those 18 years of age or greater.

Well, there aren't any 18-year-olds with absent iron stores. We do see some small proportion in the 17- and 16-year-olds, none in the adults, and a clear gradient for ferritin less than 26 in the younger donors compared to the adults.

In the bottom, we will need to control for the number of trailing donations to assess what is the impact of donation on the iron status of teens. Is it different in the teens than the adults? But what we can see is what general proportion of repeat female donors in this age range has low iron. We see that there's a really large proportion in the younger donors. There's a really large proportion, as we saw in RISE, as we saw in the STRIDE, in the 19- to 49-year-olds as well. So it's high across the board for repeat females, higher in the younger compared to older, and then a different pattern, not a clear gradient, but higher proportion with ferritin less than 26 in the younger males compared to the older males.

We have plotted the data from the CHILL donors against NHANES
data as a reference. So we want to understand, do we see a certain proportion, an
amount that has triggered concern and discussion, of low iron stores in these
donors, but do they look different than population norms? And we see that they
don’t.

On the left-hand side are CHILL donors, male and female, and on
the right-hand side are NHANES donors. The last NHANES that had robust
numbers for males and females in the age range of interest is 2001 to 2002, but
we don’t have any reason to think that the 15 years difference should compromise
the inferences, and what we can see is that first-time 16-year-old males look like
their counterparts in NHANES, likewise for females, and this is true across the
age groups for females and males and in the control population. These are the
means and the 95 percent confidence interval around the mean, 95 distribution
of the entire population. You can see that the average values of our first-time
donors -- so unaltered by blood donation, looks a lot like the general population.

In this graph, again the statistical models will control for the actual
intensity of donation, but this shows the drop such that repeat donors,
unsurprisingly, based on what we have heard this morning, no longer look like
their population counterpart. So it is a meaningful drop across the board for all
demographic and gender, age and gender subgroups.

So I think I will close with that.

DR. LEITMAN: Thank you very much. Our next speaker, as
scheduled, is Dr. Mindy Goldman from Canadian Blood Services, who will be
talking about iron deficiency and ferritin testing in Canadian blood donors.

Iron Deficiency and Ferritin Testing in Canadian Blood

Donors, Mindy Goldman, MD, Canadian Blood Services
DR. GOLDMAN: Thank you very much. I would like to thank the committee for inviting me to present our data and provide some foreign content to the meeting. So just to remind you what current criteria are at Canadian Blood Services, so for us the minimum age for donation is 17. The minimum hemoglobin level is 125 grams per liter for both males and females. The minimum inter-donation interval is 56 days for seven donations a year for both males and females. There's no difference based on age. And we do a finger stick hemoglobin measure pre-donation, using a hemoglobinometer, and there's a 56-day deferral if the donor fails their hemoglobin.

We have a very high average donation frequency with the average donation frequency for whole blood donors being slightly over two donations a year, and that's quite a bit higher than most U.S. blood suppliers, and we do not collect double red cells.

So we did an initial study with 550 successful donors and 50 donors who failed their hemoglobin, and these donors were interviewed in person, and they provided consent. They were all in one geographic location chosen because that's where our study person was. So in Ottawa.

Iron deficiency was found to be frequent, particularly in females and in frequent donors. The return rate and the frequency of donation was reduced in donors informed of their low ferritin results, but there was no retest of ferritin. So these results were published in transfusion in 2014 for the initial results, and in 2016 for the follow-up results.

So what I'm going to talk about now is a large national study that we are doing. Some of this was presented at a leading poster at AABB, and the rest has not been published yet. But it's in press in Transfusion.
So the goal of this study was to gain more information on the frequency and risk groups for iron deficiency in a large representative sample of donors to assess the feasibility of largescale ferritin testing in our donors and assess the impact on our donors of ferritin testing, both the acceptability, which we would judge by how often they called us, also by an electronic donor survey that we would send them about six months after sending them their ferritin results.

The impact on their donation career. So did they come back to donate and how often did they come back, and on their iron stores, and we were going to assess that by doing repeat ferritin testing on some of them, and also in our electronic donor survey, where we are going to ask them if they actually took our advice and started iron supplements.

And the study only includes donors who pass their hemoglobin, since you'll see we are using retention samples, which are from people who donated. So you will see that there's two major differences in study design between this study and all the ones you have heard before. So this is really an operational feasibility study. It's not a randomized controlled trial. Nobody is signing consent or being selected, and second of all, this study lacks a catchy acronym, and I think it's too late to correct that design flaw.

(Laughter.)

So this is what we did. In our pre-donation pamphlet that all donors are supposed to read, we do have a little bit of information about iron and we also mentioned that we may be measuring their ferritin. So there's no consent. We selected clinics all across the country to be representative of our overall donor base, and on this index donation we tested over 12,000 donors. These are all
whole blood donors, 45 percent female, 55 percent male.

If the donor had a ferritin level of less than 25 microgram per liter, then they got a form letter from me and an information sheet with some Q&As. We did not call them for six months, but we did not put a deferral code in their file on the computer. So we told them in the sheet that their ferritin was low. They should go see their physician. They should stop donating for six months, and then come back.

Partly why we told them to stop donating for six months is that in our criteria, if you are on iron for iron deficiency without anemia, you have a three-month deferral, and you have to have been rechecked by your physician to say that your iron stores are normal. So we didn't want them to take our advice, start on iron, come to donate. We ask all donors are you on medication in the last three days. They'll say yes and then be deferred. This would not be good for my survival in the organization.

So it was better to just say don't come back for six months. And then those who had a ferritin above 25 had no intervention. We did not write to them, and we didn't do anything in that group.

Afterwards, we retested ferritin on a subset of the initial cohort. To date we have retested close to a third of the initial group that had low ferritin, and about 20 percent of those who were initially normal, and the testing, we started the retesting in January of this year. It's being done a mean of 14.4 months after the initial test for these guys, and the mean was a little bit longer for these, this group.

But it does vary quite a bit per donor, because the enrollment in the study started in July 2014 and concluded in December 2015. So some of these
donors were tested close to two years after enrollment, while others were retested just a couple of months after their index donation.

So our results. In over 95 percent of cases, we were able to retrieve the so-called retention sample from the donation. We tested basically 2.6 percent of our entire donor base between July 2014 and December 2015. Study donors were more likely to be male repeat donors with more donations in the past 12 months compared to our general donor base, and this is understandable, since these donors are donating more frequently, they had a greater chance of being sampled in this study.

So this slide shows our results for female donors. On the X-axis, you see the number of donations in the last 12 months. So we have first-time and reactivated. We defined reactivated as no donations in the 12 months prior to this index donation, rather than 24, as was done in Dr. Cable's study. You have one to two donations, three to four, and five-plus.

In red on the Y-axis, you have ferritin levels, and on this Y-axis, you have the percentage of donors with a ferritin below 25. So you can see that in first-time and reactivated female donors, we have a mean ferritin level of 47 micrograms per liter. Actually, in the youngest group, so for that 17 to 24, it was considerably lower. It was I think 33 micrograms per liter. In the oldest group, which is women over 45, it was 67, and the group in between is in between.

You can see that the mean ferritin goes down with the number of donations in the last 12 months, and the percentage of female donors with a ferritin below 25 goes up such that in the women who were donating five or more times in 12 months, 81 percent have a ferritin level below 25, and the mean ferritin is 18.
These are results in our male donors. So again, on the X-axis we have the frequency or number of donations in the last 12 months. Here we split out first time from reactivated, because there’s quite a big difference between the reactivated and the first time in the males, unlike our female donors, and then we have grouped the number of donations a little bit differently, since the male donors are donating more frequently. So here it’s one to three, four to five, and six-plus.

So in our first-time male donors, as with the other studies you have heard about, very few actually have a ferritin level below 25. It’s just about 3 percent, and the mean ferritin is a nice 144 micrograms per liter. In male donors who have not donated for a year, you can see that their ferritin level is still considerably lower than first-time male donors, and 22 percent have a ferritin level below 25. You have to look at males who have not returned for two years or more to really get them to be equivalent to first-time donors.

Then when the groups are people who are donating more and more frequently, you can see the ferritin level goes down and the percentage of donors with ferritin below 25 goes up.

How about looking at hemoglobin level in the male donors and seeing how this correlates with ferritin. Well, we know it correlates very poorly. If we just look at the 125 to 129 gram per liter group of males compared to males with a hemoglobin of 130 grams per liter or above, you can see that the mean ferritin is considerably lower in this group, 36 compared to 64, and the number of donors with low ferritin with using 25 as a cutoff, is quite high, 56 percent here, 32 percent here.

Another interesting fact is that the men with lower hemoglobin had
donated on average about one unit more in the past 12 months prior to this ferritin test than those who had higher hemoglobin. So again, aligning with studies showing the ferritin level tends to drop with frequency in males, and likely many of these males here are not at their hemoglobin level which is really normal hemoglobin for them.

I have to say that only about 4 percent of males with ferritin below 25 micrograms per liter find themselves in this low hemoglobin group. So it is not a very sensitive predictor of low ferritin.

So how about acceptability and impact on donation career? So luckily for me, we got very few calls from donors. Went very smoothly, very little negative feedback, actually got some positive feedback, including one 49-year-old frequent male donor who wrote a very heartfelt letter saying he did see his physician. He had early stage colon cancer and he is going to be fine.

I think that type of thing also shows how difficult it is for the blood center to come up with a uniform strategy for all donors with low ferritin, because certainly this man was 49. So not that old in my book, and he was donating frequently. So the low ferritin could have been totally attributed to Canadian Blood Services, and yet here he had a very significant underlying condition. So we have to be careful in our messaging to our donors.

After mean follow-up of about a year in these groups, 76 percent of donors with normal ferritin and 58 percent of donors with low ferritin on their index donation have returned to successfully donate. So they made a donation. They passed their hemoglobin. So you can see there’s quite a big difference there in the two groups.

Returning donors with low ferritin on index donation also donated
less often. So they made a mean of one unit less donation on the close to 12 months of follow-up.

So these are our ferritin test results on these retested cohorts. So we have retested about close to 25 percent of the initial cohort. We keep -- we are keeping on with this, and we have our two groups. We have those that were low on index donation. So just to remind you what we did to those people, we sent them a letter, a form letter, and an information sheet, and we didn't hassle them for six months. Those with normal ferritin, we did nothing.

So looking at those with low ferritin, the women, so obviously the index ferritin on these women was very low, 13.6, and the ferritin on retest was a little bit higher, 25.7 micrograms per liter. In between these two measurements, they had made a mean of 2.3 whole blood donations.

For the male donors, again, initial ferritin is low. The number of donations between the tests was a little higher, 2.9, and the mean ferritin on retest was 31.1.

If we look at the donors with normal ferritin, you can obviously they started with higher ferritin results. They made a rather impressive number of donations in between the index and repeat testing, about one unit more per donor than those with low ferritin, and their ferritin was considerably lower on retest than it had been initially.

So if you were a glass is half full type of person, you would look at these results and you would say, gee, only one form letter from a Dr. Goldman, and now 50, close to 50 percent of these donors, are over 25 micrograms per liter. So we did something significant there.

If you are a glass is half empty person, you will say, you know what?
Over half the donors still have low ferritin, and you did this test right before you took another donation. So they are heading down. So just sending them one letter was not the most efficacious thing to do.

And if you look at the normals, you can see that this is not a static situation, right? I think in the studies we tend to look at a static situation, but a donor has a long donation career and we are just looking at them as a snapshot.

So our conclusions. Like everyone else, we found that iron deficiency is common in our donors with very similar risks. Female donors, males with a borderline hemoglobin, high frequency of donation as found in U.S. and other international studies. Females are in a much more precarious iron balance compared to males, with close to a third of first-time female donors having low iron levels compared to only about 3 percent of male donors. And females donating one to two times a year have the same mean ferritin levels as males donating four or five times a year.

So in our view, this data provides a strong rationale for longer inter-donation intervals or fewer permissible donations per year in female donors, as is in the case in most countries other than Canada and the United States. So Canadian Blood Services will be increasing the minimum inter-donation interval for female donors to 84 days and the maximum number of donations per year will go down to four donations a year from the current seven in 2016-2017.

So we are making the initial change in our donor rebooking system in December, and then 84 days after that, the actual criteria will change in our computer system. Female donors failing their hemoglobin will be deferred for 84 days, and the minimum hemoglobin for males will increase to 130 as in the case in the United States.
These changes in criteria will impact a minority of iron-deficient donors. We have about 4 percent of our females donating four or more times a year, 15 percent of females failing their hemoglobin, and about 2.5 percent of males are in the 125 to 129 gram per liter. So what about all the rest of those iron-deficient donors?

So selective ferritin testing followed by donor education, a change in donation patterns, and increased iron intake, may impact many more donors. In our study, we showed that donors informed of low ferritin results had a lower return rate, donated less often, and had an increase of ferritin on return, compared to donors with normal ferritin that received no intervention.

However, I really think a longer observation period is necessary to strengthen these observations. Electronic surveys and in-depth donor interviews will help us determine if donors followed our advice regarding seeing their healthcare provider and increasing their iron intake.

The form letter and the information sheet approach used in our study may be suboptimal to educate donors and address barriers to starting and staying, sticking with the iron supplementation. Since donors with initially normal ferritin often have reduced levels on repeat testing, further education about iron needs is obviously important for all our donors.

I would just like to thank all the people who are part of this study team, Sheila O’Brien, who is head of our epidemiology department, Vito Scalia who runs our national testing lab, the other people in the epidemiology group. When you do a study that’s really looking at feasibility and operations, you involve a lot of operations groups that need to collaborate with you so you can see them all listed there, and finally I’d like to thank our volunteer donors and you
for your attention. Thank you very much.

DR. LEITMAN: Thank you, Dr. Goldman.

And our last speaker is Dr. Jed Gorlin, from Innovative Blood Resources in Minneapolis, entitled ferritin testing and iron supplementation, a feasibility study.

**Ferritin Testing and Iron Supplementation: A Feasibility Study, Jed Gorlin, MD, MBA, Innovative Blood Resources**

DR. GORLIN: At least when it comes to iron stores, we have met the enemy and they, as Mindy points out, is us. So I would like to set the context for this study. It was set after RISE that you have heard so elegantly about this morning, but before many of the other wonderful studies had been done, talk about, a little bit about the AABB efforts to mitigate iron depletion, and then specifically address our study, which was an ABC, American Blood Centers Foundation study, to address screening of donor ferritin; really as Mindy pointed out, this was a practicality as opposed to a randomized study. Just the practicality of dispensing iron and to jump ahead to topic 1B to address the hemoglobin cutoff in females of 12 to -- within the range of 12 to 12.4.

So as you have heard, United States and Canada were unique in having both the identical cutoffs for men and women, and as you heard, that men have already gone up to 13 in the United States and will be shortly in Canada. In Hema-Quebec, females who are of African heritage actually are down to 11.5 cutoff, consistent with that distribution, and again, the frequency of allowing every 56 days is unique to United States and Canada, though you have heard that will be changing in Canada shortly.

Hemoglobin distribution in men and women are not identical.
Neither is height distribution. I did show this slide at the workshop in 2011, and Mindy wanted you to know that she is 5'2", not 5 feet, where I had her before. This is UConn, and you notice that UConn also has a large number of women approaching 6 feet, which explains their prowess in basketball.

It was entirely appropriate to increase the minimum hemoglobin for males. The hemoglobin cutoff of 12.5 on the NHANES data is almost three standard deviations below the mean. However, the hemoglobin cutoff is 12.5 for females is less than one and a half standard deviations below the mean, and therefore it is almost inevitable that we are having 10 to 14 percent of women deferred for hemoglobin, because that's where the normal distribution goes down to.

You have seen this data from Bryan Spencer on the original RISE data, but this was what informed our study, that yes, there was iron deficiency in first-time donors, but virtually 95 percent of female repeat donors had some degree of iron deficiency, and this frequency slide you have seen and the fact that it takes about half a year to replace your iron stores.

So in the setting of the 2011 workshop, we heard that hemoglobin is a truly awful predictor of iron status that the FDA, as you are considering now, really had two tools, hemoglobin cutoff and interval, and that there were some, at that point, some pilot studies documenting that ferritin could be measured and replaced. So the AABB then set off an interorganizational committee of which I had the honor to chair, and the charges were to develop a donor information sheet, an association bulletin, and to monitor the mitigation approaches, and those were done.

Specific recommendations were to do something, whether it was
measuring serum or plasma ferritin, some sort of iron replacement strategy,

doing some change in intervals, but most importantly to learn and profit from
those interventions to give us better ideas of what interventions were most
efficacious.

So we decided to start a very modest feasibility study, funded by
America's Blood Centers, to simply look then at the practicality of measuring
ferritin and providing iron replacement. This again was before the STRIDE,
HEIRS, and other studies.

I do, for conflict of interest, the iron was provided by CVS and
Ortho allowed us to use their ECI machine to do the ferritin testing and provided
the ferritin reagent.

So this was a modest grant, and we were hoping to measure ferritin
levels, and the ferritin levels were measured at my site. We collaborated with
Louie Katz of then the Davenport, Iowa site, Mississippi Valley Regional Blood
Center, and we were targeting those that we have suspected would be most at risk
for iron deficiency, females between 12 and 13, males between 12.5 and 13, and
these were done at a fixed site, which almost by definition means you're going to
get repeat donors.

We chose ferrous gluconate at a dose of 38 milligrams elemental
iron, simply because like previous studies have been informed that that was a
very tolerable dose, and the iron that we got with a wholesale cost of about $2 a
bottle came in tablets of 100, and we sent out those. We deferred for 112 days,
simply because we were batch testing the ferritin and we were mailing out the
iron, which took about a week or two to get out, then follow up for improvement
with ferritin and deferral rate.
So the males pretty straightforward. Measured those males who were between 12.5 and 13.5 were offered enrollment in the study. I'll tell you more about a point of care test that Dr. Katz did at his site, measuring zinc protoporphyrin. Then we arbitrarily said for men the cutoff was 30. For women the cutoff was 20. But similar to the cutoffs used by other investigators. For those above 30, no intervention. For those under 30, deferred for 112 days and sent out the iron.

For females a little more complex. If they were above 12.5 and an eligible donor, we offered the study, very similar to the male enrollment, where we would be measuring, drawing the unit, measuring the ferritin on the unit. If it was above 20, again, no intervention below 20, deferring for 112 days.

For those women between 12 and 12.5, we asked for a variance to draw the unit, but in the meantime, we would measure the ferritin and then ask for this FDA variance, and I will get back to that in a second. So we first asked the FDA for a variance to draw the unit and about a year later got back saying, no, you'll need an IND, and so we submitted the IND and they said, well, if the ferritin is okay, then you can draw the unit, and by this time, two years into it, we were mostly enrolling at a few fixed sites and it was the same donors coming back again and again.

And at the same time, the FDA informed Ortho that they probably shouldn't be validating non-blood bank studies in a blood bank. So Ortho took their ECI machine away, and so we couldn't measure the ferritin anymore. So I'm embarrassed to say we were unable to enroll any donors under the IND, but we do appreciate having received it, and I am also bringing this up because I think it informs 1B, which is the genesis of this request for the donors between 12 and
Like other studies, no surprise, 86 percent of the donors were in the low ferritin group. And that was actually 90 percent of the females and about 80 percent of males. To show you that in -- how eager donors are, these just happen to be the first five donors in the study, and you can see these are people that are really trying hard. So they have -- one successful donation in six attempts. This is not an uncommon thing, and unfortunately many donors will in fact, having been deferred for low hemoglobin, will not come back, but an energetic group.

To address the question you will be addressing in 1B, are we protecting females with the hemoglobins of 12 to 12.4 by not drawing them? The average ferritins were absolutely statistically identical between the two groups. So you're not protecting -- this is the females below 12.5, females above 12.5. You're not protecting this group in the sense that these are equally identically iron deficient.

In Minnesota, our women are strong, our men are good-looking, and apparently all of our donors are above average in compliance, because at least only three out of 109 admitted to not taking the iron and almost 90 percent here took it either daily or almost every day. So of course, people that sign up for studies are also probably more compliant than average anyway.

For the hematologists in the audience, if your MCV is low because of low iron and you take iron, guess what? Your MCV goes up. Not surprising.

Deferral rates. This actually was a bit of a surprise. For the group in the low -- I mean in the non-low ferritin group who therefore did not get iron, when they came back, they had an almost one out of four deferred, and in fact, that was actually one out of three for females, whereas if you were in the low
ferritin group and took the iron, you actually had a significantly lower than
historic rate of deferral, suggesting again that it is actually in the blood collector's
interest as well as the donor's interest to be prescribed, as you have heard from
other presenters, because it will lower the deferral rate.

So getting to Dr. Katz's wonderful study, one of the problems about
ferritin is from a practical standpoint it really is done much better on a sample
that you are drawing anyway from a unit. It's very difficult -- not a convenient
point of care test. So Dr. Katz posed the question could you use zinc
protoporphyrin as a point of care assay to determine the donor's iron status.
Again, the heme ring is in a zinc protoporphyrin and then the iron comes in and
displaces the zinc.

So if you are seeing free zinc protoporphyrin, it means that the
person's in relative iron-deficient state, and you can see this is a straight line here
would be it's completely useless. What we would like to see is a very rapid rise in
over, and so this is insufficiently sensitive or specific to be used as a point of care
assay, as the take-home lesson, and Dr. Katz is here if you have more questions.

So in conclusion, despite AABB's association bulletin of 12/03, very
few U.S. centers anyway have implemented changes that truly mitigate low iron
stores. Hemoglobin is a poor indicator of iron stores. Most other countries have
different hemoglobin cutoffs for females and males, which United States has now
addressed. Some have different gender-specific intervals.

Most fixed site donors who are therefore repeat donors are iron
deficient. Donors deferred for 112 days and given iron are dramatically less likely
to remain iron deficient and significantly less likely to be deferred for low
hemoglobin upon their return. Blood programs that estimate iron stores and
provide iron replacement are feasible, as you have heard from the wonderful REDS studies, and furthermore it is operationally possible to measure ferritin levels in selected donors, distribute iron to donors, have very high compliance with taking iron with very low donor side effects, and have donors return and measure significant improvement.

So if a large preponderance of donors of frequency twice or more have low ferritin, why measure the ferritin at all? Is it even necessary? Are there better ways to distribute? One of the studies we would love to do is looking at instead of just handing out the iron, which is very logistically difficult, considering the number of fixed sites and mobile drives we have, could we give a coupon, which would offer a free bottle of iron, and exactly what that dosage and duration should, still needs to be studied, would that be an equally efficacious, and that is a question that needs to be addressed, and then of course, what your subject will be in 1B, and I ended there, having caught you up in time.

DR. LEITMAN: We have just heard from six speakers, and questions for the speakers from the BPAC committee are welcome right now, and please state which speaker you are addressing the question to, or you could be making a comment in the form of a question to the rest of the panel. But this is really for the speakers, directly to the speakers.

Yes, Dr. Brittenham?

DR. BRITTENHAM: If I may, can I make two comments that were not mentioned extensively anywhere? The first is we should also think about the effects of iron deficiency from donors on the recipient. There's animal data that suggests that the survival of blood that's been stored, that the iron-deficient cells don't tolerate refrigerated storage as well. There's a trial under way to examine
this in more detail, to follow up on the animal data, but that is a consideration
that I think the agency should be aware of for the future.

The next thing is I did want to comment on the zinc
protoporphyrin, because it is a way that you can have immediate results at the
site of donation, and I think what Dr. Katz did is compare the iron status as
determined by using the serum ferritin, but the serum ferritin and zinc
protoporphyrin measure different things. The zinc protoporphyrin is more
comparable to what you see with serum transferrin.

What ferritin tells you is when their iron stores are absent, but then
it doesn't change very much as you get more and more deficient. What the zinc
protoporphyrin tells you is that when the lack of iron is sufficient to interfere with
the production of new red cells.

Finally, if I may just do one more thing, we heard a little bit about
donor retention, but I think that's a very important aspect that hasn't really been
discussed very much here. Individuals who get deferred, even though they try
many times, because they are iron deficient, it's really the most frequent cause of
deferral, are lost. And all the information that you hear here doesn't really take
account of those who are dropping out of the donor pool, because they are iron
deficient.

So I think there are advantages certainly for the donors, possibly for
the recipients, and for the blood collection agencies to replace the iron they take.
Each time you give blood, you're losing 250 milligrams and that should be
replaced, one way or another.

DR. LEITMAN: Thank you, Dr. Brittenham. I have a supplement to
that that I was going to bring up and I'm glad you mentioned it. There are data at
NIH on donors and studies undergoing autologous chromium 51 in vivo survival
of red cells after 42 days in storage, and it wasn't intended to look at iron
deficiency, but we had accidentally some subjects who were iron deficient with
ferritins of less than 12.

The in vivo survival was in the mid-60 percent autologous in vivo
survival after storage in that group versus greater than 75 percent, which is the
FDA benchmark for storage vehicles. So a profound difference in in vivo recovery
and survival of red cells from iron deficient subjects. So you are not doing the
recipient any favor by giving them a unit derived from an iron-depleted or
deficient donor. It's a very important point.

DR. ESCOBAR: I have a question and a comment. We can see in the
studies the initial studies they used a cutoff of ferritin. They start with 12, which
to me is severe iron deficient. I mean, those patients have to be very
symptomatic.

Then some of the newer studies now, they are using 25 of ferritin, a
cutoff of 25 for the ferritin to be saying that patient is iron deficient or not. But I
think maybe, first of all, where that number came from, the number 25. But is it
possible maybe to even use a higher-level cutoff, 30 or 50, because I mean, no
matter what, those patients most of them are going to get iron deficient if you
keep drawing blood on them.

If you catch them up earlier, you know, be able to capture those
earlier iron deficiency when the ferritin is dropping, you might be able to replace
it and they might not need to wait too long to get -- to donate again. You know,
especially in the females, especially the young females.

DR. LEITMAN: I believe that the number of 26 was derived from
the RISE, REDS-II RISE study, when they looked at the log of the serum transferrin receptor over the ferritin greater than 2.07, which defined iron-depleted erythropoiesis, that corresponded to a mean ferritin of 26. I need a RISE investigator, Dr. Cable, to confirm that.

DR. CABLE: Yes, that is correct. And I should have been more clear about that. It was on the slide, but I didn't point out that ferritin 26 and that other measure log RF correlated very well at 26. You could see it from the numbers, and we have seen it in other points; 25 and 26 aren't different. But Dr. Kiss showed 50 was in the HEIRS study was where the effect of iron was no longer present. So if people respond to iron with positive results, that would suggest they are iron deficient as well.

DR. LEITMAN: Correct. So, but the number of 26 is really the first scientifically sort of validated number that perhaps could be used as a benchmark, I think, by other studies based on the RISE data.

Dr. Ragni?

DR. RAGNI: I think it's worth pointing out some things that were not discussed about donors and the cognitive and emotional social issues that impact of iron deficiency. I take care of a number of people, especially von Willebrand disease women who drop out of school because they can't concentrate, and I think the impact is enormous. I think we don't know much about it.

I think many of these younger folks don't have physicians they routinely go to, and to put the onus on them -- I'm not talking about the von Willebrand patients, but that's my experience -- to put the onus on them to start a treatment program, I think, is very hard without a physician involved who
encourages them and who is part of the planning and who is informed.

So for example, for a potential donor, just notifying a donor that they have a low ferritin and suggesting they do something, and they don't have a physician and they don't have someone really working with them one on one to encourage them, and also when they develop some of the GI side effects, which is not uncommon, to try to continue that. I really think there is a component here that's critical in terms of how we work with donors. They are giving blood altruistically, and we are sending them letters, and I think we owe them a lot more than that.

And I think there's evidence at least in clinical studies that working with a patient on a very close basis is really critical in getting results that you're trying to aim to, whatever that is.

DR. LEITMAN: Thank you. Other questions?

Yes?

DR. STAPLETON: I guess I had a question, and not being a hematologist or blood banker, being an infectious disease person, maybe I shouldn't speak, but it also relates to Miguel's question, and that is do we have an idea of the proportion of people in that 12 to 26 range who are symptomatic or who have any clinical evidence that they are impacted by their low ferritin?

DR. LEITMAN: Which speaker would we like to address this to?

Either Dr. Kiss, Dr. Cable?

DR. STAPLETON: Any of the six speakers would be fine.

DR. KISS: I guess the question is of those that are laboratory iron deficient, how many have symptoms? The long answer, or the short answer is we don't exactly know the answer to that question. Studies that Dr. Leitman has been
part of, pica is seen or this craving, for iron, compulsive craving of ice, which is a
symptom, and it can be quite behaviorally modifying to their daily life. It's seen in
around 10 percent or so, if I'm quoting you correctly, Susan.

So the interesting thing to me is I do manage -- let me give you the
balance here, because I do see donors. I do provide occasionally counseling for
these issues. Many are not seemingly affected, but another observation that
comes from NIH is when they start taking iron is oh, my gosh, I was. But I
adjusted to it, just like people do normally, the normal activities of daily living.

So I think there is a hidden tip of the iceberg here of symptoms and
behavioral issues and whether or not it impacts things like restless legs, and I'm
actually -- I'm concerned about the cognitive issues that we are not picking up in
terms of people's everyday lives, and I wanted to give you the flip side.

I have donors mad at me for deferring them for three months to
reaccumulate their iron. They get a note from their doctor. My doctor said I can
donate. I have no side effects, no issues.

So it is a very -- it's a subset of the population that we see have
laboratory evidence of iron deficiency, which as alluded to earlier, is kind of -- it
depends where you define iron deficiency there, but there is a discrete subset of
individuals that will have symptoms, may not realize it, may not be getting
medical care. It's not being addressed right now, and we are just kind of it's all
one size fits all.

DR. LEITMAN: A brief comment on that. When we in our study
looked at donors who had a ferritin of less than 12, a little bit more than 10
percent had pica. They are very -- compulsive craving for nonnutritive
substances, which is mostly ice pica, but could be dirt, could be clay. And they
were very embarrassed about it, and so if you asked them if they craved ice, they
would say no. They wouldn't mention it. If you said how much ice do you
consume in one day, they, a fraction, looked shocked and said how did you know?

And when we replaced their iron, their oral iron, they felt better
immediately within a week, since it was an all-consuming craving. So the
principal investigator on that study, Barb Bryant, would get hugged in the
corridor by donors at NIH who felt so much better. So that is a small fraction.

It is very hard to get at cognitive function, because we are all tired.

Dr. Ragni?

DR. RAGNI: Although it is worth mentioning that Jim Casella in his
group did an excellent study and showed that their performance on tests was
significantly worse if they were iron deficient, and if you think of younger people,
they are still myelinating their CNS. So this is a really critical issue, I think, for
young people.

DR. LERNER: There is NHANES data to support that, as well, and
that's fairly old data.

DR. MURRAY-KOLB: I just wanted to follow up on the cognitive
symptoms. I think that we definitely have data to show that individuals -- women
-- who are iron deficient, not yet to the point of anemia do have worse attention,
worse ability to learn, worse memory, than those who are iron sufficient, and as
was already mentioned, most of them wouldn't come in saying they feel that way,
but once they're supplemented, all of a sudden they have this realization that,
wow, that's how I was feeling, and I think beyond the cognitive symptoms, there
are also affective symptoms. So depressive symptoms, anxiety, stress, and those
are important for everyday functioning. So I think those need to also be on the
table.

DR. BRITTENHAM: I just wanted to fourth or fifth, I suppose, those things. I think it is a very important consideration. There are now randomized controlled trials in iron-deficient women, not blood donors necessarily, that show that treatment with iron produces resolution of this. Iron deficiency is typically an insidious thing that comes on and women adapt to. There's an Australian study that suggests that women who are iron deficient feel as bad as someone with chronic renal failure, but they don't realize it, and as you pointed out, treatment with iron produces prompt behavioral symptoms. People feel terrific after that without having realized how bad they felt before.

DR. CHITLUR: I just wanted to make a comment. Considering I was wondering how much, what percentage of donors are actually between that 16- to 18-year age group? I think that is a population that would be quite significantly affected by the symptoms that we are addressing here. So if you have a junior or senior in high school who is making two or three donations a year, that would be really important for this child to get the iron supplement they need.

DR. LEITMAN: That is going to be the topic of the next session. The answer is 10 percent of the donors are in that age range, but it will be discussed at length.

I think we can continue these comments, and when we answer the questions, because we are all -- these are direct questions to the speakers, and they're tending towards comments.

But I have one question for the speakers. When we refer donors with low ferritins to their local practitioners and some of them were referred, we found two disturbing responses. If you were a female and your hemoglobin was
between 12 and 12.5 and you have a low ferritin and you went to your doctor, the
comment was frequent -- and the CBC was repeated and the hemoglobin was
between 12 and 12.5, often iron testing was not done. They were told that was
normal, and they were told if they were deferred, then just don't donate. And that
was not a very adequate solution, but it was a common finding.

And for males, especially repeat males where we felt strongly we
were responsible for the low hemoglobin low ferritin, if they are above 40 and
they go to their physician with that story, they get a colonoscopy. And that
sometimes one finds things, as Dr. Goldman told us, but that is very, very
uncommon, and that might have been, of course, as you suggested, incidental and
not related.

So you have to be, in terms of if we give iron and if we make a
recommendation to give iron, what do we think about sending the donor to their
practitioner for further workup or having the blood center do that? Which would
give the best or more correct messaging?

Could I ask Dr. Kiss or Dr. Cable if they have feelings on that?

DR. CABLE: Getting back to the encouraging donors aspect, in
Denmark they have a -- in Copenhagen, they have a whole staff of physicians who
do this and it's been described in this elaborate algorithm, and it's quite nice as a
clinical enterprise. The thing I think practically we all have to recognize is I don't
think it's going to happen that blood centers are going to hire 500 physicians to
take care of all these people. So it would be nice, but that's not going to happen,
and probably for the same reason that the PCP is not taking care of it. They don't
have time either.

So I think maybe it has to be a public health issue rather than a
clinical issue in how we handle that. That would be my impression. I don't think a clinical algorithm or a clinical approach would be at all effective. We created it through public health. Giving blood is not a particularly medical procedure.

There's rules, but it's -- you go to a blood drive, it doesn't look like a clinic, and I think you need to figure out a way to do it without too much physician intervention, whether it's from the blood center or the PCP. That would be my take, and of course not everybody has a physician and I won't mention any politics here. But what can I say?

DR. BRITTENHAM: This is a question really for Dr. Spencer. It was somewhat surprising that you see no difference between 38 milligrams and 19 milligrams in treating iron deficiency, because it can't be physiologically based. I think all studies show that if you increase the amount of iron you give, you increase the amount of iron that you absorb. So why does he think that this came out in this particular study to be equivalent?

DR. SPENCER: I cannot say definitively why they look to be equivalent, but we have examined it every possible way and they show no difference. Dr. Kiss mentioned the work by Radke that did in fact show a difference between a dose of 20 versus 40, 20 maintaining ferritin values, and 40 leading to increases in these groups. I mean, they were very iron deficient at enrollment. They both increased a lot.

It may be that there's something about who dropped out versus who stayed in that we haven't yet detected, but again, the dropping out doesn't look to be related to their iron status. It looks to be related to some discomfort with taking pills and not knowing what was in them, because they continued as blood donors and continued to donate frequently, but I can't say why there's no
difference, but that's what the best statistical analysis of the data we have showed.

DR. CABLE: These people were on iron for two years, though. It was a very long-term study, so I don't know whether studies you're referring to were short-term therapeutic studies versus long-term homeostatic kind of. It may be that over two years the difference washes out as people reach some level where they're not absorbing as much. I don't know. It was a surprise to us, although the data seemed quite good.

DR. LEITMAN: Okay, let's move on to the open public hearing. Mr. Emery?

**Open Public Hearing**

LCDR EMERY: At this time, we are going to hold the open public hearing. This session is designed for those members of the public who are not on the agenda to bring their issues and comments before the committee. We have received three requests at this time for this open public hearing session, and I will have the chair -- she will read the open public hearing statement.

DR. LEITMAN: Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it's 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 relationship that you may have with any company or any group that is likely to be impacted by the topic of the meeting. For example
the financial information may include the companies' or groups' 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 the issues of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Our first request for presentation at the open public hearing is by Dr. George Schreiber, representing PPTA. Dr. Schreiber?

DR. SCHREIBER: Thank you very much. I have some slides to show. I thought it might be much easier to look at our data. I work for PPTA. So I represent the plasma industry, and what we would like to do is show you some data that we have collected in a cohort study, looking at iron deficiency in frequent plasma donors.

What I'll do is let me give you the conclusion first, save a lot of time, in case they yank me off the stage. Female frequent donors have higher ferritin levels than donors -- than who have made no donations. For males, although frequent donors had lower ferritins than those who had never made a donation, the differences were not statistically or clinically significant, and few source plasma donors have absent iron stores, and for most of these, the ferritin values are well within the normal range. Iron depletion seen with frequent whole blood donation does not occur in frequent source plasma.

The source plasma donation is associated with little red blood cell, as you know, red blood cell loss, as you all know. There's no information, however, on iron status for frequent source plasma donors, and as you'll see,
frequent donors, we're talking about whole blood donors donating maybe twice a year, but we have a high group of donors that are donating about 85 times a year. So there's a quite a difference between the plasma donor and the whole blood donor.

Despite the little red blood cell loss, questions were on accumulated iron loss for frequent donors were raised at the November FDA workshop, and because of that, the industry decided to conduct a large cohort study of the association between frequent donation and ferritin levels. The study was designed to examine ferritin levels of source plasma donors associated with donation frequency. We went through the standard procedures, IRB approval. Donors had an informed consent, and the study was conducted in a delinked manner.

This slide has a lot of information on it, but I'll just show you we have four groups. The first one is no prior donations in 12 months. The second group is 1 to 24 donations in 12 months. The high group, the first high group, 25 to 69, and the last group is 70-plus donations. This just shows you that we have roughly 300 in each group, and the male and female split. We were targeting about 150 females and 125 males, and the reason the sample size was bigger for females is because their underlying ferritin levels are lower.

This shows you the mean age. As you can see clearly, there is no difference in either the males or females in any of the groups, but what we do see is an increasing age as the donation frequency. So they are with the system a lot longer and partly it's due to the fact that the no donation group is highly skewed towards the younger people, and as you are with the system longer, they give more donations.
Mean hematocrits, you can see the obvious difference between males and females, but you'll also notice that between the four donation groups, there's no statistical significance and there's no drop in the high group.

This is the number of source plasma donations, and again, you can see that the number for the males and females in each of the groups are about the same. So it's the low group which is the 1 to 24, next group is 25 to 69, and 70-plus, and you can see that we are talking about roughly 85 donations in a 12-month period for the high group. The second high group is about 46, and the low group is about 13 or 14.

This is the mean ferritin. What you see here is that the mean ferritin for the whole group, for the females, we actually have a rise and when you compare the no donation group to the high donation group, the difference is statistically significant so that the high group has a higher ferritin level than does the low group, and that's significant at the .02 level.

For the males, we have a somewhat of a drop, but the drop is not very significant. What this shows is the difference between each group compared to the no donations, and what you can see is that the females in the second column, it goes up for the high group and the difference is about 13 nanograms of ferritin. For the males, we actually go down a little, and the low group is actually a little bit higher than the no donation group, and that's none of those differences for the males are statistically significant.

We have heard a lot about the effect of age, and this is exactly what you would expect. For males, which is the first line, you see a drop as we go into the higher donation group, but the high donation in the males age 50 have higher ferritins than do the younger males, and again, we have a drop, but it's not
For the females, you can see that in the females who are older than 50 as you would expect, we have much higher ferritin levels than in the younger females, and for the younger females we actually have a rise in the ferritin levels as you go into the higher donation groups.

This just shows the absent iron stores, and as you can see, the number of absent iron stores is low in the high group compared to low group, and for the males it's almost no effect. This compares the ferritin levels for RISE versus our study, and as you can see, that we have median ferritins are much higher for the high donation group than they are for the RISE group, and we have a much lower rate of absent iron stores for the high group for the females, and the same thing that we see in the males when you compare RISE to our study.

Ferritin levels, unlike whole blood and platelet donation, iron deficiency is neither a short- nor long-term issue associated with source plasma donation, and our data confirm that iron depletion and deficiency are not outcomes of source plasma donation. Thus measures needed to protect whole blood donors and platelet donors are not needed for source plasma donors.

Thank you very much.

DR. LEITMAN: Thank you, Dr. Schreiber.

The next speaker in the open public hearing session will be Dr. Lou Katz from ABC, America's Blood Centers.

DR. KATZ: Thank you, Dr. Leitman, and thanks to the committee for their attention. ABC is an association of independent FDA licensed blood centers in the United States that supply about half the blood supply.

I want to start with a declarative statement so that everybody
understands where my group of physicians and administrators are coming from.

We recognize that iron deficiency in donors is frequent and it demands remediation. So the bottom line is we need to be doing something, and we have probably been listening to this data for a little bit longer than we ought to have.

There remains great uncertainty in the information about its clinical impact on well donors, and we believe that is a critical missing piece. Absent definitive data that our historical phlebotomy practices are producing measurable donor morbidity in otherwise well-qualified donors as opposed to the general population or other groups, the time is not yet right for FDA guidance that may adversely impact what’s probably becoming a tenuous blood supply.

Recent changes in May of this year in the donor hemoglobin thresholds to protect against iron depletion are producing substantial increases in donor deferrals, more than doubling for example amongst male donors from 1.8 percent to 4.2 percent of presenting male donors in early data, and their impact on the prevalence of iron depletion at this point is not well understood.

This is of particular importance given the increasing and disproportionate demands for group O red blood cells and AB platelets and plasma in support of acutely bleeding patients and others. So we want to be sure that whatever we do, which is clinically appropriate for our donors, doesn't deplete those supplies further.

We respectfully suggest that professional responsibility, as in primum non nocere, not guidance or rulemaking by the agency at this point, should drive this. Regulatory action can await a better understanding of the impact of iron depletion on donor health, the impact of such programs on donor iron depletion, and on the available supply of red blood cells and platelets.
Professional standards, for example, from AABB can and should help provide
momentum for the appropriate sets of actions.

Our member blood centers in the greater blood community have an
affirmative responsibility to be engines of innovation in this area for
implementing the spectrum of mitigation strategies, evaluating their impact on
iron depletion, and the adequacy of the blood supply, and thereby develop a
menu of best practices.

The data that are generated need to be sufficiently granular to
inform procedures in a variety of donor subgroups, not necessarily limited to old
and young donors, depending how that's defined, males and females. Fixed site
versus mobile donors, frequency of donation, subgroups, and whatnot.

There are mixtures, as you have heard this morning, of donor
education counseling, extension of inter-donation intervals for high-risk donors,
iron supplementation, assessment of iron stores in the laboratory, are all
potentially and probably acceptable. All should be investigated for their clinical
and operational effects.

Algorithms to which ABC has contributed are being evaluated by
the AABB and are a good starting point for the discussion and for the
interventions. High quality research into the clinical impact of iron depletion on
blood donors, not the general population, on otherwise well blood donors, should
remain a priority at the appropriate funding institutions, NHLBI, FDA, our own
funding mechanisms within the blood community.

And finally, if mitigation is important, we need a public consensus
on what is an acceptable prevalence afterwards of donor iron depletion in order
to judge the adequacy and ultimate utility of these programs.
Thank you, and if you have questions, I'll try to answer.

DR. LEITMAN: Thank you, Dr. Katz.

The third speaker at the open public hearing is from AABB, Allene Carr-Greer. Oh, not Allene.

DR. KLEINMAN: I think I don't look like Allene. I'm Steve Kleinman. I'm senior medical advisor to AABB. Thanks for the opportunity to present this.

AABB is pleased to have this opportunity to provide comment to the FDA. AABB is an international not-for-profit association representing individuals and institutions involved in transfusion medicine and cellular therapy. The association is committed to improving health by developing and delivering standards, accreditation, and educational programs that focus on optimizing patient and donor care and safety. Membership consists of nearly 2,000 institutions and 8,000 individuals, multiple disciplines. AABB members are located in more than 80 countries.

So four years ago in December, 2012, AABB issued an association bulletin with recommendations for strategies to monitor, limit, or prevent iron deficiency in blood donors. Given the subsequent completion and publication of important research studies, AABB established a donor health and safety committee that is actively preparing updated recommendations to be issued in an association bulletin with the goal of protecting the health and safety of our donors and the patients we serve.

Because a unit of donated whole blood contains approximately 250 milligrams of iron, iron deficiency commonly results from regular blood donation. This is of particular concern for premenopausal women, who typically
have lower iron reserves and experience greater physiological iron loss as compared to men. Indeed, almost two-thirds and half of male frequent blood donors are iron deficient.

Iron deficiency in addition to predisposing individuals to fatigue and impaired cognitive performance can with continued blood donation lead to iron deficiency anemia. Therefore, strategies to mitigate iron loss are required to protect the health of our altruistic volunteer donors while ensuring we maintain continuous blood supply availability for the patients we serve.

Interventions such as changing the donation interval or limiting donations in high school aged donors must be evaluated with respect to group and type-specific inventories. For example, O negative as well as overall inventories.

Blood collection facilities can provide valuable data on donation frequency by blood group, Rh type, and age, so that the impact of changes in allowable donation frequency can be evaluated. Iron supplementation programs have proven effective in two U.S. member collection facilities and in several international member centers. How these programs are implemented and maintained needs to be examined along with the utility of performing ferritin testing to identify and triage treatment of iron deficiency in donors.

AABB has been actively examining these issues through its donor health and safety committee and stands ready to facilitate evidence based discussions to formulate recommendation strategies. Furthermore, AABB’s structure and organization positions the association to develop impactful standards, promote donor awareness, and provide supportive educational materials. Thank you.
DR. LEITMAN: Thank you, Dr. Kleinman.

Open Committee Discussion

DR. LEITMAN: So let’s move to the questions for the committee. These are revised, and so the revised questions are in your packets. It’s not what you received in the mail. Slightly revised. So there are five questions, and questions one and two are voting questions. I’ll ask for a vote and we will count the hands, and one has A, B, and C, and two is A and B, and then questions three, four, and five are comments, and I will say that FDA always says that they are as much influenced by the comments of the panel as by the votes. So they review those comments. They think about them carefully, and those comments are important.

The first question, which should be up on the screen. Does the available scientific evidence support the need for routine monitoring of iron stores in, A, all blood donors, B, frequent donors, male and female, and C, premenopausal female donors. So this is a monitoring question. I’ll point out the second question is an iron supplementation question. So they are split.

So how best to do this? Let’s open it up to comments from everyone for the whole committee, and then I’m going to go around the table for individual comments by each panel member. If you don’t have any, you can pass after all of us make comments.

Comments? Toby?

DR. SIMON: I was interested, of course, in the discussion from a historical perspective, because I have been involved in looking at this in the 1980s. It was nice to hear my 1981 study, but actually we did one in 1984, a follow-up study, in which we randomized female donors premenopausal to either
iron, iron plus vitamin C, or vitamin C alone, which turned out to be a placebo.

It's interesting looking back at our conclusions. We basically showed that if you started the women on iron, their ferritins and hemoglobins went up, even as they continued donating regularly. So we said based on this study, we offer several recommendations. Actively menstruating women wishing to donate blood should be advised to take a daily iron supplement containing at least 30 to 40 milligrams of elemental iron.

On this regimen of iron supplementation, donation up to five times per year appears safe. In the absence of iron supplementation, women who are menstruating actively should consider limiting donation to one to two times per year. It seems to me that a lot of the data we have heard today kind of reinforced that.

So I think when we look at these two, we do need to either supplement the most vulnerable group, which would be the postmenopausal women, and then those occasional men who donate so frequently that they too can become iron deficient or have some other mechanism to monitor the vulnerable groups.

But I think it was interesting to hear the new data that the information letter, while not quite as effective as actually giving the pills, did have a positive impact, indicating that we probably can do this through information as a potential, and as the industry representative, I think there is a great interest in the blood banking community in getting some more time to work on this in a -- in other words, short of FDA regulations, and I think that would probably be a more effective way to move forward, but I think in terms of one and two, there are certainly available scientific evidence supporting the need to do something for the
vulnerable populations, which would be the premenopausal females and very
frequent donors.

DR. LEITMAN: You didn't mention monitoring, and I think that's --
this is a monitoring question -- that's very important, because I think to
paraphrase, if some intervention is made, we know what the monitoring data
show from large studies. So you can take a donor, male, female, age, frequency of
donation, and look at that donor, probably put them on a curve, because you
know where they will fall or have a high likelihood of knowing where they will
fall.

So maybe monitoring is -- if you are going to use the data as one
should, to mitigate in some manner. Maybe you don't need to monitor? Is that
correct?

DR. SIMON: I think there is a lot of data that the regular iron
supplementation is effective, and I think it would be -- Dr. Brittenham and his
group did studies later on using carbonyl iron. A lot of the resistance to iron
supplementation was based on poisoning children, babies, and also the
gastrointestinal distress. So that's why the carbonyl iron, I think, provided
another alternative there.

So I think if one has iron supplementation and provides
information on it, I don't know that if monitoring here means measuring a
specific analyte each time the person donates, I think that is going to be difficult.

DR. BRITTENHAM: For me the two questions are interrelated. I
think just as Toby was saying, that if you are supplementing in a routine basis to
the vulnerable populations, then monitoring probably isn't necessary. Conversely,
if you are not supplementing, you should be monitoring. So it's difficult to answer
these questions specifically without knowing what the interrelationship is between these.

And then in our approach, what we were trying to do was to replace the iron that was lost, not continuously supplement. So if someone came to donate, then they have lost 250 milligrams. So we wanted to give the regimen that would replace that 250 milligrams. Our other concern for using carbonyl iron was really one of safety. Iron poisoning was and can be a real problem. You're giving especially women iron which can be poisonous to children, and that was -- the reason for looking at carbonyl iron is it is very difficult to poison yourself with that.

DR. LEITMAN: So many pharmacies -- I know our hospital pharmacy only releases ferrous sulfate and ferrous gluconate in blister packs, and it's so difficult to open them that you have to use something sharp. You can't even use your nail. That probably mitigates against that problem with small children. I'm not sure whether CVS does that.

DR. BRITTENHAM: Although the pharmaceutical industry opposed that regulation and got it reversed. So it's not -- it's the way it should be, in my view anyway, but it's not the way that all iron supplements are prepared.

DR. LEITMAN: Thank you. Additional comments?

MR. TEMPLIN: I think monitoring would be good, and it's sort of a sad situation that people could go donate blood and never have seen like a primary physician, where if you go to donate plasma, you get a physical at least once a year. So I think monitoring would be a good thing, and I know when they do the local blood drives, the people are there long enough that maybe they could have like a physician assistant in the bus or wherever they do it. I think people
need to see a doctor when they are donating blood, at least once a year, would probably be a good thing.

DR. LEITMAN: So the comment was made at a consensus conference more than a decade ago that blood centers cannot enter into a therapeutic relationship with a donor, because they don't have the structure to do that, and therefore they can't give a medication, even if it is a nonprescription medication. But what Dr. Brittenham just stated, that one is not giving a therapeutic medicine for an indication, one is replacing a gift, replacing what was given, I think I have always thought gets along that enter into a therapeutic relationship, with one exception.

So the young female or maybe the young 16- to 19-year-old male that comes for their first blood donation, having never donated, and fails the hemoglobin threshold criteria, has never donated to your organization. Yet you know that the overwhelming likelihood in the female at least is that they have iron deficiency, overwhelmingly likely in the male as well, but not as much. So would you just think about including the first-time donor in your recommendations for mitigation of something that you have and the blood center hasn't done. Would you be influenced by the age of the donor or any other demographic as you consider that?

Okay, so I'm going to go around the room and I think it makes more sense and we know that question one is linked to question two, but we will cover question one first, to answer C first with your comments, then B, then A, going from perhaps what's easiest to answer or to understand and feel comfortable with your recommendation to something which may be more problematic or difficult. So let's start to my right with Dr. Ortel.
DR. ORTEL: Just so I can clarify, you want me to comment or address each one of these?

DR. LEITMAN: So the answer would either be a yes or a no, or abstain, for each -- is that correct? So that's just -- thank you very much. Let's just have comments. So we see how you are thinking and then we'll go around and just get votes after everyone speaks.

DR. ORTEL: My comment is going to come from the perspective of a physician taking care of the patient at the back end of this instead of from the blood bank perspective, and so the monitoring I think is important, but linking the patient to somebody becomes important to making sure they are going to somebody. A lot of patients come in to see me having information from a blood bank that they first sought care from Dr. Google on the internet to try to figure out what to do.

So I think we have to make sure we link people in, and I'm a little cautious about just treating, giving patients iron without making sure their provider also knows that some kind of intervention like that is being done. So depending on what level you're doing, I'm very concerned about it. The A and the B are the two that I'm most concerned about as far as linking them with, whereas C I don't think you need to test.

(Pause.)

DR. LEITMAN: Okay. Slight change in procedure, because this is going to take a long time. Let's discuss each one, just open discussion, which I think we have had, but we can add more, and then we will vote, because I seem to be sort of making people comment in a way that maybe is not necessary for the general deliberation.
So monitoring and premenopausal female donors. Comments?

Routine, routine monitoring, in premenopausal female donors who present to donate.

DR. STAPLETON: I think what Dr. Simon said makes a lot of sense. If you are going to recommend mitigation, monitoring doesn't seem to make sense to me.

DR. MURRAY-KOLB: I think that gets back to what Dr. Brittenham said, too. These two are so linked that it is difficult to sort of vote on the one separate from the other, because if you say that supplementation should be done and it's being done, then I think that -- then my answer for routine monitoring would be different than if supplementation weren't occurring.

DR. BRITTENHAM: The other point was the point you made. Do you mean all premenopausal or the first-time donors or repeat donors? This is always what happens I think to the FDA. We refine the questions, yeah.

DR. RAGNI: This is out of turn, but I was trying to -- it just seems to me if we know that a lot of donors are at risk, if we do not know who is low, we won't approach their management well, and if we don't continue to monitor, we won't know when we can stop iron or restart it, and I think these are critical issues.

They are giving blood for an altruistic reason. I think the blood banking industry needs to consider what is appropriate approach to these people even if there's not supposed to be a therapeutic relationship. What about educating their physicians? What about -- there's got to be a way to do it. I mean, I'm saying that I don't believe there shouldn't be some approach, even though there's -- I don't know what this means about no therapeutic relationship, but I'm
concerned that there is not one.

DR. LEITMAN: If there was a general mitigation strategy adopted
by a center, could -- I think what the question is asking, part of, is asking would
you -- would the panel feel one needs monitoring, or could you give a prescription
or a voucher or tablets or a letter to a primary care provider in the absence of
monitoring?

And the FDA would like to comment.

DR. ILLOH: Just hearing the discussions, I think we would like to
clarify that we probably will want responses based on supplementation versus no
supplementation. So breaking the question into, I guess, two parts.

DR. LEITMAN: So it's a little difficult. So we can -- Dr. Brittenham?

DR. BRITTENHAM: Also, another complication is what kind of
monitoring. I think ferritin is -- has advantages, but it's difficult to implement.
Zinc protoporphyrin has a way of identifying individuals who are sufficiently iron
deficient to have trouble in making red cells, and if you could -- if you monitored
that way, it might be a different answer than having to do a ferritin and then
come back, to different strategies.

DR. LEITMAN: Let me say that to get a point of care ferritin, to do a
donor ferritin like you do a donor hemoglobin, is not possible right now. So there
is no point of care or finger stick assay, and blood centers generally don't have
devices that can do that. So you collect the sample at the same time that you
collect the blood unit, and you perform the test on a retention sample. It's
expensive, requires shipments of samples, and then notification of the donor of
results.

It's very complex. There has to be someone in charge of it, several
people in charge of it, with databases established for keeping donor data. This is a complex endeavor and will probably be one of the most difficult things for I think for blood centers to do. So mitigation strategies that don’t involve monitoring are going to be much easier than mitigation strategies that do, and monitoring alone is -- and the interventions based on monitoring is very complex.

So, Toby?

DR. SIMON: I think the FDA is going to come up with some wording maybe that goes along with this, but the question number two, whether the available evidence confirms that iron supplementation, I think that the data are fairly overwhelming that it's a yes. So if you looked at question number one as does available scientific evidence support the need for some type of intervention to assure iron stores are adequate in A, B, and C, I think it makes it a little bit easier to progress to a response, and it seems to me that the B and C would be the groups. So I would just offer that commentary.

DR. LEITMAN: The FDA, the committee is having difficulty with question number one as it is phrased for routine monitoring, because it is so closely linked to two and three.

Dr. Epstein?

DR. EPSTEIN: What we are proposing is to ask question one, parts A, B, and C twice, first in the instance of in the absence of iron supplementation, and then when we go through them again with adequate iron supplementation, and I think that will help clarify the logic here.

So we are going to ask you to go through questions one, A, B, and C twice, but first in the absence of iron supplementation and then with adequate iron supplementation, leaving open what we mean by that, of course.
DR. LEITMAN: Okay, so we are specifically looking at iron supplementation, not at modifying the donor interval between donations, the inter-donation interval.

DR. EPSTEIN: Right now that is what we are asking, without modifying the --

DR. LEITMAN: It's iron supplementation. Okay. Thank you.

DR. LERNER: Can I just make one quick comment. I am not a blood banker. Nonetheless, it seems to me that so much of this is being dictated by the lack of availability of a reasonable point of care ferritin test. If we all sat around and talked about how we would think about this were that available, it comes down to the pragmatics of that. I wonder to what degree we can expedite something like that. There are loads of point of care tests available for things.

DR. LEITMAN: Industry usually rises to the challenge, and they always have for all emerging infectious agents, but I have no idea whether chemistry analyzer manufacturers understanding that there is a big need and presumably some type --

DR. LERNER: I really do feel it would change our perspective in how we approach these questions.

DR. LEITMAN: Is that likely? Anyone from the audience can help us with that?

Dr. Cable?

DR. CABLE: I don't have any inside information, but there are people who are doing market surveys for companies on this point and asking so-called thought leaders how they would use point of care testing. So my guess is that there is some interest. Someone is paying a consultant to do this who
actually could make these things or thinks they could make these things.

So I think there's enough -- I think this is kind of like the Babesia test, Jay. It's like if FDA got out the signal that we could make people use this if you made it, please make it, that would go a long way toward getting people to do the point of care testing.

I did just want to say one thing about zinc protoporphyrin. It's a good test, but we did studies in 1984 on it, and it was absolutely unreliable on finger stick samples, because there's chromogens -- fluorigens in what comes out of your finger that doesn't appear to be in the blood. It appears to be tissue stuff, and it fluoresces, and we basically concluded without ever publishing it that zinc protoporphyrin could not be done on a finger stick sample.

So I think at least for me, that is a -- now the guy who -- I am not supposed to say anything about individual products here, I know that. Somebody selling this still is a possibility. I think it's -- and I have no conflict of interest in saying so. I think it's a dead end. But that's just a comment on the side. I can't even find the data to show it anymore, but I think if somebody does want to go down the zinc protoporphyrin avenue, they need to validate a finger stick sampling method for it.

DR. LEITMAN: Okay, thank you.

Joe Kiss, one last comment?

DR. KISS: Can I just make a comment, provide a little perspective? We are struggling and hoping for a point of care test, and one may be developed, but we don't have it now. I think the changes that occur in iron deficiency, I think Dr. Brittenham mentioned, they are kind of chronic changes. They have been there for a while, and even if we grab a unit of blood, as long as -- even if it is post
hoc testing, they have donated a unit and theoretically they are going to get worse. They are still identified with a pre-donation ferritin level. So we have a starting point. Even if we get it a day later or two days later from the lab.

So I think focusing on point of care, while it would be nice to have and we may not have it in the near future, shouldn't impeded developing policies that say, okay, yeah, they did donate a unit. Okay, they are going to lose 250 milligrams more of iron than they had before. But we now know what their baseline is, and that could take action.

I would not want to see a screening test put in place to qualify a donor necessarily. High schools may be different. We may have a different attitude at the end of the day regarding that potentially vulnerable population, but I think there are workarounds that we could employ with this without being fixed on the absence of a point of care test.

DR. LEITMAN: Thank you. We are going to vote, and the first question is in the absence of a policy for iron supplementation in blood donors, does the available evidence support the need for some kind of monitoring, some kind of routine monitoring, in all blood donors, frequent donors, and premenopausal female donors, and I am going to be the first to vote. Do you want us to vote -- oh, all at the same time, okay.

So in the absence of a policy for iron supplementation, how does the panel feel about all blood donors, and routine monitoring doesn't have to be at every visit. It could be on the first visit and on the tenth as in Denmark, or whatever strategy for whatever, however one defines routine monitoring, and it can be on a retention sample, not point of care, but some form of monitoring of a validated assay which of course sounds like the ferritin, if iron supplementation
Okay, we will vote in the order, A. All blood donors. Raise your hands for yes?

LCDR EMERY: So the committee will vote using your keypad where your speaker is, where your microphone is. There is a button for yes. There is a button for abstain. And there is a button for no.

When we ask for the vote, what we are going to do is have you make your choice, and then we will wait until the audiovisual has compiled the votes, and then we will show the votes. That’s how we are going to do it. We are all going to vote at the same time. When the audiovisual is ready to do it, we are ready to go.

DR. RAGNI: Is this talking specifically and only about blood banks doing the iron supplementation, because a question would arise if that information were available and could be in a clearly described letter given to a physician, someone outside of the blood bank could also do the supplementation. I want to be sure I get what you mean by without and with iron supplementation. Are we talking without the blood bank doing it? I want to be so clear. Because this is about the patient, and I want to do the right thing for the patient no matter who is doing the iron.

DR. LEITMAN: I am not sure that the blood center could depend on an outside organization to do the monitoring. So the monitoring and keeping the data in a database would have to be done by the blood center.

DR. RAGNI: And is this about who does the iron supplementation?

DR. LEITMAN: No, not now.

Dr. Epstein?
DR. EPSTEIN: This is why I have suggested the wording which will be in the record. When we get to asking the questions with iron supplementation, we said with adequate supplementation without specifying how you got there. When we get around to talking about who should do what, it's a separate whole question.

DR. STAPLETON: I am sorry to add to the confusion, but it does seem that we don't have any data on cost effectiveness or any data like that on this recommendation. Cost effectiveness. I mean, we apply cost effectiveness to all screening tests we do, and we haven't discussed that at all for all blood donors.

DR. LEITMAN: Correct. We have heard that the cost of somewhere between 60 and 100 tablets of ferrous gluconate, 38 milligrams of elemental iron per tablet, is between a $1.50 and $2 if purchased in bulk. But we don't --

DR. STAPLETON: No, I am talking about monitoring, administration, loss of blood donors, all kinds of costs that we haven't even considered.

DR. LEITMAN: We could recommend studies on that. In fact, your comment already tells the FDA that we might be in favor of studies on that. But we still have to vote now.

So on A, in the absence of a strategy, any strategy of giving iron replacement or iron supplementation to blood donors, does the available scientific evidence support the need for routine monitoring of stores, of iron stores, in the absence of effective iron supplementation, for all blood donors.

We will vote one at a time. The answer should be yes, positive, no, the negative sign, or abstain, the zero. Vote, please.

(Vote taken.)
So the results are going to be collected in an automated manner, and we will see them on your screens before we go on to the next vote.

LCDR EMERY: The committee has voted and I will read the answers into the record. Dr. Brittenham, yes. Dr. Rabe, no. Dr. DeMaria, no. Dr. Stapleton, no. Dr. Ragni, yes. Mr. Templin, yes. Dr. Escobar, yes. Dr. Leitman, yes. Dr. Ortel, yes. Dr. Lerner, yes. Dr. DeVan, no. Dr. Rees, no. Dr. Sandberg, yes. Dr. Chitlur, yes. Dr. Laura Murray-Kolb, abstain.

The committee has voted. We are going to move to 1B.

DR. LEITMAN: Again, does the available scientific evidence support the need for routine monitoring of iron stores in the absence of a policy for effective iron supplementation, B, for frequent donors, male and female.

Please vote the positive sign, the negative sign, or abstain by voting zero.

(Vote taken.)

And the results are in.

LCDR EMERY: First, I would like to read the total results from 1A. There are 9 yeses, there are 5 noes, and 1 abstention.

In 1B, the answers are also up, which I will read into the record. Dr. Brittenham, yes. Dr. Rabe, yes. Dr. DeMaria, yes. Dr. Stapleton, yes. Dr. Ragni, yes. Mr. Templin, yes. Dr. Escobar, yes. Dr. Leitman, yes. Dr. Ortel, yes. Dr. Lerner, yes. Dr. DeVan, no. Dr. Rees, yes. Dr. Sandberg, yes. Dr. Chitlur, yes. Dr. Murray-Kolb, yes.

DR. LEITMAN: Thank you. While those are being finally tabulated, and we will read the tabulation after it's done. So let's vote on C, same question, this time for premenopausal female donors. Vote yes for the positive sign, no with a negative sign, and abstain with a zero. Okay, please vote.
(Vote taken.)

LCDR EMERY: All right, votes have been gotten for 1C, but I will read the totals for 1B first, before I go through 1C. There are 14 yeses, 1 no, and 0 abstentions. The committee voted in majority on 1B.

And 1C, the committee has also voted in majority, but I will read the individuals into record. Dr. Brittenham, yes. Dr. Rabe, yes. Dr. DeMaria has abstained. Dr. Stapleton, yes. Dr. Ragni, yes. Dr. Templin, yes. Dr. Escobar, yes. Dr. Leitman, yes. Dr. Ortel, yes. Dr. Lerner, yes. Dr. DeVan, yes. Dr. Rees, yes. Dr. Sandberg, yes. Dr. Chitlur, yes. Dr. Murray-Kolb, yes.

And the total is 15 yeses, 0 noes, and 1 abstention. I repeat -- I correct myself: 14 yeses, 0 noes, and 1 abstention.

DR. LEITMAN: Thank you very much. We are now going to repeat that vote. Thank you. We just voted on what it states right now, if you look at your screens. We just voted without iron supplementation, and now that question should be changed to with effective iron supplementation.

To read it again, does the available scientific evidence support the need for routine monitoring of iron stores in the presence of a program for effective iron supplementation in blood donors. Okay, vote of the committee on all blood donors. Again, three options are shown. Please vote.

I'm sorry, could you kindly stop? I made a mistake. Could we erase all those? I hit the wrong button. It happens. And could we start all over again? Is that possible? Thank you.

Yes?

DR. DE MARIA: Just while they're doing that, is it possible -- are we talking about premenopausal first-time donors, or that's my issue.
Clarification? Which premenopausal donors are we talking about here?

DR. LEITMAN: No, we are on A, which is all donors. But later on C, we will --

DR. DE MARIA: Because it could be either. So we are just talking any premenopausal woman, any donation?

DR. LEITMAN: Yes.

Okay, but we are voting on all blood donors, A, with effective iron supplementation. Is there scientific evidence to support the need for routine monitoring of iron stores. Please vote.

(Vote taken.)

LCDR EMERY: The committee has voted and I will read the results into the record. Dr. Brittenham, no. Dr. Rabe, no. Dr. DeMaria, no. Dr. Stapleton, no. Dr. Ragni, yes. Mr. Templin, yes. Dr. Escobar, yes. Dr. Leitman, no. Dr. Ortel, no. Dr. Lerner, abstain. Mr. Rees, no. Dr. Sandberg, no. Dr. Chitlur, yes. Dr. Murray-Kolb, no. Dr. DeVan is no.

The totals are 4 yeses, 10 noes, and 1 abstention.

DR. LEITMAN: Moving on to B, same question. In the presence of effective supplementation, does the evidence support the need for monitoring of iron stores in frequent male and female blood donors. Please vote.

(Vote taken.)

LCDR EMERY: The committee has voted. I will read the results into the record. For 1B, Dr. Brittenham is yes. Dr. Rabe is yes. Dr. DeMaria is yes. Dr. Stapleton is no. Dr. Ragni is yes. Dr. Templin is yes. Dr. Escobar is yes. Dr. Leitman is no. Dr. Ortel is yes. Dr. Lerner is yes. Dr. DeVan is yes. Mr. Rees is no. Dr. Sandberg is no. Dr. Chitlur is yes. Dr. Murray-Kolb is yes.
DR. LEITMAN: The vote suggests to me that the committee doesn't think that the iron supplementation program was particularly effective.

Okay, same question. It does say effective. But maybe that's an issue, even with effective iron supplementation, should there be routine monitoring? Does the evidence support routine monitoring in -- so we are voting on C -- in premenopausal female donors. Please vote.

(Vote taken.)

LCDR EMERY: The committee has voted. Dr. Brittenham, yes. Dr. Rabe, yes. Dr. DeMaria has abstained. Dr. Stapleton is no. Dr. Ragni is yes. Mr. Templin is yes. Dr. Escobar is yes. Dr. Leitman is no. Dr. Ortel is yes. Dr. Lerner is yes. Dr. DeVan is yes. Mr. Rees is no. Dr. Sandberg is no. Dr. Chitlur is yes. Dr. Murray-Kolb is yes.

And for 1B, the totals are 11 yeses and 4 noes. For 1C, the totals are 10 yeses, 4 noes, and 1 abstention.

DR. LEITMAN: Thank you very much. We are done with the vote for number one.

Vote for number two, I hope, will be easier, and I don't think I need to ask FDA for clarification, but I'll read the question before you on the screens. Does the available scientific evidence confirm that iron supplementation in blood donors -- we will vote on A first -- mitigates iron deficiency; B, improves hemoglobin recovery?

Let's vote on A, mitigates iron deficiency. Please vote.

(Vote taken.)

LCDR EMERY: For 2A, the committee has voted in majority. Dr. Brittenham, yes. Dr. Rabe, yes. Dr. DeMaria, yes. Dr. Stapleton, yes. Dr. Ragni,
yes. Mr. Templin, yes. Dr. Escobar, yes. Dr. Leitman, yes. Dr. Ortel, yes. Dr. Lerner, yes. Dr. DeVan, yes. Mr. Rees, yes. Dr. Sandberg, yes. Dr. Chitlur, no. Dr. Murray-Kolb, yes.

The totals are 14 yeses, 0 abstentions, and 1 no.

DR. LEITMAN: The part B vote, same question. Does the evidence confirm that iron supplementation of blood donors improves hemoglobin recovery? Please vote.

(Vote taken.)

LCDR EMERY: The committee has voted. I will read the results into the record for 2B. Dr. Brittenham, yes. Dr. Rabe, yes. Dr. DeMaria, no. Dr. Stapleton, no. Dr. Ragni, yes. Dr. Templin, yes. Dr. Escobar, yes. Dr. Leitman, yes. Dr. Ortel, yes. Dr. Lerner, yes. Dr. DeVan, yes. Mr. Rees, abstain. Dr. Sandberg, yes. Dr. Chitlur, yes. Dr. Murray-Kolb, yes.

DR. STAPLETON: Is it okay to make a quick -- raise a quick question? I am not saying that it doesn't improve hemoglobin recovery, but in the data presented today, there was no evidence of that presented that I saw.

LCDR EMERY: The totals for 2B are 12 yes, 2 no, and 1 abstention.

DR. LEITMAN: Next question, could we have question three shown on the screen? Please comment, no vote, comment on the feasibility of iron supplementation in consideration of A, potential adverse effects and, B, adherence.

So I wanted to start on commenting, because I have personal experience from our NIH trial on this. So we found somewhere between 8 and 12 percent GI adverse effects such that the donor did not want to take the tablet. Actually we found 18 percent initially, but that was with ferrous sulfate, which
has a lot more iron, 68 milligrams of elemental iron, and then we switched to ferrous gluconate, with 38 milligrams, and it dropped to 3 to 5 percent.

Every now and then, I think this is real, you will see a donor that takes one tablet of iron and has a horrendous adverse effect. Severe cramping, diarrhea, folding over double, and they cannot tolerate iron. In fact, they said that their parent, usually a mother, had the same complaint. So there is a very low frequency of severe adverse effects to elemental iron taken orally in the salts that I mentioned. I don't know about carbonyl iron, because I have never used that.

But subjects who have adverse effects, and the most common one was -- I know I'm taking it. They described it as dyspepsia. I just feel a little -- they don't feel right in the morning, but I can live with it. Or I don't want to live with it.

So the donor will self-regulate, and I have never seen a very severe potential adverse effect directly from taking oral iron, and in all the studies we have heard, probably covering thousands of donors, we haven't heard a single adverse event of a child in the household taking mom's or dad's iron from the cabinet. So that's in the older literature, drug toxicity literature. There's a lot of attention on that, to that now maybe pharmacy warnings on the bottles, maybe blister packs, but I don't think that's a real potential adverse effect of oral iron. So to me the adverse effects of not giving iron in this setting, as we have heard this morning, far outweigh the potential adverse effects.

For B, adherence, it depends on the message, and the message has to be a very strong, clearly worded message, and we had a nurse practitioner available to follow up on the message in addition to a letter, in addition to the initial discussions, and we found that increased adherence.
But adherence is never going to be 100 percent. I think we saw ranges of adherence from a little bit more than 50 percent to maybe 70 percent in the studies this morning, and you get -- just like all patients, donors, you do the best you can, and the subject either adheres or doesn't adhere. You can't force adherence.

Yes, Dr. Chitlur?

DR. CHITLUR: Just a comment that I wanted to make regarding the adherence issue. There's actually a very nice talk, I think two years ago in the American Society of Hematology meeting where they discussed the physiology of iron absorption, and what they presented was very interesting to me. I don't think it's confirmed yet, but still there was evidence in studies to indicate that when you take iron, it upregulates your hepcidin, which actually inhibits further absorption of iron.

So maybe there is a role for intermittent iron substitution, which might still be effective. Indirectly in our patient population, because adherence is such an issue, you can actually see that even patients who don't take iron every day like you tell them to or three times a day like you tell them to, there is improvement in iron, in their iron levels and their hemoglobins and their ferritins.

So I think it's something to keep in mind, that even though we don't expect to see 100 percent adherence, that there is definitely a benefit to getting it, even if it's intermittent or not as perfect as we would like it to be. Just something to keep in mind in terms of adherence and I think adverse effects, we are all very familiar with, but I think is carbonyl iron, but I may be wrong. I don't know if I can use tradenames here. Can I? Can I use a tradename? It's called NovaFerrum,
and it actually has much better GI tolerability as compared to the other preparations, and I have had pretty good success with that in the practice. So there's definitely some leeway.

DR. RAGNI: We heard today that some physicians when they get information that your hemoglobin is 12 or what-have-you, that you really don't have anything we need to worry about, and I actually think a lot of the materials we got today are extraordinarily informative and that it would behoove us to consider a one-page bullet of why this is a critical issue for blood donors and what iron can do, and I think for every patient -- sorry, donor -- that is seen who has the potential, should have a letter to their physician that just talks about the critical importance, because I don't think they know.

DR. ORTEL: That was actually the point I was trying to make earlier, to close that loop with the patient's physician, because the patient who is not adherent, if they're not known by their primary that they are even supposed to be taking it, you can't follow up on that. So there's at least at our institution, there's nothing that comes from the blood bank that tells me somebody had something wrong who is a patient of mine. There is no connection, unless the patient brings it to me.

DR. SIMON: I just wanted to point out some of the data we heard that suggests that maybe a low dose as is contained in a multivite might be adequate, and actually interestingly, back in our 81 study, we did ask the donors if they were on iron, and most of them who were were on a multivite, and there was a statistically significant difference in their iron stores and the people who weren't getting any. So we may be able to get by with a lower dose that would reduce the adverse effects.
DR. LEITMAN: Thank you. So as we think about how to educate our donors, if you give a donor a piece of paper to read before they leave the blood center or to take home with them, you find it papering the floor outside the donor center. So they generally don't read it. So how to get them the educational message so that they read it and it penetrates is important. So verbal one-on-one, so train the phlebotomists and the nurses to give a simple but careful and accurate message is one way to do it, to mail something with the thank you letter for donating, if we do that, or the email or the text that thanks them, to give them a little education about iron. But one has to think about how to craft the educational message.

Yes?

DR. ESCOBAR: I think adverse events and adherence, they go together, but think of individuals with bleeding disorders, I think there's a population that I think we have to provide special attention, with is the teenaged groups, the girls. I mean, adherence is a huge problem with that group, I think. They have a lot of problems, on top of that go out and take a pill or two or three a day, it becomes a huge issue. It is something that maybe needs to be approached in a different way for that group of individuals.

MR. TEMPLIN: Maybe like a PSA, like when they are at the blood center, they could like watch a little video and the video could explain to them the importance of making sure that if they are going to chew ice or eat dirt or ChapStick or whatever, they have to do -- maybe like just show them that they are maybe iron deficient, and with adherence, stress the benefits of having proper iron in their body would be a good thing, but potential adverse effects, you were saying about if you were worried about the kids being poisoned, just teach
responsibility. I take pain medicine. I don't leave it laying around the house. I keep it locked up somewhere safe so the kids can't get it. So it's just important little tips.

DR. LEITMAN: There is the donor refreshment room or donor canteen or whatever the blood center calls it, and donors are required to stay there for a while after donation. So if they pass out, they pass out under your observation. Other reasons for that, but that's an ideal place where donors chat with each other where one could situate a skilled nurse to chat about iron and to distribute reading materials.

MR. REES: One comment, Dr. Leitman. I can relate to this having a premenstrual daughter, and she was very hesitant to do blood donations, fear of needles, et cetera, which I think you do see in high school age, especially females. She did donate one time, had some issues, medical issues, not severe, went to the physician, and she did have low iron. She was put on an iron supplement through the physician. So it can't be related directly to the donor, the donation center or the donor center. But she had some cognitive issues, which I think approaches -- or talks on what Dr. Ragni and Dr. Murray-Kolb said.

The impact of taking the iron on her, the positive outcomes of her cognitive disorder, was dramatic, and I think that overplayed her role in understanding it being a donor-related versus a health-related, and from having two children of those ages, of my son and my daughter, that I think is an area that has to be focused on, because they don't understand.

It's very black and white to them, and when it became a health issue, then obviously talking to me, she knows this is what I do or have involvement in this field, it opened up a different -- a door for her. She
understood a lot more. So again, I think even with Dr. Ortel was saying, you know, that information that's even given to them, has to be very clear or it's going to be thrown away. It's going to be put away. They're not going to ask their parents. They're not going to understand even what it's about.

DR. LEITMAN: So for donors under the age of 18, if one has a message to give them, perhaps it should be a good idea to have policies where that message is also given to their parents.

MR. REES: So that they understand why it's being done.

DR. SANDBERG: I was pleasantly surprised to see that sending a letter with a recommendation that you take iron was effective, and so I like your idea of sending them a letter saying thank you for your donation, but perhaps a coupon could be included so they don't open this letter and say, oh, now I have to spend some money to take iron because I donated blood, and it might feel like a little bit of a gift that the blood center was looking out for their health.

DR. CHITLUR: I think what you brought up was very relevant in that the first-time donor who is iron deficient is different, like you had mentioned earlier, than the multiple donor who is iron deficient, and there is also a responsibility for us as an institution I think to be able to make sure that if there is an underlying problem leading to the iron deficiency, that is addressed. And that's completely different from just iron donation leading to the iron deficiency.

So there are two different problems, and I think including the primary care physician in this population would be extremely important or even referring them to hematologists would be relevant, because you want to make sure it's not a bleeding disorder that is leading to the iron deficiency.

DR. DE MARIA: I'm not a blood banker or hematologist, but I think
getting back to this question in terms of iron supplementation adherence and adverse events, it seems to me that this is somebody with iron deficiency for whom this treatment is indicated, and regardless of how they get it, whether it is handed to them or they get a coupon or they go to a physician and get it prescribed, they still should get it. So and that need for them to be treated, and whatever they need to be treated with exists regardless of these two issues.

The other thing I think the blood bank has a significant obligation to blood donors, but that obligation is limited, and I think for example -- I do deal with infectious diseases, and occasionally somebody is diagnosed or is screened positive for hepatitis C and definitely needs further follow up, but I don’t really expect the blood bank to do that and I don’t expect them to go beyond giving that donor a letter stating what their issue is for their physician, because I think it’s impractical considering all of the potential things a blood bank can find in an individual that might need medical attention for them to enter into a direct correspondence with the physicians of those individuals.

DR. LEITMAN: Thank you. We are actually also talking as I listen to our comments, we’re talking about the question or the comments to number four as well. So could we put up number four, because I think we have already adequately commented on that, too.

Comment on whether the available data support the effectiveness of the following methods for iron supplementation in blood donors: educational material, including a letter sent after donation, plus materials provided at the time or after donation in the blood center, and iron supplements provided to the donor, either as actual pills perhaps or as a voucher. And I think we have discussed this, and if there’s a further comment on this.
DR. STAPLETON: I might make a brief comment. It seems to me that we are talking about supplementation of blood donors providing something that we are taking away from those as opposed to treating them, and that's kind of --

DR. LEITMAN: Yes, we have mentioned that, that this is supplementation or replacement, rather than treatment. Also I'll say -- it hasn't been covered, but when a donor comes in with a hemoglobin that is dramatically low, not 12.1, but 9.2 or 8.9 or something that is really low, the blood center usually brings that to the attention or should of a blood bank medical director or physician, and it's followed up by a personal interaction. That is different. That's not usually due to blood donation, even though it can be due to severe iron deficiency.

Yes, Dr. Simon?

DR. SIMON: I think we have had a lot of material from clinical studies to answer both A and B yes. I'm not sure that there has been a lot of what the NIH used to call demonstration studies, where somebody -- I know a couple of blood centers have done that, but I think we probably need more experience actually putting it into use, and it kind of doesn't really change how a blood center operates and are they able to show it effective over a long time as a part of the operational part of the center.

DR. LEITMAN: So the study presented by Dr. Kiss, the JAMA study, the HEIRS study I guess, really effectively supplies I think a yes answer to both A and B.

So I would -- because it's so late -- like to go on to question -- comment on whether there are adequate data at this time in support of a strategy
for increasing the minimal inter-donation interval for men and women to prevent
iron deficiency from blood donation without monitoring of iron stores.

Comments?

Yes, Dr. Brittenham?

DR. BRITTENHAM: It seems to me the evidence was overwhelming
that it's not an effective means.

DR. SIMON: Yes, I would agree, and I would hope since we have
demonstrated that if you do supplement iron, people can, women particularly,
can donate at great frequency and can help us provide adequate and quality
blood. So I would hate to see us go this route, which also has some other
drawbacks to it.

DR. LEITMAN: There is a first, a second, and a third of that
opinion. So I thought we saw very compelling data today that this is not an
effective strategy.

So how hungry are you? Do you want to break now for lunch, or
should we continue with 1B and get the first part over with? 1B has two
presentations, questions for speakers, and open public hearing at which there are
no requests to speak, followed by a vote. So how long is that going to take us?

We were supposed to -- that was given an hour and a half. That's a
long time. Okay, we'll break, but we are going to have a shortened lunch. We were
assigned a 45-minute lunch. Can we do lunch in 30 minutes? So it's 12:30. We are
back here at 1.

Thank you.

(Recess for lunch.)
DR. LEITMAN: 1B, considerations for blood collections from female donors with hemoglobin levels between 12.0 and 12.5 grams per deciliter, or hematocrit values between 36 to 38 percent.

We have two speakers and then we have questions for the speakers, an open public hearing, and then committee discussion and questions for the committee.

So the first speaker is Dr. Orieji Illoh from the Office of Blood Research and Review, FDA.

**Topic IB: Considerations for Blood Collections from Female Donors with Hemoglobin Levels between 12.0-12.5 g/dL, or Hematocrit Values between 36-38 percent**

**Introduction and Background, Orieji Illoh, MD, OBRR, FDA**

DR. ILLOH: I'm here.

DR. LEITMAN: Thank you.

DR. ILLOH: Good afternoon. My name is Orieji Illoh, I'm in the Office of Blood Research and Review. I'm the division director in the division of blood components and devices. I'll be introducing Topic IB titled considerations for blood collections from female donors with hemoglobin levels between 12.0 to 12.5 grams per deciliter, or the equivalent hematocrit value of 36 to 38 percent.

For my talk today the outline will include an introduction to issues for consideration, the regulatory requirements. I'll go over that briefly in terms of hemoglobin requirements for our blood donors. I'll discuss the AABB proposal very briefly because the next speaker will expand on that. And really the proposal
addresses collections from female donors with hemoglobin levels between 12 and 12.5 grams per deciliter.

I will then go into FDA's considerations concerning this topic. I'll go over previous BPAC discussions, our rationale for the revised hemoglobin standards, address iron deficiency female blood donors with low hemoglobin, and when I say low hemoglobin here I'm really referencing information on donors with hemoglobin levels below 12.5 grams per deciliter.

And then I'll briefly just give our points to consider for regarding the AABB proposal. Finally I'll go over the questions for the committee.

So our issues for consideration today, basically FDA is seeking advice on the acceptable steps and procedures to assure safety of blood collection from female donors with hemoglobin levels between 12 and 12.5 grams per deciliter or their equivalent hematocrit value of 36 to 38 percent. Specifically we would like the committee to discuss the AABB proposed strategies and also suggest any alternate strategies as applicable.

So in terms of the hemoglobin hematocrit requirements for our blood donors, I know a few in this room are aware that FDA last year in May 2015 published revised regulations for donor eligibility. These regulations included minimum hemoglobin hematocrit requirements for blood donors. This regulation became effective in May 2016, and previously for hemoglobin requirements it was 12.5 grams per deciliter or 38 percent for both male and female donors. This has now been revised to be gender-specific so the current requirement is 13 grams per deciliter or 39 percent in male donors, and 12.5 grams or 38 percent in female donors.

Now in our new regulation we put some additional requirements in
here, and what we state here is that blood establishments may collect blood from female allogeneic donors who have hemoglobin levels between 12 and 12.5 grams per deciliter on a condition. And I have it quoted here: provided that they have taken additional steps to ensure that this alternative standard is adequate to ensure that the health of the donor will not be adversely affected due to the donation in accordance with a procedure that has been found acceptable for this purpose by the FDA.

Now when we put this regulation in place, we did not describe what procedure we would like to see, but in the preamble we do mention issues about monitoring iron stores, like ferritin measurement, or iron supplementation.

So in reaction to this new regulation and our requirements for additional procedures, AABB put together a workgroup to determine what kind of strategies could be put together that blood establishments could provide to FDA for review and possible approval.

The next speaker will address this in detail, but briefly there are two strategies proposed. The first one included collection of blood, ferritin testing, followed by a 16-week deferral and iron supplements for 60 days if the ferritin level is low. The second proposal includes collection blood from such donors, a six-month deferral, and encouragement of iron supplements for 60 days. This proposal does not involve ferritin testing.

So now I'll talk about FDA's considerations. First of all, I'll just briefly discuss our previous discussion regarding this issue in the past. In July 2010, FDA convened a BPAC to discuss considerations for changing the hemoglobin acceptance standards in blood donors. At this time the committee did not support changes to minimum hemoglobin standards in female donors.
They outlined several reasons but I have a few here. One, they noted that low hemoglobin is already a major cause of deferral from donation and that reducing the acceptance standard may worsen iron deficiency and that the consequences of iron deficiency in blood donors should be considered.

So what was our rationale for the change in hemoglobin standards? We basically did this to better align with physiologic norm. Of course it’s an added advantage that for at least for female donors when you reduce the hemoglobin level, the minimum hemoglobin standard, that you can have more availability of blood donors to donate blood.

Now if you look at the literature there are different sources of information to provide you with what is considered a level anemic, but I want to just go over this table with you briefly. This was published in Blood in 2006, and what the authors did here was to try to define in the U.S. population what minimum hemoglobin level would be considered as anemic.

So what they did was to basically gather information from two large databases, the NHANES III database and the Scripps-Kaiser database. They looked at hemoglobin indices from this population. They went ahead and excluded individuals who were iron-deficient based on their ferritin levels, and then tried to determine the hemoglobin levels below which 5 percent of the normal subjects in the population will be found.

So what you see here is categorization based on race, and also age, and you can see that for white men the minimum level would be about 13.7 grams per deciliter compared to black men, 12.9, and for women, which we’re discussing today, 12.2 for white women and 11.5 for black women. In other words, if you exclude subjects with iron deficiency, this was what they proposed as the
minimum hemoglobin levels.

What was our rationale for asking for additional steps and procedures in female donors with hemoglobin levels between 12 and 12.5 grams per deciliter? At the time of when we finalized the rule, there was limited information on the risk of adverse effects when the minimum hemoglobin of 12.0 grams per deciliter is used in females. I will note that earlier on one of the speakers talked about Australia having this level, but note that they too have a different inter-donation interval, deferral period. So it's not really a good comparison.

Also, there was concern about the risk of iron deficiency also discussed at the previous BPAC meeting in premenopausal and repeat donors.

So now I'm going to talk a little bit about what we know about low-iron, low-hemoglobin and such donors. Generally, approximately two-thirds of donors who present to donate blood -- all donors, not just female donors -- are repeat donors with an average rate of donation of 1.6 donations per year. It is well known that low hemoglobin is a common reason for deferral, strongly associated with female gender and time since last donation. We've heard some of this information earlier on this morning. And it's known that approximately 40 percent of deferred donors will have hemoglobin levels between 12 and 12.4 grams per deciliter. So, putting all this together it's likely that the female donors who will be presenting to donate blood, when they have hemoglobin levels between 12 and 12.5 grams per deciliter, many of them would be repeat donors.

In terms of iron deficiency in blood donors, we've heard a lot about that this morning. There's a higher incidence in premenopausal females and repeat donors. It's commonly detected in donors with low hemoglobin levels, i.e.
hemoglobin levels less than 12.5 grams per deciliter. In one study, a Canadian study, they did detect iron deficiency -- and when I say iron deficiency here, it's really absent iron stores or decreased iron stores -- this was detected in about 90 percent of female donors with hemoglobin levels below 12.5, compared to those with hemoglobin levels between 12.5 and 12.9 where it was 67 percent.

Now this is another study that was published by Dr. Barbara Bryant and colleagues, and what they did here was to provide data on looking at the iron status, which is the ferritin level of female donors, and its association with hemoglobin levels. They grouped the donors based on hemoglobin levels. You can see that they have four groups here: those with hemoglobin levels less than 11.5, 11.5 to 11.9, 12 to 12.4, and then greater than 12.5. And then they determined their ferritin level and put them into different groups based on the ferritin levels, so they were either iron deficient, iron depleted, or iron replete. And what you see here is that as the hemoglobin levels drop, you have a higher incidence of individuals who are iron deficient, compared to those with higher hemoglobin levels here.

You also, if you look at those who are iron deficient, if we focus on those who are between 12.0 and those who are greater than 12.5, there's a slight increase in those who are iron deficient in this group compared to those in the greater-than-12.5 group. And as expected, this goes up even higher as the hemoglobin levels drop.

The last few slides I've shown you basically, while 12.0 to 12.5 is within physiologic norm for females, there is possibly a concern about iron deficiency in such donors, especially if they're repeat donors.

Our considerations, our reactions, our points to consider regarding
the AABB proposal. The one proposal has a ferritin testing strategy, which I
outlined earlier on, where the donors, you collect blood from them, and then
based on the ferritin levels you provide different interventions. We are aware that
blood collection from a donor before availability of the ferritin test results, you
know there's concern that maybe it might be worsening the iron-deficient state;
however we're well aware that point-of-care assays for determination of ferritin
levels are not readily available. We do believe that availability of ferritin results
allows for appropriate intervention even if the results are obtained at a later time.

In terms of the deferral period that is proposed, for donors with low
ferritins this strategy proposes 16-week deferral in addition to iron supplements.
We believe that this deferral period is adequate especially if the donor is taking
iron supplements.

The second proposal involves an extended deferral. If you
remember, it's a six-month deferral. There's no ferritin testing involved. The
donor is encouraged to take iron supplements. Once again, blood may be
collected from a donor who is already iron deficient, and while extended deferrals
allow for iron recovery, this may not be adequate in donors who are not taking
iron, so you know, they may or may not take supplements depending on how it's
offered to them. So in this case we wonder whether iron supplementation options
should ensure reasonable donor compliance.

In terms of iron supplementation, the proposal offers different
administration options, which include coupons, letter, and iron tablets. This
allows for operational flexibility within blood establishments. Donor compliance
may vary depending on the options selected as we discussed this morning. And
once again, we wonder whether it should be considered that a more reliable
option be taken into consideration when the donor is not tested for iron stores.

So things that the committee can deliberate on.

In summary, FDA requires additional steps and procedures to collect blood from female donors with hemoglobin levels between 12 and 12.5 grams per deciliter, and the main goal here is to maintain donor health, including iron stores. AABB has proposed two strategies that blood establishments can use to develop procedures to present to FDA for review. And FDA would like the committee to discuss these strategies and the risk and benefits of the proposed strategies, or suggest alternate strategies.

We have two questions for the committee. Question one is broken into two parts. These are all comment questions, so no voting in this round. Given that close to half of the women with hemoglobin values between 12 and 12.5 grams per deciliter will be iron deficient or iron depleted, please comment on the proposed procedures for collection of blood from female donors with hemoglobin levels between 12 and 12.5 grams per deciliter.

I'll just summarize up here. First, this is collection of blood, ferritin testing, I'll just call this the ferritin testing strategy, and particularly we'd like the committee to talk about the collection of blood prior to obtaining the ferritin test results, the proposed deferral period for females with low ferritin levels, and iron supplementation options.

The second strategy is the extended deferral strategy with no ferritin testing, and once again we're asking the committee to address collection of blood without prior knowledge of ferritin levels, the proposed deferral period, and the iron supplementation options. And finally we're asking the committee to discuss any alternative procedures that FDA should consider to permit collection
of blood from female donors between 12 and 12.5 grams per deciliter.

Thank you.

DR. LEITMAN: Thank you, Dr. Illoh.

The next speaker will be from AABB with their proposed algorithm and that is Sharon Carayiannis.

**AABB Proposed Algorithm, Sharon Carayiannis, AABB**

MS. CARAYIANNIS: Good afternoon. Thank you for the invitation to present the management of risk for iron deficiency in female donors with the hemoglobin level of 12 to 12.5.

I'm Sharon Carayiannis. I'm with Regulatory Affairs at AABB.

Based on the overview that Orieji has provided and other information you've already seen I'm going to move forward to slide nine.

We met with the FDA liaison committee last fall and discussed this topic. Everyone agreed that it would be a good idea to help establishments know what should be included in the SOPs that had to be approved by FDA under 630.10(f) if these donors were to be collected. After the meeting we asked member experts to join the working group on management of female hemoglobin levels, and that group was tasked with reviewing the literature and relevant experience with this issue and identifying a range of strategies to assist blood collection establishments to know where to begin to develop these SOPs and to provide flexible strategies that would incorporate minimal elements of an acceptable approach and allow them to be flexible enough to be refined to meet the unique operational needs and preferred approach of individual blood collection establishments.
AABB’s Donor Health and Safety Committee reviewed these templates developed by this working group, and to be clear, these strategies were developed by the working group, and have not been approved by FDA.

A blood collection establishment that elects to collect from this group of female donors under 630.10(f) must first develop SOPs based on these strategies or other protocols that they develop and submit those SOPs to FDA in a prior approval supplement. Consistent with the goal of creating flexible strategies, templates for two approaches were posted on the AABB website as mentioned by Orieji. One, using extended deferral without ferritin testing, the other using an approach based on ferritin testing.

The templates also include a Q&A document with references and data that provides the thinking behind these templates and that is intended to assist individual blood collection establishments in refining an approach so best fits at their center, and all these documents can be found on the AABB website here.

Beginning with the extended deferral without ferritin testing, we are applying this only to adult donors, 12 to 12.5, a blood establishment would collect a unit and apply an extended deferral of six months from the date of donation, encourage iron supplementation of 18 to 38 milligrams per day, and six months later, when the donor returns to donate again, if the hemoglobin is less than 12, the donor is automatically deferred for an additional six months. If, when the donor returns in six months, the hemoglobin level falls within this range, the unit’s collected, and again follows the protocol of a six-month deferral.

These two notes here are providing the flexibility where other options can be applied at the appropriate place, and we can see these in the Q&A
Why is six months the suggested deferral period in the no-ferritin-
testing algorithm? The HEIRS study showed us that recovery of hemoglobin was
highly variable and two-and-a-half to five times longer for donors not taking iron,
compared to those randomized to take iron who recovered in a month.

Why is the recommended dosing for iron supplements 18 to 38
milligrams per day? What we know to date, we believe these to be equivalent in
efficacy and protect against iron deficiency. Typically multivitamins have 18
milligrams and an iron supplement has 38. Or, I noted at the store when I was
looking at this, sometimes more.

Why suggest iron supplements for only eight weeks? Isn't longer
better? The HEIRS study showed us that nearly 90 percent of the benefit of
taking iron occurs in the first eight weeks. We're assuming that donor compliance
might be higher if the period for which these donors is asked to take iron is
shorter, although this was not part of the study.

Isn't a shorter deferral period between donations acceptable if
donors take iron? And all of these points were considered. HEIRS showed us that
the recovery of ferritin is slower than the recovery of hemoglobin. In the STRIDE
study, while we can see that donors who take iron reduced their odds of a low
ferritin level by 80 percent. By the end of the study 30 percent of those taking
iron had a ferritin level less than 26. As we all know, encouragement of iron
consumption for female donors does not ensure compliance, and it's anticipated
that some donors will choose not to take iron, the tracking of which could be
operationally cumbersome.

So a six-month deferral, in the absence of ferritin monitoring
accommodates the variable and often long recovery periods for hemoglobin and ferritin in many donors. For centers that choose to evaluate donor compliance with an iron supplementation regimen, a deferral period shorter than six months may be worked into the protocol at the appropriate stage.

Beginning with the template for ferritin testing, we again have adult female donors, a blood establishment would collect the unit and also collect a pre-donation sample for ferritin testing and apply a routine deferral. They would encourage iron supplementation just as we've mentioned before.

If the ferritin level on that pre-donation sample is less than 26, a letter would be sent to communicate the ferritin test results, and to strongly encourage iron use, and an extended deferral of 16 weeks would be used. If the pre-collection ferritin level was 26 to 200, an optional notification would provide the ferritin test results and encourage iron use as well as donation, and a routine deferral would be applied.

For donors returning to donate that had a pre-collection ferritin level of 201 to 1,000, an optional notification would be sent to provide the ferritin test result, they would be encouraged to donate with or without iron use, and a routine deferral would be used. For those donors with a pre-collection ferritin greater than 1,000, a letter would be sent instructing the donor to discontinue iron use, and to refer the donor for an evaluation.

Again, there's flexibility built in, which you've already heard about, whether the center decides to dispense the iron, offer coupons, and they should also provide educational material.

The Q&A for use with the ferritin testing template also provides some of the same thinking behind this template, but some additional
considerations. Why is 16 weeks the suggested deferral period for women with a ferritin level less than 26? The HEIRS study found that the recovery of iron was slower. Some female donors with a ferritin less than 26 will have absent iron stores, which we believe indicated by a ferritin level less than 12. The goal would be to replete them beyond the pre-donation level, optimally to greater than 26, and a longer deferral period than the current eight-week donation interval would be indicated for that.

The assumption is that many donors receiving a letter reporting their low ferritin results would in fact be responsive to the message and either delay their next donation or purchase iron and actually take the iron, or both. And as you've heard earlier, the STRIDE study found that 70 percent of donors receiving such a letter responded with one or both measures.

Isn't a shorter deferral period between donations acceptable if donors take iron? Again, it's some of the same information, the recovery of ferritin is slower. In STRIDE, we again see that it doesn't always reduce the odds of a low ferritin to 0, because 30 percent still had a ferritin level less than 26, and encouragement of iron consumption does not equal compliance.

What proportion of female donors should I expect to have a ferritin level less than 26? Based on what we know, blood establishments might expect half or more of their female donors with a hemoglobin less than 12.5 to have a ferritin level less than 26.

Above what ferritin level should donors be advised to stop taking iron supplements? It's up to the blood establishment's medical director to determine what ferritin level a donor is no longer encouraged to take an iron supplement. That level will vary. The decision is left to the individual center and
that medical director.

The Q&A provides all of these relevant studies for donor centers to consider as they develop their SOPs, and I would like to thank the members of this working group for developing these materials, Rich Gammon, Jed Gorlin, Orieji Illoh, Claire Manelise(phonetic), Bryan Spencer, and Ralph Fasello(phonetic).

DR. LEITMAN: Thank you, Sharon.

I just wanted to thank the FDA for its flexibility in working with the AABB to produce this kind of collaboration. This is not off the record because it’s on the record, but I thought that was really very nice to have this dialogue happen no matter what we decide or comment on or vote.

We are now ready for questions for these two speakers from our BPAC committee.

Okay, I have a question if nobody else wants to ask. The current number of blood units collected is about 13.5 million from about 7 million different donors. What is the AABB projection of the number of donations that would be collected if one of these two algorithms was implemented? Is there a projection?

Sharon?

PARTICIPANT: (Off mic.)

DR. LEITMAN: So someone mentioned cost-benefit analysis before, what's the benefit of -- you know we're going to hear some controversy about this, so what is the benefit? Why should we be thinking favorably?

Open Committee Discussion

MS. CARAYIANNIS: This is Sharon Carayiannis. While we don't
have the actual projections for how many donations could be recovered if people
elect to follow this protocol and get approval from FDA, we worked off of the
basis that they would be -- the centers would be able to determine themselves if it
was worth the cost and the benefit to get donors back into the donor pool.

DR. LEITMAN: Thank you. Any further questions?

DR. CHITLUR: Are patients with alpha thalassemia trait allowed to
donate?

PARTICIPANT: Yes.

DR. CHITLUR: My question, I guess, is is it possible that if you had
alpha thal trait your hemoglobin would fall in this range, and if we are only --

DR. LEITMAN: So that is the type of donor that would be
recovered, yes. So, right -- 30 percent of African Americans have one or more
alpha thal gene deletions.

DR. ESCOBAR: Based on the data that we've seen, the Canadian,
where 90 percent or over of the young females -- or at least with hemoglobin
below 12.5 -- are iron deficient, I don't think there's really any point of discussing,
should we really measure something to be able to pick up those patients. I mean
we've got to be able to do either ferritins or whatever test is decided to do, but I
think it's an obligation for us to be able to pick up and do something for those
patients. Not just to look at it from the point is it a donor, or you just reject that
donor.

They're coming, they're getting hemoglobins that low, something
needs to be done, that's the way I see it. So it has to be almost our approach. To
me there's no decision, do you monitor iron, or you don't. At least initially, I think
you should monitor the iron. I mean, you've got to do something.
DR. LEITMAN: That comment for the comment period. We're now -- specific questions for the two speakers.

Open Public Hearing

DR. LEITMAN: Seeing no specific questions, it is now time for the open public hearing, and so I will very quickly read that document again. Both the FDA and the public believe in a transparent process for information gathering, decision making, to ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes 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 relationship you may have with any company or any group that is likely to impacted by topic of this meeting.

For example, the financial information may include the companies or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. The FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships, but if you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

We did not have any individuals or organizations tell us or ask us of their intent to address the committee at the open public hearing so I now want to ask if there's anyone else from the audience who would like a couple of minutes to address the committee on this issue?

Seeing no hands, let's move on to the questions and the discussion.

This is the open committee discussion, and questions for the committee. The
questions will be put up in front of you on the screen, and you also have them in your paperwork.

The first question for topic 1B is not a voting question. It's just discussion.

**Open Committee Discussion**

DR. LEITMAN: Given that close to half of women with hemoglobin values between 12.0 and 12.5 will be iron deficient or iron depleted, please comment on the proposed procedures for collection of blood from female donors with this hemoglobin value range.

A, please comment on collection of blood, ferritin testing, followed by the 16-week deferral on iron supplementation if ferritin values are low. That's one of the algorithms we've just heard, which includes collection of blood prior to obtaining the ferritin result for the deferral period that we heard, and the iron supplementation options.

And then comment on option B, collection of the blood, obligate six-month deferral, and a system for administering iron supplements for sixty days, without ferritin testing. So again, that's collection of blood without prior knowledge of ferritin levels, comment on the proposed deferral period, and commentary on the iron supplementation options.

So let me also mention, since they're both non-voting, question two, so the discussion could include question two as well. Please discuss any alternative procedures that FDA should consider to permit collection of blood from female donors with hemoglobin values between 12.0 and 12.5.

Mr. Emery will make a statement.

LCDR EMERY: I was just going to bring to the public's attention
that there was a written statement that was sent in to the FDA about levels of hemoglobin and that statement is in the meeting folder that's at the table where you could have signed in and gotten the paperwork. So if you're interested in reading the written statement from the individual from the public you can please do that. Thank you.

DR. LEITMAN: Comments by the committee?

Yes, Dr. Simon?

DR. SIMON: I would just speak in favor of the algorithms presented by AABB and think they've been very well thought out. Based on the discussion I think I and probably most of the members of the committee would be more comfortable with the one with the ferritin testing included, but I wouldn't have any alternatives. I would think that this would give a path forward where blood centers or hospital blood banks could come forward to the FDA with proposed protocols and then guidance that the FDA could then accept.

DR. LEITMAN: Thank you.

DR. RAGNI: One part of this is a little concerning and that is the collection of blood prior to looking at the ferritin level. I'm having a hard trouble with that and it's the same thing in both sections. I think we should do everything but collect the blood. I think we should find out what the ferritin is, because we're doing them a disservice if they're already iron deficient.

DR. LEITMAN: Thank you.

DR. MURRAY-KOLB: I just want to agree. I think that to allow them to donate blood without first measuring ferritin levels given their hemoglobins is potentially doing them a disservice.

I'm also concerned that we're talking about this level of hemoglobin
based on anemia and not based on functional outcomes in these women. I think that is something we need to consider. A lot of these women are women of reproductive age, as already mentioned before, many of them may be in school, maybe higher education. We could supplement them but a semester is only so long, they already perhaps have not done so well in a course because we left them deficient for a certain period of time during that semester. A lot of them are also young moms, and they're trying to interact with their children and their children are affected by whether or not the mom is responsive to them. So this is concerning to me to think about.

DR. CHITLUR: Without the ferritin testing there's also the possibility that we may unnecessarily be supplementing iron for somebody that has alpha thal trait, and therefore has a lower hemoglobin.

DR. LEITMAN: That's true, thank you.

MR. TEMPLIN: It seems that the process could maybe be helped out if there was a working relationship with the blood centers and the PCP-type doctors, where maybe the PCP could check the ferritin level, at some sort of annual physical or something, and then they would have that information and know a little bit better.

DR. LEITMAN: It is very difficult from experience logistically to make the ability to donate blood contingent on a communication with the PCP. It's very difficult to get responses. PCPs are pretty busy, so that's a lot of work.

DR. ESCOBAR: I've got a question: the way the hemoglobin is checked during the donation, I assume is a capillary?

DR. LEITMAN: Finger-stick capillary.

DR. ESCOBAR: My understanding, there is a difference between a
capillary and a venous stick of a maybe half a gram. So is that correct?

DR. LEITMAN: I think that is correct.

DR. ESCOBAR: So does that become an issue when you are talking about levels between 12.0, 12.5, if they’re doing only capillary, you know, if you have 12 by capillary, she could be 11.5, or 11 already, and again you’re taking a blood, a unit, without knowing what their iron level is. Well, that might be also an issue.

DR. LEITMAN: Thank you.

DR. BRITTENHAM: I’d just like to support what Dr. Murray-Kolb said. If you allow collection without knowledge of the iron stores, then in effect what you’re saying is that it’s acceptable to take blood from someone who’s iron deficient and make them more iron deficient. And so both of the proposals permit the collection of blood without further evaluation, and I think that’s a concern.

DR. SIMON: I think I understand the concern but I think the logic of how we got to this that these are hemoglobin levels that are within the normal range for females, so we’ve collected from them as we’ve collected from someone who’s say at 12.7 grams and could also be iron deficient -- just the practicality of trying to get an iron sample, have somebody come in for a sample of blood, measure that, and have them come back in, I think the way it’s laid out is more practical and reasonable, and if they are iron deficient on the ferritin sample that is obtained at the time of donation, then they can be alerted and can take action accordingly so no harm should be done.

DR. RAGNI: The problem is a great proportion of them, at least half, are iron depleted. So why are we doing that?

DR. SIMON: But also many of the women who are more than 12.5
grams are also iron deficient.

DR. RAGNI: I know, but when there's that high a proportion who may be at risk for doing it, I would suggest we should not do that, do it in that order, that we first get the ferritin level.

DR. LERNER: I would like to agree with that.

DR. MURRAY-KOLB: I just wanted to say that it is true that someone with a higher hemoglobin may also have the same ferritin level, but if you deplete their ferritin it's going to take longer for their hemoglobin get below the anemic level than it is for someone who's already almost there. I think there's a difference there, the ferritin's going to be depleted first and then the hemoglobin, and those with the higher hemoglobin have farther to go until they become anemic.

DR. CHITLUR: Can there be two algorithms? One for the females who have hemoglobin between 12 and 12.5 where the ferritin would then determine whether they can donate or not? Whereas if your hemoglobin is above 13 or whatever we determine would be safe then those in that situation you could donate now, and then check the ferritin later?

DR. LEITMAN: So the female with the hemoglobin of 12.5 or greater is within the current FDA regs for donating. Nothing is required right now, so that is already true.

I'll give my comments. So I find option B without ferritin testing to be completely unacceptable, from everything we've heard this morning. These are volunteers coming in to give a gift, and there's a 50 percent likelihood that you're going to be doing them harm, and no one can guarantee that subject takes the iron that you give them, or uses the voucher, or uses the prescription, or even gets
the message because a lot of subjects don't. So without knowledge of what you're
doing with such a high risk and with consequences of that risk, I find that a not
acceptable alternative.

I find it acceptable to test and to act on data, but as has been said by
others, I'm uncomfortable with drawing first and then replacing, for the same
reasons. But one of them is being uncomfortable with, the other is being
absolutely dissatisfied with. And I don't have any other options to add.

Okay, it looks like we are done with comments on IB. FDA okay
with moving on to topic II? We need to change the composition of the committee
slightly. We have added panel members participating in topic II. So let's just take
a ten-minute break.

(Brief recess.)

**Topic II: Blood Collection and Adverse Events in Teenage**

**Blood Donors (16-18 years)**

DR. LEITMAN: There are some members of the BPAC that I'd like
to introduce. Dr. DeVan walked in a little bit late for the first session, so let me
introduce Dr. Michael DeVan who is medical director and staff pathologist at
Blood Services at the Walter Reed National Military Medical Center here in
Bethesda.

And I'd like to introduce Dr. Alain Joffe of the student health and
wellness center at Johns Hopkins University. Welcome.

And Dr. Cassandra Josephson, professor of pathology, pediatrics,
and transfusion medicine at Emory University School of Medicine. Welcome, Dr.
Josephson.

We will go right to topic II, which is Blood Collection and Adverse
Events in Teenage Blood Donors, defined as donors between the ages of 16 and 18 years. To give us background on this topic, we have Dr. Emily Storch as our first speaker, from Office of Blood FDA.

And as before we have four speakers. We already heard from Mr. Spencer, the fifth speaker. So we have four speakers, and we will follow that with questions for all four speakers.

Introduction and Background, Emily Storch, MD. OBRR, FDA

DR. STORCH: Good afternoon, my name is Emily Storch, I’m from the Division of Blood Components and Devices in the office of Blood Research and Review, and I’m going to introduce the topic blood collection and adverse events in teenage blood donors, those 16- to 18-year-olds.

To begin with an overview, I’ll discuss the issues for consideration, review some of FDA’s donor eligibility regulations, touch on blood collection demographics and trends, discuss iron status in teenage blood donors, present the questions for the committee, and finally introduce today’s speakers for this afternoon.

The issues for consideration. Today FDA is seeking advice from the committee as to whether, one, adequate mechanisms exist to prevent adverse reactions and injuries following blood donation from teenage donors, and two, whether teenage blood donors are susceptible to developing iron deficiency and the resulting short- or long-term effects.

The FDA donor eligibility regulations as of May of this year stipulated in 21 CFR 630.10 and 630.15 to include among others medical history, physical exam, hemoglobin, temperature, blood pressure, pulse, minimum
weight. The regulations also address informed consent and donor
acknowledgement. However FDA has not established a minimum or maximum
age for blood donation, and in keeping there are no federal requirements for
parental consent for minors.

So how is teenage donation regulated? It's regulated by state, and
this can be variable. In some states donors must be 17 or older. However, an
increasing number of states allow 16-year-olds to donate. In California as young
as 15-year-olds are allowed to donate with consent of parent or guardian and
written authorization of a physician or surgeon, and this is how the code is
written.

As for parental consent, in 37 states and the District of Columbia
16-year-olds are allowed to donate with parental consent. However in five states
16-year-olds can donate without requiring parental consent. Parental consent
forms are drafted by individual blood centers, and as such they do not provide
uniform or consistent information.

On this slide, we see a sample donor brochure of how risk is
presented and how it is sometimes downplayed. In this sample brochure it says,
is it safe to donate blood? It says not only is it safe, it is simple and it saves lives.
On rare occasions donors may feel light-headed. Occasionally a black-and-blue
area may develop on the arm.

As for international policies on the minimum age of donation, they
are somewhat more stringent than in the United States. In Europe, the minimum
age is generally eighteen. Some countries allow 17-year-olds, such as United
Kingdom. However they impose additional safety selection criteria for donors
less than 20 years, such as minimum estimated blood volume of 3,500 milliliters
for whole blood and platelet donations. In Australia the minimum age of
donation is 16 years with parental consent, however 16- and 17-year-olds are only
allowed to donate one time per year.

Japan takes a somewhat alternate approach. Minimum age in
Japan is 16-year-olds, but for females under 18 years old and for males under 17,
the donation is allowed to be 200 milliliters. Females 18 and older and males 17
and older are allowed to donate 400 milliliters, in contrast to the United States
where it is somewhat over 500.

This is an important issue for consideration because today in the
United States teenage donors provide a disproportionate number of blood
donations. Sixteen and 17-year-olds comprise approximately 3 percent of the
population; however they contribute 10 percent of the U.S. blood supply.

A recent BEST Collaborative study presented last month at AABB
showed an overrepresentation of the youngest age cohort in the United States,
those being from age 16 to 25. This is in contrast to other countries such as
England or the Netherlands where there's a preponderance of middle-aged
donors.

On this slide we see some of the data that was presented and on that
top graph you see the general population in the United States and the pink line is
showing the proportion of female donors over all of the population and the blue
line is males over all the population and the age categories are on the bottom. So
you can see that in the age group of 16 to 20, males and females are
approximately 4.5 percent. And in contrast, in the bottom graph on the far right,
you see the U.S. donor population, and again the 16- to 20-year-olds now
comprise almost 11 percent. So this is very disproportionate and a stark increase
from 2001, where it was under 8 percent.

This is also in contrast to data from the Netherlands where you can see the proportion of 16 -- well, here it’s 18- to 20-year-olds, it’s between 3 -- around 3 percent. And the donor population is under 2 percent, which is not much of an increase from 2001.

In this graph we see somewhat the same phenomenon of the donor proportion by age and you can see that not only is it higher in the youngest donors, but it’s also stratified by age -- by race and gender. And so with the yellow being the white females, the highest proportion, and it decreases substantially -- incrementally with age group. And in contrast the frequency of the donations goes down with decreasing age. So the age 16- to 19-years-old had the lowest frequency of donations -- this was over four years, at one point 6.3 -- it increases up to 4.91 in the highest age group.

So some general complications of blood donation. Most common is vasovagal, defined by low blood pressure and low heart rate, divided into pre-syncopal -- defined as no loss of consciousness -- and syncopal, which is a transient loss of consciousness. There's the phlebotomy related which is generally minor hematomas, can be more serious. There's allergic reactions. And then there's injury, which is distinct from reactions, it's a consequence of these reactions. However, severe injury is rare.

And there are some known donor susceptibilities to reactions and injuries, and in order of importance these are young age, first-time donors, low estimated blood volume and female gender as shown stepwise logistic analysis by one of Dr. Eder's studies from 2008. Now these factors are additive, so if you have a female with a low EBV who's a first-time donor and is young, then they are
the most susceptible donor population. So it's of little surprise that teenage donor reactions and injuries are disproportionately high.

This graph shows more data from Dr. Eder and it demonstrates the drastic decrease in reactions with increasing age groups, so on the bottom you have different age categories, from 16 to over 80, and it's primarily what you're seeing is vasovagal reactions that are composing the predominance, and it decreases with age.

In 2008, AABB put forth a bulletin Strategies to Reduce Adverse Reactions and Injuries in Younger Donors, stressing pre-donation education the drive setup and environment, water ingestion before donation and within 10 to 20 minutes, muscle tension during phlebotomy, staff supervision and phlebotomist skills, distraction during phlebotomy, importantly donor selection and collection, donor eligibility criteria based on height and weight restrictions, and emphasizing automated red cell collections; and providing post-reaction instructions to donor and parents.

So what has been the impact of the interventions? Well, there have been inconsistent results. We'll hear more about this later this afternoon from the various speakers. Some studies show effects only in females, however bottom-line is no studies have reported decrease in syncope-related injuries.

Another aspect of teenage donation to be considered is iron loss, as we've heard this morning in detail. What are the short-term effects of iron loss in teenagers and what are the long-term effects of iron loss? Whole blood donation we know removes a little over 500 milliliters of whole blood which corresponds to 200 to 250 milligrams of iron, and the iron status of teenage blood donors is not well characterized.
What we do know is that adverse consequences of iron deficiency in teenagers somewhat mirror that of adults, with anemia, reduced physical endurance, impaired immune response, changes in energy, metabolism, and decreased cognitive function. However, the teenage population is more susceptible to these phenomena due to increased growth requirements, sometimes poor nutrition, the new onset of menses in teenage females, and we also know that iron deficiency impacts cognition, even in the absence of anemia. Therefore iron-deficient adolescents at risk of impaired executive functioning.

And in this study in Pediatrics, we have seen that there's a twice as high a risk of low math scores for adolescents with iron deficiency. So in the graph looking at math scores, in 12- to 16-year-old females, the shaded bars show those of normal iron status. You can see that's dramatically higher than the pale bar that represents the iron-deficient females.

So this is an ongoing study, an NHLBI sponsored study, a comparison of the history of donation and iron levels in teen blood donors or the CHILL study, which we heard a little bit about this morning and we'll hear some more of. It's an assessment of iron stores in high school blood donors, and we'll hear more of the initial results.

As for pros and cons of teenage donations, there are advantages. Provide a ready source to contribute to the blood supply and for various reasons are less likely to be deferred. However, there are some strong disadvantages, which is potential harms to the donor, in terms of donation reactions and iron loss, the variability in minimum age between states, and there's a lack of standard parental consent and sometimes inadequate information conveyed to parents and guardians.
So in summary, teenage blood donation carries a higher risk of adverse reactions and injuries compared to adult donations. Minimum age limits are established by the states and they vary. Parental consent is inconsistent both in the process and the content of the form, and in state requirements between states and even within states. Mitigation measures have had limited success, and the implication of iron deficiency in teens is unresolved.

So to begin with the questions for the committee. Number one, does the available evidence indicate that adverse reactions and injuries after blood donation in teenage donors is a notable enough concern to require intervention?

Number two, considering possible mechanisms to reduce the risk of adverse reactions and injuries in teenage blood donors, A, does the available evidence support applying donor-specific selection criteria, for example, EBV less than 3,500 milliliters, as a means to mitigate donor reactions? B, do the available data indicate that the specific measures such as applied muscled tension to mitigate reactions are effective?

Number three, please comment on the need to ensure parental consent material contains adequate information on the increased risk of adverse reactions and injuries in teenage donors.

Four, considering available evidence related to iron deficiency in teenage blood donors, A, does the available scientific evidence suggest that teenage blood donors are susceptible to developing iron deficiency. B, if so, please comment on possible interventions including, 1, further studies evaluating the effect of iron deficiency in teenage blood donors, two, donor education, three, iron management by ferritin testing, iron supplementation, or limiting donation frequency.
Number five, please discuss whether there's enough associated risk in teenage donors to warrant restriction of the donor pool to individuals aged 18 and over.

For today's speakers, next will be Dr. Anne Eder, here from the FDA speaking on teen blood donation adverse reactions, Dr. Hany Kamel, from Blood Systems Inc., who will speak on experience with mitigating strategies, Dr. Christopher France from Ohio University to discuss predicting and preventing syncopal and pre-syncopal reaction in young donors, and finally Bryan Spencer from American Red Cross to review the CHILL study, Iron Loss and Deficiency in teen donors.

Thank you.

DR. LEITMAN: Thank you very much Dr. Storch.

We'd like to welcome Dr. Anne Eder to the podium to speak, thank you.

Teen Blood Donation and Adverse Reactions, Anne Eder, MD, PhD, OBRR, FDA

DR. EDER: Thank you. I'm with the FDA in the Division of Emerging and Transfusion Transmitted Diseases, but in today's talk I am going to share work I was involved with and published when I was with the American Red Cross.

In this introductory talk I'm going to cover these three topics. I'm going to describe the trends in collections from high school donors, that is donors 16- to 18-years-old, review the requirements and practices for minimum age and parental consent for voluntary blood donation, and discuss the risks and adverse reactions after blood donation among teen blood donors. And I want to say off
the bat that blood donors are healthy volunteers, not patients.

If they have a reaction they can become patients, but they're healthy volunteers. And this slide shows the first donor under age 18 in Colorado, from a Colorado newspaper, and it makes me laugh because he's making a face but the needle's already in his arm so the hard part's over. I don't know why he's grimacing. He's sixteen, that's why.

I am going to take you through a history of recent studies, but this goes back to 1942, and don't worry, I'll still finish within my 30 minutes. But in 1942 this study from the Army blood program was published in Lancet, and they concluded to an organization that bleeds a 100,000 volunteer blood donors a year, the prevention of faints is of considerable importance. Only about 3 percent fainted, that even a small minority has a disproportionately large influence against recruiting. On two occasions a donor has injured himself by fainting after a return to work, and such accidents must be avoided, and they noted that fainting was more likely in young donors.

All of this is still true. The most notable difference, however, is in the study that I'm going to show you from the American Red Cross. There are over 100,000 16-year-old donors. So to put that into the current-day context.

So, advancing about 74 years, these are our governing specifications for collecting blood today, the regulations and volunteer standards. Very quickly, FDA has no minimum or maximum age, and no requirement specifically for parental consent for minors. AABB does have a standard that says blood centers must conform to applicable state law or donors must be 16 years or older.

However, I put up an example here. So the AABB standard points to the state law, and in one state's law they say that a 16-year-old may donate with consent.
provided it's approved by AABB. A bit circular. AABB points to the state law, the state law points to AABB.

There isn’t a standard that says when you need parental consent for minors. But if it is required, there is an AABB standard that says the collection facility must have a process to provide information concerning the donation process to the parents or legally authorized representatives of the donor.

These are some trends that most people aren’t very familiar with, trends in whole blood collection. These data are from the National Blood Utilization and Collection Surveys between 2001 and 2013, and that shows the total whole blood or red cell collections in millions over these years. And as many of you know, the demand was increasing up until around 2008, when it took a downturn and has since been decreasing. The overall demand for blood has been decreasing each year since about 2008.

As far as minor donors, however, before 2006 only a handful of states allowed collection from 16-year-olds, so during this period only a handful of states allowed 16-year-olds to donate. In 2007, states began lowering their donation age to 16 -- many states began lowering their donation age to 16, when during this period of time that blood collection was increasing and there was no ceiling in sight, but in 2011 16- to 18-year-olds provide about 10.5 percent of the blood supply. That’s 1.6 million donations, and this has not really slowed down, even as blood demand has decreased. In 2013 it’s still about 10 percent of the blood supply, about 1.3 million donations in our country.

This shows the specific trends among young donors in the American Red Cross over these years. What I want to point out here is that after 2007, states started lowering their donation age and very rapidly collections from
16-year-olds increased. However, and that accounted for most of the proportional increase — this is the percentage of all whole blood donors by these ages, 16, 17, and 18-year-olds.

So this increase is entirely from the increase in collections from 16-year-olds, notably collections from 17-year-olds actually starts dropping off, and when you consider the absolute collections or the total collections behind these numbers, which is shown on this slide, what you see is that total whole blood donations in these years from 16- to 18-year-olds and 16-year-olds, and you can see that collections from 16-year-olds increased after 2007.

I also want to point out that actually collection from 17- and 18-year-olds without 16-year-olds increased, as the demand was increasing, but then as demand turned the other way, actually collections from 17- and 18-year-olds has dropped off, and while collections from 16-year-olds has increased. The end result of all of this is not more collections when demand has been decreasing, but actually just more collections from younger donors.

I also want to point out that parental consent is required for -- at the time was required for 16-year-olds in the American Red Cross regardless of state law, and that was no deterrent for collecting them on the high school drives.

This puts all of the state laws into the various buckets. So if you read what's in the codes, and you look at what they say about 15-year-olds, with California saying, yes, they can donate if they have a parent's permission — 15, 16, 17, 18-year-olds, or no statute, so this just puts the states into their various buckets. So most states that mention it in their laws require parental consent for 16-year-olds, but five don't. Most states don't require parental consent or permission or authorization for 17-year-olds, but three states do, and two states
require notification.

I want to point out that this is what's in the law. It doesn't actually reflect actual practice. There are states where 16-year-olds are collected, either through variances to the state law, or otherwise. So if you don't see your state up here, it just means that it's not specifically mentioned in their code.

So, left to individual states, the laws vary. They're like snowflakes. No two are the same. So these are actually two states that basically say the same thing, and these are two of the states actually that have the minimum age of 17 and don't allow collection of 16-year-olds, but if you look at them they're worded a little different, but basically you have to be 17, you have to have parental consent, and you can't be paid. And there's some other words.

And so, I'd never make it as a lawyer, but I can read, and so I want to show you some other provisions that are in these state regulations about donation by minors. A few states -- and to me it suggests that even if they didn't require parental permission -- it suggests to me that three was still concern about young donors, because a few states stipulate that parents must be notified even if parental consent, written parental consent is not required. North Dakota requires that any notification of a medical condition must be given to the donor's parent or guardian.

So the teenager can donate, but if any test is positive we're going to tell your parents. That's not how most centers work. If parental consent is required, parents in the consent process are told we will only give the results to your child, not to you. And if parental consent is not required for 17-year-olds, well, you don't have to tell the parent anything.

Two states don't require written parental consent, but still have this
provision that there should be reasonable attempts to disseminate information, information to the parents and guardians, and notify them. Two states say the parents can object in writing if they don’t want their teenager to donate. South Dakota says that it’s okay for them to donate unless the parent says that it’s not okay. Parents don’t usually need permission to object to what their kids do. There you go.

And two states have something to say about financial responsibility which is that the parent or legal -- or the parent who donates blood shall not be financially responsible for any medical complications from the blood donation. And that's just not how it works. If your dependent child is on your health insurance, that's just not how it works.

So I want to switch to talk about this 10 percent -- so 10 percent of the nation's blood supply is provided by 16- to 18-year-old donors, but it's not a constant 10 percent. So this slide shows the proportion of young donors in the different months on this axis. So this middle curve is the proportion of young donors. So it's not a constant 10 percent you can see. Of course when school's in session young donors account for upwards of 20 percent, and then in the summer months it falls close to 5 percent. This aggravates summer shortages, so it's not -- when you hear 10 percent, it has this seasonality to it in the spring and fall months when school is in session.

Also, that means that as a system when you look at the complication rates in your system, the highest months with complications are no surprise, the spring and the fall, when the higher proportion -- this is looking at all donors, all complications -- and you see that the months with the highest complication rate is because of these -- a large proportion of the supply is from young donors. So
you see this periodicity with syncopal reactions or the vasovagal type reactions, with the high school drives.

You've seen this slide once, I'm going to show it again. It's what I call the ski slope. So this shows the age dependence of adverse reactions. This is the rate per 10,000 donations per donor age, 16-years-old up to over 80, octogenarians. And the biggest bar are the pre-syncopal reactions or the vasovagal. These are the symptomatic lightness, dizziness, nausea, and it's the most common reaction, but in the youngest donors it's about ten percent, and it decreases as donors get older.

What you can also see though is the second bar, the second stacked bar is LOC, loss of consciousness. So loss of consciousness is -- we're going to take a deep dive into the data, but just at a high level this shows the age dependence for reactions in the younger donors.

And as a system, young donors -- this age group accounts for almost a third of all adverse reactions. This isn't unique to the American Red Cross or any one blood center. It is a pattern that's seen in other blood centers. This is the AABB donor hemovigilance report with six blood centers that are not the American Red Cross centers, of over a million collections, and it's the same ski slope with the highest rates in the youngest donors, and not only that, but they report that 16- to 18-year-olds account for about 30 percent of all adverse reactions in their system.

So now we're going to take a deep dive into the data. This report was published in 2008, during that period of time when demand was increasing, and collections from 16-year-olds were accelerating in an effort, or the argument was, to increase collections during a time when the demand was increasing. So
this study included nine American Red Cross centers, 16- and 17-year-olds were about 8 percent of the total whole blood collections, 16-year-olds were about 2.5 percent of the total, and this study reported a higher incidence of complications and injury among 16- and 17-year-old donors compared with older donors. So if you're sitting there thinking, well, that's because they're all first-time donors, that's a common misconception, that these are all first-time donors, and that's why they have higher reaction rates or higher risk of reaction.

Many studies have shown that when you control for factors that are responsible or that contribute to the reaction rates, and you do it in a stratified analysis for age, sex, and donation status, what you see in every strata is that youngest donors have highest reaction rates. In this case about 12 percent for the 16- and 127-year-old first-time female donors, but this is the highest in every strata, the repeat donors, and it's higher than what you see in older donors. So compare the underage donors to older adults in each strata.

While most reactions are minor symptoms, the concern is about loss of consciousness or syncope, and the injuries that result from syncope-related falls, and if you look at young donors, and this study showed that 16- and 17-year-olds had a higher rate compared to 18- and 19-year-olds, about twofold higher, and about fourteen-fold higher than the older adults. So while injuries are unlikely, when they occur, they are more likely to occur among young donors, and overall as a system, 16- and 17-year-olds account for half of the injuries in the system.

So this study concluded -- and remember at the time, demand was increasing -- but in 2008 this study concluded that the increase in dependence on recruiting and retaining young blood donors requires a committed approach to
donor safety, especially at high school blood drives. AABB convened a working
group which established a framework of, not only just do something, but do more
than one thing, because there's not a magic bullet. There's not any one thing that
will even fix most of the problem.

So this bulletin that's still available set up this framework to address
many things that should be done: pre-donation education, controlling the
environment and setup, water, drinking water -- we're going to talk about the
studies about drinking water -- muscle tension exercises during phlebotomy, staff
supervision and skills, and distraction during phlebotomy.

I'm going to focus on the donor eligibility criteria, the height and
weight restrictions to prevent loss of more than 15 percent of a donor's blood
volume. But also discuss post-reaction instructions to donors and parents.

So when you look at these two teenagers, who's more likely to have
a reaction? This is the quiz. Well, I'm sure you all appreciate that she's more
likely to have a reaction, a vasovagal-type reaction, because she weighs 50
kilograms, which is an acceptable minimum weight, 110 pounds. So with a
routine blood donation of over 500 mLs, or about 525 milliliters, if you do the
math, she stands to lose up to 20 percent of her total blood volume, whereas the
boy likely will only lose about 13 percent. So he's losing less than 15 percent of his
blood volume, but she's losing probably almost 20 percent.

We were concerned about this. Red Cross introduced additional
criteria for 16- to 18-year-old whole blood donors. This shows the algorithm that
was used, and it shows that for donors based on their height and weight and sex,
this algorithm was developed to prevent loss of more than 15 percent of
somebody's blood volume with standard blood donation, and it was predicted to
prevent about 16 percent of these vasovagal-type reactions, but deferring, or not allowing some of the lightweights to donate in this age group, and this was really tolerable, or this wasn’t a huge effect.

However it wasn't predicted to have -- it was only predicted to prevent about 20 percent, but even that would be an improvement. If you could prevent one in five reactions, that would be a huge improvement, and of course the hope was that it would prevent the more serious syncope and injuries from syncope.

This shows the data. So it compared a baseline period in these years -- 2005 to 2007 -- so this shows the reaction rate for 16, 17, 18, 19, and 20-year-olds. The interventions were only done for young donors, so nothing changed for 19- and 20-year-old donors, they just serve as an internal comparison.

But you can see in the baseline years, for 16-year-olds, the rate of reactions was up around 10-11 percent. 2008 was a transition year. 2009 was when all of the regions -- all 36 regions in the Red Cross had implemented the full program, and had implemented the height and weight criteria most importantly that prevented donors from losing 15 percent of their blood volume, and you can see a significant reduction, even though 16-year-olds still have a higher rate than the older donors.

Looking at taking a deep dive into this to look at the types of reactions, this table shows the rate of reactions for 16-year-olds, 17- and 18-year-olds, for the pre-faint symptomatic reactions, loss of consciousness, and injury during the baseline period and the full implementation period, and this was a significant reduction, from 10.5 percent -- this is per 10,000 -- but this is 10.5 percent to 7.3 percent of 16-year-olds had these reactions, and this was a
significant reduction that was actually maintained, although it’s creeping up
again, maintained in 2010, a follow-up year, of 20 percent.

So it was pretty much seen for 16, 17, and 18-year-olds, pretty much
along what was predicted from what it would do. There was an inconsistent effect
on loss of consciousness, no significant change in two of the age groups, but in
the 16-year-olds, unfortunately this wasn’t consistent over the years, and even
though this study was certainly big enough to see a difference if there was one,
there was no difference in the rate of injuries at high school drives. So this study
had more than 100,000 16-year-olds, it was big enough to see a difference if there
was one, but no study has shown a decrease in injury among young donors.

One of the interventions, and you’ll hear more about this by
speakers that follow me, was water, having donors drink 16 ounces of water
before the donation, and in the study it was difficult to tease out -- actually
couldn’t tease out individual benefit of some of the interventions, but there was a
survey, and this looked at a subset of survey responses -- overall there was no
benefit in the very practical, pragmatic, this is not randomized, this is real-world,
overall there wasn’t an effect, and compliance was an issue. Only about half of the
kids drank the water. But in the subgroup of female first-time donors with 8,000
responses, there was a trend that water might prevent reactions, decreasing the
rate from about 11 percent to 9 percent.

So I want to leave you with this big picture. The overall effect of the
selection criteria. For the symptomatic reactions, the pre-faint reactions, there
was a significant decrease, and again this is an important one, but a relatively
small one, with the rate going from 9 percent to 7 percent, it is a 20 percent
reduction. There wasn’t a consistent decrease in syncope or loss of consciousness,
and no effect on injury.

So just to leave you with if over a million donors, if there are over a million 16- and 17-year-old donors, and this is the rate of complications, that means that about 4,000 donors will lose consciousness at high school drives and about 600 will sustain injuries, and what injuries am I talking about?

Usually it's injuries from falling, so it's head injury, lacerations, cuts, dental injuries, and in the JAMA study there was a broken jaw.

The speakers that come after me, you will hear Dr. Kamel talk about the BSI study, which is just shown on this, because these were both not randomized studies, but again, real-world studies of different height and weight criteria for total blood volume to prevent loss of 15 percent of a donor's blood volume, and both showed benefit and specifically benefit to 16-year-olds.

The other interventions you'll hear about in randomized studies, so depending on the outcome, also demonstrate benefit, and today's speakers will address muscle tension and water. So these will be covered more in the speakers who follow me.

What about automated red cell collections? This is not an apples-to-apples comparison. This is a very apples-to-oranges comparison. So this compares -- this is the reaction curve again with whole blood donation, and it compares it to the reaction curve. High school donors can also give double red cell donations if they choose. The point here is that from -- the view from the plane, the view from high altitude -- this doesn't look like a ski slope.

The total reaction rate in young donors who give two-unit red cells, the immediate reaction rate is blunted here, and of course that's because donors are selected differently. They have to be bigger. They have to have a higher
hematocrit. They get fluid replacement during the automated collection. So this is a very crude comparison, but oftentimes parents are concerned about automated collections, but from an immediate reaction perspective young donors are actually less likely to have immediate reactions or vasovagal-type reactions after a two-unit red cell donation than a whole blood donation.

In conclusion, lowering the donation age to 16 years in many states has resulted in more donations from young donors, despite decreasing collections in the last five years. The approach to parental consent for 16- to 17-year-old donors varies in different states and sometimes among different blood centers in the same state, for voluntary blood donation.

Conclusions about risks. Young 16- and 17-year-old donors are at the highest risk of adverse reactions. For syncope or fainting it's about 4 per 1,000, and again with the million donations, that's about 4,000 faints at high school drives. And for injury, about .6 per 1,000 donations, so about 400 injuries, back-of-the-envelope calculation.

The odds that a 16- or 17-year-old will experience a serious injury after whole blood donation is two-and-a-half-fold higher than an 18- or 19-year-old, and fourteen-fold higher than adults 20 or older.

In this large sort of operational trial, the selection criteria for estimated blood volume to prevent loss of more than 15 percent total blood volume decreased symptomatic reactions by about 20 percent, with the effect most evident among the youngest donors, but it had no consistent effect on the rates of syncope or loss of consciousness or related injury. No study has shown a decrease in related injuries.

Other interventions to decrease immediate reactions demonstrated
limited success in practice in this observational study.

Thank you.

DR. LEITMAN: Thank you very much, Dr. Eder.

The next speaker is Dr. Hany Kamel, from Blood Systems, talking about their experience with mitigation strategies.

DR. KAMEL: Thank you very much for the invitation. Maybe I'll start that the best strategies for reducing the instances of syncopal reaction remain uncertain, so I don't want to raise any expectations that we found a solution. And really we don't fully understand the pathophysiology of vasovagal reaction during and after blood donations.

Having said that, this is what I'll try to cover today: review factors predictive of vasovagal reactions, describe interventions designed to reduce vasovagal reactions, list physiologic strategies to prevent fainting responses during and after whole blood donations, and share some outcomes of interventions.

A few background slides. Blood donation safe in our five-year database of more than 3.6 million donations, you'll see that we had 48,000 vasovagal events, 7,800 loss of consciousness, and 500 injuries. In perspective, this is per 10,000 donations, 134 vasovagal reactions, 22 per 10,000 loss of consciousness, and 1.4 per 10,000 injuries.

Things are a bit worse for young first-time donors. These rates are three times higher in that young first-time donors. But I'd like to point that 1.4
per 10,000, there are quite few number of blood centers that their annual
collection is in ten- or twenty-thousands, so they may not see too many injuries.
One or two per year. Ninety-five percent of injuries are associated with loss of
consciousness.

    Looking at young first-time donors, we always think of young
donors as healthy, so I thought to give you some background information on
them. Half are white, 35 percent are Hispanics, the majority are in high school
and 25 percent in college. That’s consistent with their ages. Seventy percent of
them donate at blood drives. Ninety-five percent of female first-time donors
donate whole blood, but almost one-third of young male donors donate double
red cells. And in terms of donors with blood volume greater than 4 liters, virtually
all males have blood volume greater than four, but less than half of the young
girls’ blood volume greater than 4 liters.

    And as much as we think they are healthy, you’ll see -- the red is for
female, the blue bar is for males -- this is the prevalence of prehypertension,
overweight, and obesity. Stage one or two hypertension. We test all donors for
cholesterol, and hypercholesterolemia is higher in females compared to males,
and again, these are in their first donation, we find 6 percent of young females are
anemic -- that’s hemoglobin less than 12 -- and 3 percent of males are anemic,
hemoglobin less than 13.

    When we look at loss-of-consciousness rate per 10,000 stratified by
donor blood volume, you’ll see that 16-year-olds with blood volume of four liters,
that’s the green bar, their loss-of-consciousness rate is equal to an 18-years-old
donor with blood volume of 3.5 liters to 3.999, so essentially you can see there's
500 mL differential in reaction rate between 16- and 18-years-old.
Finally, in introduction, mechanisms underlying vasovagal reactions, there are three basic physiology. There's psychological stress, fear of needles, pain, and sight of blood, hypovolemia, as we take 500 mL in a donation, and orthostatic effects superimposed on the hypovolemic state.

In the next few slides, I will review the predictive factors of reactions and our first attempt to implement an intervention. In this study we looked at faint and pre-faint reactions in whole blood donors, and essentially the strongest predictive factor was small blood volume, less than 3,500 compared to a blood volume of 4,775 mL. That ratio was 2.8. In terms of age, 17- to 18-years-old compared to 25 to 65, that ratio was 2.75, and the 19 to 24 were at risk as well, with a ratio of 2.4.

Again this is in multivariable regression analysis. First-time donors had more than double the risk of repeat donors, and female donors were marginally significant, 1.2 compared to male donors. With that in mind, in this same study we plotted donor age against donor experience on top, gender in the middle, and blood volume in the bottom panel, and as you can see it is almost up to age 30 where things to start to flatten out. Always again first-time donor always have had higher reaction rates when compared to first-time donor.

And female consistently had rates than male donors. And smaller blood volume, you see the gradation from less than 35 -- 36 to 4,000 -- and so forth. But as I mentioned, the rates started to flatten out at age 30. When we developed our intervention we decided to go with age younger than 23 years.

Second, we looked at delayed adverse reactions, and again the factors predictive of a delayed reaction, and defined delayed in this study as 15 minutes or more. So if the reaction started 16 minutes or later we defined that as
delayed reactions. Again, small blood volume had almost four times the risk of delayed reactions. You will notice here that female became a significant risk, almost three times higher than in male donors to have a reaction starting greater than 15 minutes. Young donor as well had almost 2.5 other issue, first-time and repeat still was a factor.

What was important in this study is that compared to onsite reactions, significantly higher proportion of offsite reactions were classified as severe, 22 percent compared to 14, and the frequency of prolonged loss of consciousness, falls, head trauma, were higher in donors having offsite reactions, and offsite reactions required medical care nearly three times more often than onsite reactions.

I will skip this slide, because it is AABB policy has been discussed twice.

So we designed our first intervention to limit donations in young donors and again we were talking about younger than 23. If their blood volume was less than 3,500 were deferred. We encouraged applied muscle tension during donations and we provided donors with 500 mL of water for the donor to drink within 30 minutes before donations.

In addition, in terms of high school drives, we provided patient sessions for school nurses. We developed instruction manual for school nurses. We developed discharge sheet for high school reactions. When reaction happened for the student, we informed the school nurse just in case if we leave when a student had reactions, they are aware and we insist to inform their parents of reaction when student reacts.

To examine how successful that intervention was, we compared
donations 12 months before in 2007 and 12 months after the intervention, and
we had 99,000 donors before and 130,000 after.

Dr. Eder just showed the overall vasovagal reaction rate was
reduced by 24 percent, and the loss of conscious rate was reduced by 22 percent,
and the rates were significantly reduced in all phases of the donation. I will get
into more details, but during the donor being on the donation bed or shortly after
and offsite, all these reactions were reduced after the intervention.

We obviously noted limitation to this study, implementing the
minimum blood volume was very successful, because we control it by our staff
and it had no impact on availability. We did not have a specific requirement or
SOPs. So it has been encouragement. We provide the water and so forth. But
most significant is staff and donor engagement. As I mentioned, during selection
we were very successful in controlling but donor accepted or complied with pre-
donation hydration more frequently than AMT somehow. We couldn't drive the
message of AMT to donor, for donors to practice.

Now after realizing that, we studied the time course of blood
donations as well as reactions, and the very far left, the small band, these are
people who lost consciousness even before we put a needle in their arm. So that is
definitely psychological in nature.

But as blood donation progressed, loss of consciousness goes up to
the first peak at 0. -- and I will explain that in a minute -- then after removing the
needle, we have two peaks at 5 and 9, and the red line is onsite reactions, and the
blue line is offsite reactions. As you can see, reaction rate tapers after maybe 17 to
20 minutes, but we have had reactions reported to us up to 4 hours after
donations.
The bar graph on the right essentially gives the overall loss of consciousness across time course. In period 1, the rate is very, very low. The highest reaction happens in period 3A, which as you can see in the graph, this is after the donor leaves the donor chair, but they are still on the blood drive site.

This is another way to look at the three periods. Period 1 and period 3, the donor is ambulatory, moving from one place to another, but during period 2, they are lying down, recumbent, or similarly semi-recumbent position donor bed or chair. Period 2 starts with venipuncture up to 4 minutes after end of phlebotomy, and period 3 starts more than 4 minutes after end of phlebotomy.

We divided this into two subgroups, 3A onsite and 3B offsite.

Again, the 4 minute after we took the needle out, we asked the donor to sit down on the donor bed, dangle your feet a little bit, before we ask you to stand up and go to the refreshment area.

We have done multivariable regression analysis again to identify factors associated with loss of consciousness in each of these periods, and granted, you will see young age as a predictor in all phases or all periods, but for different degrees.

The number in parentheses are other issue, compared to a reference factor variable that we are looking at. So in period 1, difference young age was highly significant predictor, and first time as well. Period 2, low blood volume was first, and same in 3A and 3B, but in the most significant thing in 3B was female gender being a significant factor as well.

Talk quickly about injuries. Again, if somebody lose consciousness on the donor bed, the likelihood of injury is low compared to if someone lose consciousness after they stand up. Looking at the same data different way, as you
can see again, losing consciousness offsite has the highest risk of injury on the far right side.

So to recap, injury most associated with loss of consciousness after standing up, 60 percent of faints occurred in period 3, 84 percent of injury resulted from reactions starting in period 3. Fainting while upright was mostly associated with small blood volume, female gender, and young age, which essentially tells us how to -- what to do with if we want to develop a new intervention based on this review where different strategies were reviewed. We developed our new SOPs, applied muscle tension, blood volume restoration, sodium and fluid, and information update, minor donor permit, discharge sheet.

Muscle tension, as you see, it works almost instantaneously. It takes 2 to 3 seconds before you see increase in blood pressure, and based on that, we advise our donors to do it at any time during donation or whenever they feel dizzy, but particularly during, at the end of the donation, and up to an hour after donations.

Once a person stands up, almost 500 mL pools down in the lower limbs, and just happens fast. So on top of 500 donation, 500 mL pools to the lower limbs, essentially the donor is 1 liter short in functional circulation, muscle lower, whole body muscle tensing, or lower body muscle tensing, push the blood to the thorax and improve brain perfusion. That was nicely shown by a study by Dr. France's group where muscle tension improves cerebral oxygenation.

In terms of blood volume restoration, obviously compared to placebo, individual on salt, their plasma volume increased and their time to presyncope was delayed by 10 minutes.

Most recently, a study from the French hemovigilance compared
salt and water versus water alone, and essentially isotone solution showed improvement in the post-donation period offsite, but did not show much difference during or post-donation onsite.

Our second intervention, as we mentioned, we formalized muscle tensing and plasma restoration, but more than that in the minor donor permit, we gave specific instruction, written to the student what do they need to do and towards their parents, we asked them to on the day before make sure that they increased their sodium intake and on the day of donation to make sure that their student listen to our instruction and explain what our staff will do.

During donation, we look, essentially at distraction, but more importantly, the AMT, we teach the donor how and when to perform, and give a bottle of fluids. After donation, again, the goal is to give the donor 1,000 milligrams sodium. We give specific examples again how to achieve that, and in the thank you form that we hand each donor at the time they leave, instructions to stay for 15 minutes and what to do for the rest of the day. Again, at the bottom, if you start to feel dizzy, that's what you really need to know, to do, lie down flat, do muscle tensing, don't stand up suddenly, don't lean over.

Was that successful? Here we see loss of conscious rate in 18 years old donor in 2007 before any intervention, and on the right we see 16-year-old donor have very much similar loss of conscious rate as 18-year-old donor before any intervention, and for the 18-year-old donor there was significant reduction in loss of consciousness after the second intervention.

DR. LEITMAN: Dr. Kamel, unfortunately the time is up.

DR. KAMEL: One more slide. So based on the French study, this is the last issue of Transfusion, Dr. Levine proposed an improvement to include
glucose to enhance the absorption of sodium. This is our pictorial for period 3, what happens, what are the physiology behind it, but also interactions.

In conclusion, blood donation is safe. However, fainting and injury after blood donation in the younger donors, and we define that as 16 to 22, as a concern, that the rates are higher. The best strategies remain uncertain. In observational studies, interventions reduce reaction, but did not prevent their occurrence in known high-risk groups.

The physiologic mechanism to reduce risk. We think that selection criteria was effective. AMT was effective in combating orthostatic and emotional vasovagal reactions, plasma volume was effective in both patient sitting and in randomized controlled trials in donors, there may be smaller studies, but as they work in patients, there is no reason to think that they won't work.

But AMT and plasma volume restoration, restoration require compliance by the donors. Similar to type II diabetes, medicine by itself will not work. Diet and exercise are important, similar in vasovagal reactions and donor compliance with AMT and volume replacements will be essential for successful intervention.

Thank you very much.

DR. LEITMAN: Thank you very much.

The next speaker is Dr. Christopher France, speaking again on predicting and preventing syncopal and pre-syncopal reactions among younger blood donors.

Predicting and Preventing Syncopal and Pre-Syncopal Reactions among Young Donors, Christopher France, PhD, Ohio University
DR. FRANCE: Thank you very much. I appreciate the invitation to come present this work. There’s going to be some overlap here with what Dr. Kamel has spoken about, as well as Dr. Eder, and I will try to minimize that overlap for everybody.

To start with, we are focusing on faint and pre-faint reactions, as has been described. These are the most common types of complications that occur during blood collections. Another piece of information that's important to know, and that will be more important later on in my presentation here, is that the perception of risk of these reactions is way overestimated by young donors. If you look here it shows that 87 percent of young adults -- this is up to 22 years of ages -- will overestimate the likelihood of having these reactions if they are to give blood. And this is true of both nondonors and donors alike. Donors -- people who have given blood before at this age -- they think about 40 percent -- tend to think about 39 percent of people are having these reactions. Non-donors think it's 44 percent. So they're way overestimating the risk, and I think that's going to be pertinent when I talk about fear a little bit later.

We've seen this already, that fainting reactions in fact are quite uncommon, although as you look at faint and pre-faint reactions they increase in risk as you look at different kinds of risk factors. In addition to being associated with increased risk of fainting, young donors -- being young is associated with increase of injury, as we've been told. This graph I think illustrates that in a really quick picture that there's something unusual here, where a young donor, if they faint, is more likely to become injured and the exact reason for that is not clear.

But I think we can probably postulate with some combination of not having had this kind of experience before, not knowing how to prepare or cope
for such an experience. But one thing I want to make abundantly clear, given that
the reason why I do this kind of work is that these faint and pre-faint reactions
are not just associated with injury -- they are, at a very low rate, fortunately -- but
they're associated at a pretty high rate with decreased satisfaction with donation,
and what they do is, in turn, they decrease folks from wanting to come back.
So we've been talking earlier today about how important these
young donors are to our donor pool, maintaining our donor pool. These kinds of
reactions really decrease their willingness to keep coming back.
Dr. Kamel was focusing on this issue, the fact that these reactions
don't occur uniformly at one point in time during the donation process. They
vary, so 1.4 percent of them are happening pre-donation, just somebody waiting
to donate, so clearly psychological factors are at play there. When they're in the
chair it's a little higher, around needle removal it's higher, and onsite post-
donation gets the highest rate, about 49 percent. Then 10 percent of the reactions
are happening when people leave the site, which is important because that's when
it's greatest risk for injury. There's nobody's supervising.
The other point that was made is there are different types of
underlying factors that are associated with these reactions at different time points
during the donation process. And psychological factors are predominant of
course pre-donation. They're also very high when somebody's in the donation
chair, psychological factors are going to be the predominant reason why
somebody is reacting at that time point.
However, the reduction in blood volume is coming into play as you
get further into the donation process. When you're talking about off-site -- on-site
post-donation and off-site post-donation reactions, it's presumably physiological
factors that are most likely to be associated with those reactions. Both reduction in blood volume and the orthostatic stress associated with the standing that happens post-donation.

And the result of that is that the interventions that one might consider to try and address these reactions is going to differ, depending on what point in the donation process you're trying to influence, and I'm going to talk about these a little bit. So I'm going to talk about the muscle tensing techniques and the literature that relates to that, what we have so far. Then I'm going to talk about information on fluid loading or hydration, attempts to reduce reactions. And then lastly I'll talk about education and donor coping strategies, and specifically the use of distraction to try and help donors when they're having these reactions early on or during -- while they're in the chair, having blood drawn.

So I'm going to show you a tabular form -- I've put up all of the RCTs that are associated with applied muscle tensing. These are all of the RCTs that have been done to date, and on the right column is whether overall the authors concluded that these interventions were successful in reducing reactions.

And what you can see is these are mostly green, which suggests that they were somewhat effective, but you can also see in parentheses there's kind of an asterisk associated with this. So sometimes there effective for all the donors of a study, sometimes they're only effective within subgroups of the donors, for example, female donors in the sample, or novice donors in the sample, and there's one study there that shows -- it's actually one component of a study -- that showed there was not a significant effect, and that's actually instructive.

This is a dismantling study, where they looked at the effects of
muscle contraction in different parts of the body. So this was looking at upper
arms only. If the donor is asked to tense the upper arms only, it’s not really
restoring blood flow very much. It's not increasing cerebral oxygenation, and
therefore it's not surprising it doesn't have an effect.

As we also heard about, there's been some very largescale studies in
terms of looking at the effects within the American Red Cross system, and BSI,
and these studies on the whole have concluded when you combine a number of
different types of approaches, you can get a significant reduction in reactions.
And that is encouraging, but these studies also have significant limitations. So
you can see that on the bottom.

These are not randomized controlled trials. The one -- the biggest
things from my perspective is that there's good data that -- the interventionists --
the people that are trying to teach this were reluctant to do so in the BSI study.
The staff was reluctant to teach the donors muscle tensing, and if you can
imagine what effect the professionals not wanting to teach the technique or being
reluctant to teach the technique has on adherence or compliance, you get a good
sense of why these might not be the optimum intervention strategies.

Also, as was reported in both studies, inconsistent dosing was in
one study. And only 52 percent of the donors took the water in the other study.

So what I'm going to do is just kind of just summarize those, tell
you what I think we know from these studies and what we don't know.

First, what do we know? We know that muscle tensing can reduce
reactions, at least within higher-risk groups in the sample. We also know, from a
physiological perspective, that when done properly this technique will increase
blood pressure and cerebral oxygenations, so will offset the main contributor of
these kind of reactions.

But, we also know that adherence is a significant challenge. Getting someone to do this depends on the donor knowing why should I do this? The donors are going to be asking themselves why are you asking me to do this kind of unusual thing? And the staff needs to know why are we teaching them this?

And I've been to a number of situations where people are talking about using this technique, and I can tell you, they're doing it wrong. They're not doing the technique appropriately. So they're teaching the wrong technique, they don't have confidence in it, and their confidence is coming through to the donor.

So, I say all this because it's important I think that we not throw out the baby with the bathwater. We have a technique here that can work, but we haven't tested it optimally.

So what we don't know. Is it worthwhile to have all donors do this? I would say probably not. What is the optimal muscle tensing strategy? Well, it could be that you have people contract core muscles and the limbs, you might have them dynamic exercise, you might have them do isometric exercise. You could have them do it with the legs crossed, and these kinds of comparisons have been done in the physiological literature to see what would be the most effective way to do this, have not been done in the context of blood donation. So we haven't tried to optimize this strategy in the donation context.

Similarly, when should they do this? All of the RCTs that I talked about had them do it through the whole donation. You get in the chair, you start doing it, you keep doing it till you get up. That's pretty intensive. And you can see why maybe adherence goes down.

So maybe we only need to do it towards the end of the donation,
when they're at greatest risk for these reactions, as Dr. Kamel showed. Maybe we
only need to do it just about when they're standing up, or when they first stand
up. Maybe they should be doing that technique then. Maybe they should be doing
it PRN. Maybe they should be doing it as they feel symptoms. These are open
questions and I would argue that because they're open questions we really don't
have the answers that we need.

How much of the benefit is due to the physical effects of these
strategies versus psychological effects? Also an open question. These techniques
are distracting. If I ask you to tense your muscles every five seconds while you're
giving blood, clearly your attention is on tensing your muscles every five seconds
while giving blood. That's a distractor. It'll distract you from the needle, and a
whole bunch of other thoughts that you might have that might increase your risk
for reactions. And, psychologically the increased confidence. If you've convinced
somebody ahead of time appropriately that this is a useful intervention, then
they're more confident that they're going to have a good experience. That's true
for any medication, it would be true for an appropriate AMT intervention.

Turning my attention to fluid loading studies. This is the same kind
of graph that shows all the RCTs that have been done in the context of fluid
loading. If you look on the right-hand side, they're mostly green, which mostly
suggests that these studies are successful, but once again, they show that they're
sometimes more successful in particular subgroups, so amongst novice donors, or
amongst women. You can see some reds. These are studies that said this was not
effective. The van den Berg study stands out because it was a large study and
found no significant benefit.

However, it was in South African donors who were reacting at a
really low rate compared to North American donors, and therefore it was a challenging comparison to make a difference. And then the most recent one that Dr. Kamel talked about that just came out from French investigators found that water loading was marginally effective -- they got a .06 there -- there found that isotonic fluid was not effective when the person was in the phlebotomy process, but it was marginally effective when they got out of the chair and significant when they left the site, so reduced off-site reactions. And that makes sense from a physiological perspective about what an isotonic solution should be doing, enhancing blood volume, whereas straight water is producing a pressor effect, it's increasing vascular resistance. We need to pay attention once again to the mechanisms in these effects.

To summarize, again, what do we know? Fluid loading is associated with reduced reactions particularly among higher-risk subgroups. Again, adherence is a significant challenge. Donors don't know why they're doing it, and staff often don't know why they're encouraging it.

What we don't know. Again, is it worthwhile to have all donors do it? I'd say no. Probably best to be looking for high-risk donors. What's the optimum loading strategy? Again we don't really know. Presumably, based on the literature that we have so far, it should be loading them pretty close to the time of donation with straight water, about ten minutes before, but glucose-salt rehydration fluid should be offered post-donation. It might reduce reactions on- and offsite.

And again, I’ll come back to it -- we don't know if the benefit of this is coming from the physiological effects or if it's coming from the psychological effects.
So let me turn my attention now to the last part of this, the pre-
donation, the fear part of it. After all, I’m a psychologist. Why do we need to
prepare donors for this experience? Well, let me show you this to kind of give you
a sense of that. This is about a thousand college students. I asked them in one or
two words I want to tell you what feelings you have about blood donations, and
these -- they were asked this anonymously, online.

So they gave me their responses, and I turned the responses into a
word cloud. So word cloud here, it’s the frequency of the response is reflected in
the size of the word. So you asked these folks, these young adults, they say blood
donation makes them feel it's good, helpful, happy, generous, positive. You see
these words, they're very positive words.

You can see some negative words creeping in there, you can see
nervous creeping in there, if you look closely you can see painful creeping in, so I
asked them that, and on the whole they're very positive reactions towards
donation. Then I asked them as well, do you intend to donate in the next eight
weeks? Fifty-one percent of these folks said no. Had no intention of donating in
the next eight weeks.

I took their responses and turned it into a word cloud, and that's
their word cloud. This is a subsample of that original group. Scary, fear, anxiety,
pain, nervous, scared, you see also nausea, fainting, et cetera. Good and helpful,
positive words show up, but you can see these folks are -- on their mind are some
very negative kind of terms, a lot of it is fear.

So, maybe it's a problem, but, you might say to me, but is it a
problem for donors? Those were not necessarily donors. In fact they said they're
not going to donate. So maybe we don't have to worry. Is fear an issue amongst
We did this study at Community Blood Center of Kansas City. We got whole blood donors, and at the health screening we asked them one extra question. We asked them, how afraid are you of having blood drawn from your arm? And they were to respond from zero, not at all afraid, to four, extremely afraid, and they in fact what they did was at the health screening, they were given a piece of paper and pencil, and they were to answer this and put it in an envelope and give it back to the health screening person, because we don't want them to have to say orally I'm afraid, because they might not want to do that.

So we let them do it that way. And half the folks at the pre-donation we asked them that, and about half the folks we didn't ask. This is what the distribution of fear looks like in high school students, in this sample at least. Not all afraid, it's a little bit more than half, but a third of them is saying I'm somewhat afraid, and then the rest of it is moderately, very afraid, and extremely afraid. So you can see a little under a half of the donors who are appearing for a high school drive report some level of fear of the donation process.

Why do we care? This is the relationship between their fear report and their reactions. So whether they had a reaction coded by the phlebotomist -- you can see not at all afraid in this sample is about 11 percent -- it doubled the risk if they said they were somewhat afraid -- tripled it if they were moderately or very afraid -- and six times the risk if they reported they were extremely afraid.

So these fears are related to the risks for reactions. This graph -- you're not supposed to be able to see this, it's very small print, I know -- what it's just showing you is the individual predictors of these reactions. We've looked at the individual predictors. All the usual suspects are there, being a young donor, a
light donor, a low-estimated blood volume, being female, first-time donor --

those are all predictive.

But when you put them all into a logistic regression to see how they
predict together, three variables stay in that model. The first variable that goes
into that model is fear. Fear is the strongest predictor amongst all these
predictors. Estimated blood volume also stays in the model, and sex stays in the
model. But if you look when you're controlling for fear and you're controlling for
estimated blood volume, men are more likely to react than women.

I would also point out that we had a hard time getting a blood
collection agency to let us do this study. I asked many of them, and nobody
wanted to do this study, because they said to me you can't ask our donors about
fear, because you're going to cause them to have a reaction.

So I said, here's the design I want you to do. We're going to ask
some of them fear -- about their fear -- and some we won't. And we look and see
what the rate of reactions is. So this is the overall rate of reactions if we asked
about fear and if we didn't. That's not significantly different, and in fact it's a little
higher amongst those we didn't ask.

We did this same study with a community sample. These aren't high
school samples. So community sample. Once again, the strongest predictor of
reactions in the community sample, average age 45, lots of donations going on
here on average, was how afraid are you of having blood drawn from your arm.
The other predictors are still there, but they are not as strong as asking about
fear.

We did a longitudinal study where we treated people using applied
muscle tension and fluid loading, and these are the results looking at return
behavior amongst those donors. I'm going to highlight for you what I want you to see, which is in this predictive model, anxiety predicted increased needle pain. Those who were more anxious found the needle to be more painful. Those who found the needle to be more painful had more reactions. It's probably not surprising.

In turn, anxiety had a direct effect on intention. People who were more anxious didn't want to come back, and they were less likely to come back in terms of their behavior, and anxiety had an indirect effect on return behavior by flowing through reactions. So it increases reactions that decreases returns, and it also directly reduces return rates.

So what should we be doing to address fear? Well, onsite, please, let's ask the question. We should be asking donors how afraid are you of having blood drawn from your arm, and I would say we should follow that up. If they say -- if they give you anything but a zero, you should ask them and what is it you are afraid of? Are you afraid of the blood, the needles, pain, fainting? Because what we do will vary depending on what they say they are afraid of. So there's different interventions you can depending on what the fear is. I just have some listed there.

You can also prepare them ahead of the donation, and we have done that. So a number of years ago, we developed this coping brochure. It was a way to educate donors. Really we were focused on high school kids who had never given before, and what can you expect while you are donating, and what kind of strategies might you use to try to help reduce the risk of reactions? Because we knew that they were going to have risk for these fainting reactions.

Well, the brochures that existed at the time didn't talk about fainting reactions. So they sure couldn't talk about coping. Well, these kids know
about them. As I told you, they are overpredicting the risk of these reactions. So they know about them. If you see a blood donation in the media, almost always somebody is fainting, because it's dramatic. So that's what they think happens.

Anyway, so we have used this. We have developed this survey, this brochure, and what we found is if you teach these kids about the fact that there's reactions, but there's ways to cope, it reduces their anxiety. It increases their confidence and increases their intention to give blood. And these could be distributed in a very inexpensive way and we have developed them for the web, for the iPhones, for iPads, et cetera.

This is recently tested with the Australian Red Cross. We had a situation where we compared it against their standard brochure. We developed a coping brochure that talked about reactions, ways to cope with them, and when we distributed that in the context of where the mobile was at the University of Queensland and we either gave them our coping brochure or the standard Australian Red Cross brochure, and we found that our coping brochure significantly increased the donors' confidence, significantly increased their intention of giving, and significantly increased the likelihood of them actually turning out to donate in the next 30 days. The odds were 3.67 more likely to come out and donate, and again, the effect is flowing through confidence. They get the brochure, they feel more confident, they have higher retention and return.

Lastly, this is where we are now. So we know fear is important, and one thing I want to point out is unlike a lot of the stuff that we talked about, estimated blood volume, sex, height, weight, blood pressure, heart rate, BMI, you can't do anything about those things. Those donors are coming, and the best we can do is not let them come. We have to turn them away.
You can do something about fear. There are ways to intervene with fear. One of the things is we are living in a time now where we have an access to some really exciting ways to try to reduce fear amongst donors. So virtual reality technology offers a really neat way to reduce fear. This is an image from a virtual reality exposure to blood collection that we have developed. We have had people put a VR headset on and go there and learn to be in the mobile for the first time. We do a virtual exposure to the needle and complete with a -- you get a cold nail that's touched on your antecubital fossa. So you can feel what it must feel like.

But there are ways to try to take these individuals who are interested in donating, but they have some anxiety. You can help reduce their anxiety before they ever get there. You could also use this technique to teach them coping strategies.

And then lastly, onsite, one could also use this technology. What you are seeing here is a picture of something called SnowWorld. This is a VR technology that is used to help treat people who are getting debridement for wounds, burn wounds, and they put these VR headsets on. This shows an illustration of kids, but they do it for adults as well. You put it on. They play this game while they are going through the debridement procedure, which can be very painful procedure, to try to get this dressing changed all the time in burn units, and the reports of pain are significantly diminished. People who have gone through this, it makes the experience much less aversive. There's no reason why we couldn't do something similar for blood donors. The costs have come way down.

And I'll add one last piece of information, because some people are concerned that you might say, well, you're going to go completely obscure their
vision. The new technology, the HoloLens technology, allows you to superimpose on what's really going on and keep the rest of the world intact. So you can actually cover up or produce some game so that they're playing something where they can't see what's going on on their arm, but everything else they see is real.

I just throw that out there as an opportunity for you to mull over.

Thank you very much.

DR. LEITMAN: Thank you, Dr. France.

The final presentation of this session will be Mr. Spencer, and he'll talk about iron loss and iron deficiency in teenage donors, the CHILL study.

**Iron Loss/Deficiency in Teenage Donors: CHILL Study,**

**Bryan Spencer, MPH, American Red Cross**

MR. SPENCER: So thank you for the opportunity to present results from the CHILL study. This study has been a long time in the planning and the execution, and it's nice to have results to share.

We have already heard a lot about these two, first two bullet points, on the background, the association between repeat blood donation and iron depletion, and as Dr. Eder pointed out in her nice introduction, the increasing reliance in recent years of blood centers on younger donors and especially in the last several years as 17- and 18-year-olds have leveled off, a reliance on 16-year-olds, with evermore states, nearly all of the states, allowing donation by 16-year-olds.

We have heard results from many recent studies today of looking at the association between blood donation and iron depletion, but these have been limited to adults. So this really is the first study to present these results examined systematically in teen donors.
Well, why do we care? We know why we care, but it's clear and we heard some detail about how this is still an age group that is maturing physically. They are maturing neurologically. Their cognitive maturation is incomplete. They are undergoing myelination and adding muscle, and so they need iron. These are processes which require iron.

So this study had some pretty simple aims, as laid out at the bottom. Our hypothesis was that the prevalence of low iron stores would be higher in teen donors, 16, 17, 18 years of age, compared to donors 19 to 49, controlling for other factors, and we heard in the introduction why that might be the case. We expect that teens probably don't have quite as good a diet as adults do. They may be less likely -- in fact, some of the data showed earlier from Connecticut region of the American Red Cross suggests they probably are in fact quite a bit less likely -- to be supplementing with iron, and again, they are growing. They are undergoing maturation processes that require iron, and so we wanted to look at two different cutoffs of ferritin less than 12, absent iron stores, and less than 26 nanograms per mL, again correlating very closely with the definition from the REDS-II RISE study of iron deficiency erythropoiesis.

And our aims again were rather simple. We wanted to characterize the iron status of teen donors to determine the prevalence of absent iron stores in them as well as to assess the impact of blood donation on their iron status.

So there were logistical constraints at two of the REDS blood centers. So only two of the four REDS centers participated in CHILL. Their donors participated in CHILL. The data coordinating center RTI helped and is continuing to help with the statistical analysis, but with protocol development, and the ferritin testing was conducted at the central lab for the REDS-III
program blood systems research.

So the study population was limited to donors at high school drives during the last school year, 2015 to 2016, at these two REDS centers. We know that not 100 percent of all 16, 17, 18-year-old donors give in the high school setting, but we looked at the REDS donation database for historical information that we had been compiling throughout the REDS program, and we saw that pretty consistently roughly 90 percent of donors in that age group do give in that setting. So we are confident that whatever inferences might be derived from the study wouldn't be compromised by not collecting all 16, 17, 18-year-olds.

So we are in the high school setting. We defined an 8-week enrollment window at the start of the school year. So basically we turned on enrollment. We flipped a switch, and from that point until we closed that window, all donors at the high schools that held a drive during that period were eligible for the study, as long as they were between ages 16 and 49, and they made a successful donation.

We did not attempt to get blood from donors who were deferred for low hemoglobin or other reasons, nor from donors who had an incomplete donation because of a reaction or other reasons. So a successful donation was a necessary criterion, and from that we had to have a plasma sample on which we could conduct ferritin analysis, and much like Dr. Goldman's study in Canada, we were very successful with that.

So most of the successful donors, high 90 percentile, had an available sample. From these donors, all of their repeat donations later during the school year were also included in the study, and this study was of course reviewed and approved by the IRBs of both blood centers, the coordinating center and the
So at that first blood drive of the school year, enrollment was automatic for donors at those drives. There was no research staff on site. If they were age eligible, made a successful donation, they were included. We didn't draw any extra blood. We used operationally collected blood and processed that. We had enrollment target of about 3,000 samples per blood center during the study period, and based again on having mined historical data from the two sites within the REDS donation database, we expected that we would have about one returned donation for every two donors we enrolled, and again, we got blood samples from those donors when they came back at a second, third, or fourth blood drive during the school year.

At those follow-up drives, we only got samples from those who had appeared at the first drive, and we did the ferritin testing, not in real time, but after the last high school blood drive for each high school, and I want to note that the design we had of kind of frontloading it at the beginning of the school year, that led to our oversampling high schools with multiple blood drives per year, and I'll show a graph a little bit later on that quantifies that to some extent.

So once the -- we began the ferritin testing about midway through. Once those first few high schools that only hosted one blood drive had held that blood drive, and then continued it on a rolling basis through midsummer this year. We spent quite a bit of time trying to determine what we thought were appropriate alternate cutoffs for sending results to donors and what would be the appropriate messaging and ultimately reconciled that by deciding it was unquestionably ethical and appropriate to provide the ferritin results to every single donor whom we tested.
So that's what we decided to do. We of course did have to
differentiate the messaging on the basis of the results that we obtained, and that
led to our having language in the letter that referred to adequate iron stores at the
time they made their donation or low iron stores, and we used a cutoff 26
nanograms per mL for ferritin to make that determination. There was attendant
counseling that made reference to having a discussion with their clinician about
blood donation and iron supplementation and that recent research had shown
that iron supplementation was shown to help donors improve their iron stores.
We didn't tell them to take iron, but recommended a discussion
with their clinician. Some donors, as we will see in a moment, many donors, did
in fact have more than one sample tested. We provided the result from the more
recent one as being of greater relevance to their current status.
So the analyses that we have either undertaken or will undertake
will be simply -- we will look at this today -- describing what proportion of donors
have absent iron stores, ferritin less than 12, or less than 26 nanograms per mL,
to break that out by different demographic factors and donation frequency.
Ultimately we would like to have a reasonably good estimate of
what is the proportion of high school donors at these two sites at least that have
ferritins less than 26 or less than 12, but to do that we will have to standardize the
results that we are looking at today, and of course to understand the impact of
donation on our younger donors compared to adult controls, we're going to need
multivariable modeling and we won't -- we don't have these results yet. That's
still in the works.
So I mentioned in the brief introduction this morning, we enrolled
4,265 donors, very evenly distributed across both genders. Again, as expected,
and also as expected with the large preponderance of 17-year-olds, of the two blood centers, only blood center Wisconsin enrolled 16. The state of Connecticut does not allow donation from 16-year-olds. So only 17- and 18-year-olds were enrolled there, and also as we expected, somewhat less than 15 percent of the subjects were in the control age range 19 to 49, and we see 1,954 return donations. So about that two to one ratio that we had projected.

We see here what was, again, the proportion of follow-up visits and how many of those represent second, third, fourth, fifth. So at a couple of Red Cross centers there were five blood drives between September and May, so a 9-month period, and some donors made donations at each of those blood drives.

At that first visit in September or October, two-thirds of the donors were first-time donors. Some were repeat. A little bit higher proportion of repeat blood donors at Wisconsin, most likely because they had a wider age range of eligible donors than Red Cross did.

And we see here the expected gradient of high to decreasing proportion of first-time donors as you go from the younger to older age range. So not all of the 16-year-olds were in fact first-timers. Only 80 percent, give or take, were first-time donors, and about half as many, at the 18-year-old range, pretty similar for the adult controls.

We connected the data from the CHILL donors to the donation database to see what was their prior donation frequency, for both the prior one year and two years, and unsurprisingly, it's not that great for the younger donors who haven't been eligible for very long, but not much difference between males and females, and in fact you see in the 18-year-olds not much difference between them and the adults.
So the older teens are donating at a frequency almost as great as the adults over the prior year. There’s a little bit of a difference over the prior two years, but still compared to the average donor, that’s a meaningful donation rate, bearing in mind that on the day they enrolled, they are all adding one to the numbers there. This is before adding the donation that got them in the study.

So we saw this histogram this morning. Again, the point showing that 40 percent or so of the donations in this group, 6,000-plus donations over a 9-month period, 85 percent of which are from the 16, 17, 18-year-olds, are either below 26 nanograms per mL ferritin or less than 12. So again, a large share of donors in this of donations from our younger donors represent an intermediate or advanced stage of iron depletion.

This slide is limited to the results from the 16, 17, 18-year-olds, and it shows the comparison by gender, females on the left, males on the right, between the distribution of ferritin values at their first visit. This would be those who are first-time and repeat donors mixed together, and the distribution at follow-on.

You can see for the males the curve shifts sharply to the left, but even more so for the females, that becomes a very tight distribution on the low end of the ferritin curve, and again, these are the results just from the teen donors showing over a 9-month period what the donation frequency that we observed does to their ferritin values.

We also saw this this morning. Again, showing that in the first-time donors on the top row, that younger donors are much more likely to have ferritin less than 26 than the older, than the adult controls, or ferritin less than 12, lower prevalence in male donors, unsurprisingly, but higher in them than in the males,
and we see a similar pattern on the bottom. Again, the models will help us tease out how much of that is donation frequency, but remember, the earlier slide that showed that at least over the prior 24 months, there is a difference in donation frequency between the teens and the adults. So this greater prevalence of ferritin less than 26 is not because they are donating more. They are in fact donating less.

We also saw this this morning that shows for first-time teen donors that for each age group, 16, 17, 18, and the adults, comparing CHILL average ferritin values to NHANES population values, the first-time donors look very similar to the population norms. So we are seeing low levels of ferritin, but based on NHANES, we were not surprised to see that. Those data have been out there. So this is the first time that it is being documented in blood donors, but what this is telling us is what we would have expected to see, just that they look like their counterparts in the population.

This slide mimics that which Dr. Eder showed, showing that the proportion of donations from teens has held steady. Her data stopped I think at 2013 from the NBCUS, but here we are seeing the results across all four REDS-III blood centers, and what is the collection of red cell components over the four-year period, and year one, two, three, and four correspond to mid-2012 to mid-2016. So it is very recent data, and like much of the rest of the industry, these blood centers are collecting less blood than previously while holding steady the share coming from high school donors. That means that while there has been a 20 percent decline overall, there's also has been a 20 percent decline in the high school donors, but we haven't reduced our reliance on them at all in a relative perspective.

So I mentioned the need to standardize these results to get an
estimate of ferritin less than 12, ferritin less than 26, and high school donors from these two sites. We know that ferritin, low ferritin in these donors, is not entirely caused by blood donation, because we see some low ferritin in first-time donors, but we expect that blood donation is contributing quite a bit to it. What we suspect but haven’t yet analyzed is the relationship between blood drive frequency at a high school -- so opportunity to donate -- and donation frequency by the donors themselves.

So the blue bars here represent -- this is Wisconsin on the left -- half of their high school sponsors hold one blood drive per year, but only 10 percent of the high schools that were part of this study held only one blood drive. That was true at the Red Cross as well, 50 percent and 10 percent. So we way under-sampled high schools that have only one blood drive, and to the extent that those with more blood drives have a greater donation frequency in the donors, which I expect we will find, then we are probably overestimating the proportion of low ferritin in high school donors overall within these two centers, but because we have all that data in the REDS database, we can standardize our estimates.

So to summarize, we have found that many teen donors at these two REDS-III blood centers have low ferritin levels. These, the average ferritin values of these first-time teen donors are equivalent however to population norms. Prevalence of iron deficiency is greater in the first-time teens compared to the adult control donors and the average ferritin values are lower in the first-time teens compared to the adult control donors.

We also see a prevalence of iron deficiency that is greater in the repeat teen donors compared to the adults and completion of the multivariable modeling will help us assess whether the impact of donating is any greater on
teen donors compared to adults.

So next the impact of donation on teen donors is not well understood, and it warrants further evaluation. What we are getting at and much of what has been discussed is the extent to which teens might be a potentially vulnerable population here, you can break that down many different ways. Are they more susceptible to having low iron at the point of collection, and we see from normal comparisons to NHANES that that is true.

We have not yet examined the extent to which donation might cause or extend or exacerbate iron depletion in these donors differentially compared to adults, and we have not addressed any of the ramifications in terms of cognitive function or fatigue or other manifestations of iron depletion. So all of that remains unexamined, but given the potential health risks from iron deficiency, we think that appropriate mitigation measures should be implemented.

So I would like to express appreciation to all of the investigators on this study. It took a lot of effort to get it developed and implemented.

That’s it. Thank you.

DR. LEITMAN: Thank you very much.

Okay, this session is now open to questions from the committee to the speakers, to Dr. Eder, Dr. Kamel, Dr. France, and Mr. Spencer.

Yes, Dr. Josephson?

DR. JOSEPHSON: I just have two questions for Dr. France. One is about the randomized controlled trials for the muscle tension. Just did I understand correctly that those studies were only done in 20-and-above-year-olds? They are only in adults? They were not done in the 16- to 18-year-olds, the
randomized controlled trials that you showed us?

DR. FRANCE: They are not done in 16- and 17-year-olds. They are done in college aged samples.

DR. JOSEPHSON: College age. Okay, so nothing has really been looked at in that age group, and I only asked because of the maybe physiologic difference.

The other question that I had was about the Australian intervention study, and you said that there was a decrease in fear with the -- a decrease with the coping brochure. Did you actually see a decrease, or has that not been analyzed yet of the reactions?

DR. FRANCE: It has not been analyzed yet.

DR. JOSEPHSON: But that is the next step is to look at whether there has been a decrease in reaction?

DR. FRANCE: Yes. We know who those people are, yes.

DR. JOSEPHSON: Okay, thank you.

DR. SIMON: I would like to ask Dr. Kamel and Bryan Spencer, have your organizations made any changes in the number of times per year or what is your policy in the number of times per year you go to a given high school?

DR. KAMEL: Not at Blood Systems, no. We have not implemented any limitation.

DR. SIMON: You can go as many times as -- go four or five times a year to a high school?

DR. KAMEL: We have not set any maximum limit.

DR. SPENCER: These results have been discussed and are going to continue to be discussed. I think that changes are forthcoming and exactly what
they are have yet to be determined. We didn't really discuss here double red cell
donation, but we know that those are carried out in the high school setting, not in
Connecticut, but that may be something in limiting donation frequency as also in
discussion.

DR. LERNER: May I ask maybe Dr. Spencer, why is it that the
United States has such a high proportion of its donations coming from such a
young group, when compared to like European donations?

DR. SPENCER: I think what we saw earlier showed that in Europe
you have to be 18 or older, so just --

DR. LERNER: Right, but even if you look at that age group from the
initial discussion, still even if you look at maybe more like 17, 18, it seems like
there's still a much greater proportion relative to other countries.

DR. SPENCER: Right. That's not my area of responsibility. So I
really can't say. I think there's a lot of enthusiasm at the high school level for
being a partner with the Red Cross. There's a lot of interest in the young donors
to help to make a meaningful gift and commitment to someone else.

We planned for a very sizable amount of feedback, calls from
donors and parents and clinician or two, based on sending a letter to everyone,
and anticipating and in fact finding that many of them did have low iron, but we
got very few, three in total, and the response that was loudest from those few
donors was don't keep me from donating.

So part of it is maybe coming from high schools and in part from
blood centers. But I think Anne has probably spent greater attention on this and
maybe can speak to the motivation.

DR. EDER: So first of all, you know, high school students are very
motivated, but the drive in 2007 occurred as I presented when the demand was increasing and it appeared that there was a margin. So in 2007, states started lowering the donation age, which high school drives are high yield and low cost, bottom line.

So in 2007 those collections, the total number of collections on high schools as I showed didn't increase, but the proportion from 16-year-olds did, and then as demand, as collections decreased, collections from younger donors decreased somewhat, but it's still about 10 percent. So that's where we are. But it has been 10 percent for a long time, even in the data from 19 -- the earliest survey to include that data I think was 2011.

DR. LERNER: I just wonder if we can increase the enthusiasm of older, perhaps less vulnerable donors.

DR. CABLE: The question was about with respect to Europe, and I think I can speak from the historical perspective of running a Connecticut blood program. When 17-year-olds were allowed to donate, in fact I testified to the Connecticut legislature to make a change in the judicial -- it wasn't -- it didn't go to the health committee. It went to the judiciary committee of the state legislature, to allow them to consent to donate.

When only 18-year-olds could give, it wasn't a very good place to go to get blood, high schools. As soon as 17-year-olds could give, it was a great place to give blood, from all the practical things, and ever since then, Connecticut went from, you know, almost no high school drives to 20 percent, in five years while I was leading the place.

A little concerned about the issues you are talking about, but they weren't in full force then, and the reason is you get all the high school students in
September. Every high school student in the state comes to the blood center.

They take tours of the blood center. They all get college applications ready. It's an event that you have never seen before, and then you have Bob's Discount Furniture giving ten high school students complete college scholarships for leading the most successful blood programs.

Those kinds of things, you cannot do in an adult population, and I don't think they worked when only 18-year-olds could give.

The 16-year-olds cannot give in Connecticut for one reason. I did not allow it, and I laid my body down and said it's not going to happen, and even to this day it hasn't happened, because I think the concerns about iron in the 16-year-olds were obviously more acute.

I have to say that in 1983 when I made this, the pediatric specialists at the Connecticut Medical Society thought this was a great thing and highly recommended 17-year-olds be allowed to donate blood. So it has been vetted against pediatric sensibilities, but I don't think we understood what we were doing. Just a historical perspective.

DR. JOFFE: For the offsite events, do we have -- or offsite injuries - do we have any data on how many of those involve situations where the donors could injure not only themselves but others, for example, driving a car, operating farm equipment?

DR. KAMEL: It would be anecdotal, so stories that we hear or claims that come as results, but not specific numbers or ratios or something like that. After all injuries again remain rare events. Oh, in the car accident, there's chance to injure one's self and others.

DR. EDER: So I can just add, I didn't present data, but when a
donor calls back and says that they had a reaction and sought outside medical
care, those data are collected by blood centers, as well as claims data. So those
data are collected, and your concern is well placed.

MR. TEMPLIN: My question is for Dr. France, or actually first a
comment. It seems like the distraction is a good technique that would help
alleviate some fear. As a person who has to inject himself, when I inject my
daughter, I use distraction techniques. With the needle, the fear of the needle or
the pain, the needle pain, is there any ability to use like any like EMLA cream or
any kind of cream prior to the injection of the needle to maybe alleviate some of
that fear of the pain?

And is there like some prophylactic maybe replacement of like
electrolytes prior to the donation, like I know if I get dehydrated, I take these
electrolyte pills, and it's like supposed to put electrolytes in the body, but also like
fluid replacement after the donation for like the most vulnerable of people that
are the youngest and maybe right at that weight limit. Would you be able to give
them like 250 mL or 500 mL bottle of saline, sodium chloride or something like
that? Would that be possible or would that need some sort of medical physician
onsite?

DR. FRANCE: Thank you. I'm going to let Dr. Eder answer the first
part of the question, because it really is kind of a medical and pragmatic question
what you can do onsite.

For the second one, there are different strategies that one might use
to enhance salt uptake and glucose as well would be helpful to restore volume. It's
probably best to start that as soon as possible after they get out of the chair. But
they should be continuing salty snacks for example to try to help restore fluid
One could do that 24 hours before they go to give blood, but it's unlikely. You got people who eat a lot of canned soup 24 hours before. It would also help them have more fluid on board when they get there, but that's not very reasonable.

DR. EDER: The first part of your question was about EMLA cream, cream or some, which is often used in the hospital setting, especially in young children. The problem is it takes time. So you would have to -- so it slows down, from a practical perspective, it takes about 20 minutes. So it's not operationally -- it's disruptive to the operations.

You also have to consider that you are collecting a unit of blood, and whatever you are doing to the skin has to be approved for that use. So it is often -- it has been considered, but it's really not feasible.

MR. TEMPLIN: I just know like for people with hemophilia, they use the EMLA cream prior to injecting with the IV. So I would just think that it would already be approved.

DR. EDER: Right, time, expense, and approval, really from a blood donor standpoint.

DR. LEITMAN: Thank you. I think Dr. Kiss wanted to respond to a previous question.

DR. KISS: Yeah, I just wanted to give a quick response to Dr. Simon's question about have we altered the frequency of blood donations. We have a plan on the books. We have not enacted it yet, but we did a year or two ago, before the results of CHILL came out, we did two a year. We were going to restrict our recruiters to twice a year, not drives, but donation frequencies, cap it
at twice a year in high schools, and with the CHILL data, we are looking at a third
donation, we would not deny the opportunity to donate, but we were going to do
ferritin testing then. Now with bringing the CHILL data to light, we are
considering doing ferritin testing before they even start, because the incidence is
high enough to warrant additional monitoring before they donate. That's our plan
on the books that we are considering.

DR. JOSEPHSON: I had another question for Bryan. It was about
the nurse practitioner and the -- when you decided to disclose to all of the donors
their ferritin level and you had the low and the adequate, who was the nurse
practitioner actually talking to? Was it a parent? Was it a child? Was it a doctor?

DR. SPENCER: You're saying when they called back? So we sent
results by mail. It was a heavily --

DR. JOSEPHSON: Was it sent to the parent? Was it sent to the
physician? Who is it sent to?

DR. SPENCER: It was sent to the child. So similar, we handled it
the same as infectious disease screening results that go to the child, not to the
parent.

DR. JOSEPHSON: So you don't have any idea whether they actually
received it. None of that is really --

DR. SPENCER: Well, we know how many came back, because of
change of address, which was a small proportion. The rest are assumed to have
been received, and again, the response was less than expected.

So with the tone of the letter, we had pediatric hematologists and
adult hematologists consulting with us on wordsmithing. We didn't have
experience with largescale notifications to donors of ferritin results, but we
wanted to strike an appropriate tone between this is something that matters and setting off alarm bells. So we recommended that they share it with their physician at their next visit. We gave some explanation of what could be the causes of low ferritin, including blood donation.

DR. JOSEPHSON: And then the nurse practitioners spoke to whomever called from wherever it was? Was that how it worked?

DR. SPENCER: So they called back to the research office and research staff including Dr. Cable were available to speak with them.

DR. ESCOBAR: Looking from a different perspective, we have heard from the morning and afternoon that there was a vulnerable population. The young and the females, they have all these problems. You know, they are iron deficient, they get more all the side effects. So what will be the impact of saying, okay, let's go out and start at 18, get rid of the teenagers or below 18. Certainly you're going to lose that 10 percent of donations. But at the same time, there's data showing that maybe that blood that is iron deficient is not going to be good. I mean, what is the impact in terms of cost and things that could really mean forward, if you decide to make a cut of higher than involving the 17- and 16-year-olds?

DR. LEITMAN: I think if they now currently occupy or compose 9 percent of the donors of units currently collected, the impact is huge. So the blood supply would not bear that without making it up somewhere else. So that would have to -- I'm speaking for some of the speakers, but that's not something you could just go ahead and do overnight.

Dr. Eder, do you want to comment on that?

DR. EDER: Your point is important, well taken. Again, we are --
those are the questions that the committee is to discuss. When the minimum
donation age was 17, back in 1997, I showed that there was an increase that didn't
rely on recruiting 16-year-olds, and you don't need to collect 15-year-olds in
California. So at some point you have to say too young, in my opinion.

But it did use to be 17, and that was when blood demand was
increasing every year, and so where do you look for additional donors? The
concern is, the argument is, well, if you get them to donate young, they become
committed donors, but the study that BEST did suggests that you don't see that if
you look over time. So you continue to recruit at high school drives because it's
high yield and low cost. You can collect a lot of units, but those kids aren't -- you
don't see them progressing in later years to continue to donate. So it's a concern,
from that perspective as well. That doesn't answer your question, but those are
the questions for the committee.

DR. LEITMAN: In fact, I can't remember if you presented that, Dr.
Eder, but there is a lull. There is a hiatus then in the college years, presumably
because there aren't active drives on campus, and because of other things going
on in the lives of subjects that age.

DR. EDER: You also have to look at where they are holding the
drives. So if you are not -- if you are recruiting high schools.

DR. LEITMAN: Dr. Lerner?

DR. LERNER: This is kind of what I was getting at in terms of
restricting it to a little older, such as you are saying, and again, why not go to
college campuses and put our enthusiasm there in terms of getting donors, and
also the need for blood apparently is falling. So I wonder if we still need to use
those particular kind of young donors.
DR. SIMON: I think we are in kind of a quandary. As one who has
been around a long time, I remember when the purpose of the high school drive
was to educate students about blood donation and hopefully recruit them into
lifelong donation, and then I think we have evolved into a situation where it's
been found, as Anne said, a very easy place to recruit and we have become overly
dependent. Certainly I think college drives are very common, but it's a population
that's not as nicely captive as -- because of the way campuses are set up. So it's a
little more difficult to get those numbers. So I think that's what we are seeing.

And unfortunately, our great opportunity when we talk about blood
need decreasing, it's now starting to go the other way, and with all the restrictions
related to the flaviviruses and travel and so forth, what I'm hearing from the
blood centers is we are now beginning to see a tightening of supply. So I think it
makes it a very difficult issue to consider.

DR. JOSEPHSON: Are we still asking questions to them, or are we
commenting now?

DR. LEITMAN: This should not be the commentary period,
although it seems -- this is questions for specifically for the speakers.

Dr. Chitlur?

DR. CHITLUR: There was -- I can't find the reference now. I
thought they said in some countries they restrict younger children to one
donation per year. Has there been any thought to implement such a practice so
that in the girls at least, so then you can that if it's a high school kid between 16
and 18, then the 16-year-old girl can donate only once a year? Maybe that would
somewhat mitigate the issue.

DR. LEITMAN: Dr. Kamel, did you want to comment?
DR. KAMEL: It is a comment in terms of what group is at risk. So when we defined young, it was younger than 23 years old in terms of reactions and loss of consciousness. I don't know about CHILL study again, we look at 16, 17, 18, then 19 and older. I wonder if we isolate 16 to 18, would 19 to 24, would it be at higher risk than greater than 24 years old again. So if we exclude the bottom group, maybe the next group will find out that they are at high risk as well, compared to adults 25 and older.

And Bryan, sorry, Bryan, do you have any plan to analyze 19 to 22 for instance, rather than lumping all 19 and above?

DR. SPENCER: As the data showed, our control group 19 to 49 was only 13 percent of the population. So we actually broke it out by 19, 20, 21, et cetera. There's not a lot, but we can look at it to see do we see gradations across that 16 to 22 age range.

DR. LEITMAN: What I am getting a sense for from the committee is that no one was really serving as an advocate for the group that's 16 and 17, or 15, 16, and 17, and when the professional group that should be their advocate, which are pediatricians, were asked, perhaps they didn't have the data. They were concerned, as they should be, but didn't have adequate data to say that there was something they should be more concerned about.

DR. DE MARIA: I am not sure this is a question for the speakers, but well, it probably is. Just to put this in context, finding in the course of testing donors a high rate of iron deficiency, is this something being addressed at a broader level and among pediatricians? It seems to me it's hard to interpret, because they are donors that might have been frequent donors, might be repeat donors.
So the curve is affected by the fact that they are donors, but even considering that, it seems like there's a high rate of iron deficiency in this population, and what we have heard about the cognitive and developmental implications of iron deficiency, we are talking about not drawing them, but what's going on sort of more globally?

DR. LEITMAN: That's a very compelling question. In the panel, we have pediatricians and pediatric hematologists. Can we ask any of them to respond to that?

DR. CHITLUR: Yes, there is some effort being put in this direction, especially in the females who are in the teenage group with iron deficiency. The thought process is that there's probably a mild underlying bleeding disorder leading to heavy menstrual bleeding, which is the most common cause of iron deficiency in this age group.

So a lot of education is being put into educating physicians who manage these patients to recognize this and to investigate for this reason, because dietary iron deficiency is very unusual at this age. It has to be something else, and it's usually heavy menstrual bleeding as the cause. So while there are efforts in that direction, I can't say that we have achieved what we need to.

DR. DE MARIA: There seems to be a higher rate in the males, as well. Is that -- is anybody looking for a --

DR. CHITLUR: We should be. There should be no reason for a boy over the age of four or five with a normal diet to be iron deficient. So they should be looking for GI blood loss or other reasons for it. There's I think in the males, there's a better recognition and I'm surprised at the incidence of low ferritin that was reported.
DR. LEITMAN: Mr. Templin?

MR. TEMPLIN: Well, males can also have von Willebrand's disease. So they could have an underlying undiagnosed bleeding disorder that may not be recognized, because they don't menstruate. So I just wanted to add that.

DR. STAPLETON: I am just curious and wonder if any of the speakers or panel have an explanation for the discrepancy. One of the things in our briefing documents was an article about iron deficiency and cognitive achievement, and the rates of iron deficiency are far lower than what we are seeing with the CHILL data, and I just am curious. I am looking at this and 12- to 16-year-old females, 7 percent, as opposed to 60, 70 percent in the CHILL data. Does anyone have an explanation for -- that was quite different, and they used the same sort of definitions of iron deficiency.

DR. LEITMAN: Mr. Spencer? This is a comparison of the NHANES data and the AIS and the iron-depleted and iron-deficient data.

MR. SPENCER: I think that 7 percent probably isn't referring to a cutoff of 26. If you look at NHANES data, again I think it's 2001 to 2002, and the way they are grouped, it's 16 to 19 I believe is published and the median, so 50th percentile in that age group of females is 26. So by definition there, half of them are iron deficient. It would be much less below 12.

DR. STAPLETON: I guess table 2 is confusing to me then, because it lists rates. I agree the cutoffs may be different, and that may explain a lot of it, but for boys 12 to 16 it was .8, females 7.2. That's perhaps pre-menarche, but for the females that might be part of it as well, but it's interesting.

MR. SPENCER: Right, it is probably based on the cutoff, and the valid comparison would be to the first-time donors, because once we have taken
one or more donations, then we have altered their iron balance.

DR. LEITMAN: I would like to close this part, the questions, and so we can continue in the comments unless it's a specific question for a specific speaker. One specific question?

MR. TEMPLIN: I just want to ask Dr. Spencer, it seems like once the individual is 16 years old, you don't send any information to the parents, but yet I'm going to soon have a 16-year-old son and he is still a child and he is still my responsibility. I'm still legally obligated to take care of his medical needs, and if you're sending information to him at the blood drive and he does have some infectious disease or some kind of other underlying illness, he may not bring it to the pediatrician's attention, and then the pediatrician is still going to be his pediatrician potentially up to the age of 21 if he continues to go to college and that pediatric office is willing to still see their patients.

So it just seems sort of crazy that I could have kids that have health issues and I may never even know about it, because they may not tell me. Is that some sort of HIPAA or privacy or why does your center do that?

DR. SPENCER: I understand that. I have children in that age range as well. As Dr. Eder pointed out, that is how things are run, and that's how we have to do it, and in the design of this particular study, we couldn't find a compelling reason why we would tell a teen only that, say, they are marker positive for HIV or hepatitis C, but we had to tell their parents if their ferritin was less than 26. We felt that what made sense, based on the existing practices, was to follow suit. It was reviewed by the IRB, which is established to protect donor and research subject rights and welfare, and they judged it to be an appropriate approach.
DR. LEITMAN: Thank you.

So let's take a break now. Let's limit it to a 15-minute break rather than 20 minutes, since we are about 15 minutes behind, and then we will have the open public hearing. Thank you.

(Brief recess.)

**Open Public Hearing**

DR. LEITMAN: It is time for the open public hearing and I am required to read this statement again so I will. Both the FDA and the public believe in a transparent process for information gathering and decision making to ensure such transparency at the open public hearing session at this advisory meeting.

The FDA believes it's 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 relationship you may have with a company or group that's likely to be impacted by the meeting's topic.

For example, the financial information may include the company 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 the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So we have one organization and speaker that's requested time to speak, and that is Dr. Lou Katz who will represent ABC, America's Blood Center.

DR. KATZ: So once again, I'm from ABC, I have no conflicts of
interest to declare. I hadn’t intended to show this, but it’s clear that some context is needed. This is a histogram of male blood donors from my former blood center, since I’m not at a blood center anymore, recent data, and there is an identical histogram for females and identical histograms from centers contributing to the ABC data warehouse.

So this is age of donors and number of donations, and as you can see, it's bimodal. That trough that starts after high school and extends into early middle-age is, we don’t know all the reasons for that. There are many. You’re at college, you’re busy, you're in the bar, you have a new family, you've got a new job, you haven't got time. We're not morons. We are trying to engage those age cohorts and spending a lot of time trying to engage them, but the bottom line is it's very, very difficult.

Then you get to this second mode and that mode is moving to the right as World War II and the early baby boomers are aging out of the donor base. So that's point one, about the histogram.

Now, point two is that somewhere in the range of 80 percent of the blood supply at this point is from organizations operating at negative margins. It's a whole different topic that I won't much get into, but we're losing money because of competition and all kinds of reasons.

By a mile and a half, the most efficient blood drives are at high schools. It's a billion kids, all in one place, essentially having a party, and it's the cheapest way we can get a unit of blood for the guy in the emergency room that just rolled his car and needs 35 units, like I did.

So it's not a thoughtless thing that this has happened. It's in order to maintain an adequate blood supply, we have to go where the donors are. I
suppose that's the blood banking corollary of Sutton's law. That's the context I wanted to give you.

DR. LEITMAN: What is on the Y-axis of the histogram?

DR. KATZ: Oh, that's number of donors, donations. This is a year's worth of data, and this is the number of donations according to age.

All right, so I'm not going to address iron deficiency. We've talked about that and the rest of my comments really have to do really with vagal reactions because that's the big issue. So by virtue of their inexperience, environmental, physiologic reasons, these young donors have vasovagal reactions at much higher rates than other age cohorts and that's been well established.

Most of the reactions are of no long-term significant health-wise, but they make the donors much less likely to come back for the next donation. So we're incredibly interested in having fewer of them. We're very much engaged and as you heard, the work that's being done is being done by the blood organizations to try and drive these rates down, because we need these donors to fill in the trough that you see on my histogram.

Given the tenuous state of the U.S. blood supply and particularly time-specific tenuous state following recent imposition of stricter hemoglobin requirements and vital sign requirements and whatnot and the final rule, the participation of these high school donors just keeps getting more and more important. They have less reasons to be told go away in general. They tend to qualify as donors at very high rates.

So accordingly, considerations of concern about adverse reactions across this critical group of donors demand a lot of caution, particularly when initiating a pattern of high school donation that we hope will reflect a future
pattern of excellent donation behavior across literally decades. It's about availability.

So our plea is that immediate initiatives focus on interventions that don't decrease the number of eligible donors. Don't tell us we can't draw 16-year-old donors. Tell us we have to figure out a way to mitigate the risk of these events.

Again, and this is virtually verbatim what I said before, professional responsibility, primum non nocere, not guidance and law and rule-making, is what should drive this. We need to do this because we ought to as physicians and blood bankers and we think that regulatory imperatives should await a better understanding of the best approaches to preventing reactions and any adverse effects on the adequacy of the blood supply.

Again, professional standards from organizations like AABB and CAP might help us all volunteer to do the right thing a little more quickly than we might otherwise. Unfulfilled need for blood across the country serves as our motivation to treat our donors as well as we can and prevent bad outcomes. My organization of blood community in general has a responsibility to do these innovations, implement them, and study their impact so that we can develop the best practices that we need in this case.

You can see that the active participation of ABC members, Blood Systems in particular, has been valuable in informing us as far as we've gone so far. There is a big mixture of donor and parental education, counseling at consent, and other physical interventions.

The impacts of formal fluid loading and fluid and electrolyte loading, dietary advice, applied muscle tension, distraction, adjustments to the environment in which these blood drives are held. For example, setting up your
beds so donor A doesn't see donor B get pale. Things as simple as that that we
need to formally evaluate and measure the impact of, so those adjustments,
restrictions on total blood volume should be characterized across many centers
and in many matrices of intervention and inform any regulation and standards
that are evolving.

If mitigation is important, once again, I make a plea, tell us what's
an acceptable rate. We're not going to make vasovagal reactions go away. So far
how do we have to push the rate down before everybody is a bit happier?

I'm into continuous quality improvements, but at the end of the
day, I need O negative red blood cells in the refrigerator at every trauma hospital
in the country. I have to have blood on the shelves to take care of people who
need it and with that, I will answer questions or disappear.

DR. SIMON: Do you have a slide like this for females?

DR. KATZ: I do and it is identical. I just hadn't planned to show it,
and I just wanted to show one. It's identical in terms of its -- and as is our data
from the data warehouse, which is a much bigger data set.

DR. LEITMAN: Is there anyone else in the audience who would like
to participate in the open public hearing? Yes, identify yourself, please.

MS. ALLENE CARR-GREER: Allene Carr-Greer and I work for
AABB and as you know, AABB does not have a prepared statement for this
section, but because it was mentioned a couple of times earlier today, we do have
the Donor Health and Safety Committee, and a new charge of that committee for
this year is to go back into the association bulletin that was mentioned as a part
of the topic summary for this topic.

It's eight years old, that association bulletin, and that committee
will be looking at those recommendations again, and to see what needs to be
done eight years later. I think that's important especially after what Dr. Katz has
just said. We all believe it's important for the blood centers, the hospital blood
banks, to be taking a strong look at this.

We believe it's a good way to make the changes that are necessary
and so we do have the committee, ABC, ARC, works on the AABB committees and
we'll be taking a look at it. So I help that's helpful to your discussions.

DR. LEITMAN: Thank you. I know Dr. Kamel wanted to add
something. Thank you.

DR. KAMEL: Hany Kamel from Blood Systems. In response to the
concern about iron deficiency in teenage, Blood Systems would implement in late
December this year a ferritin testing of all 16- to 18-year-olds, and essentially if
we identify low ferritin, that's regardless of donor hemoglobin.

So a low hemoglobin would trigger deferral 12 months for young
female donors with ferritin below 20, and 6 months' deferral for young men with
ferritin less than 30. These donors would be notified and copy of the letter would
go to their parents with specific instructions in terms of how to improve their iron
intake, in terms of what dose to take for how long. So this would implement in
late December in our centers that have a computer system that allows for that.

We have other affiliates with different computer systems. It will
give them longer, but essentially they will follow the same policy once they can
get their computer system developed in that direction.

DR. LEITMAN: Dr. Kamel, is that on every donation? A routine
ferritin screen will be done on a donation sample on every donor between the
ages of 16 to 18?
DR. KAMEL: That’s correct.

DR. LEITMAN: Thank you. Anyone else in the audience? Okay, I close the open public hearing session, and we continue now to the questions posed to us by CBER, which should be on the screen momentarily.

**Open Committee Discussion**

DR. LEITMAN: This is topic two, questions 1, 2, and 4-A are voting questions. So let’s go to 1. Does the available evidence indicate that adverse reactions and injuries after blood donation in teenage donors is a notable enough concern to require intervention? This question is open for comments by the committee members.

DR. DE MARIA: Could we have a more explicit definition of intervention in this context? What exactly does FDA mean by intervention? Are we saying that this severe enough to require some regulatory intervention, sufficient enough to require the kinds of interventions that are talked about in this discussion, or beyond?

DR. LEITMAN: To me, it meant implement a strategy to mitigate such adverse effects, but I will ask Dr. Epstein if that’s what we see here.

DR. EPSTEIN: I think you stated it correctly. Should we do something? Whether we have to be big R regulators to do it, or encourage, or simply review proposals from blood organizations, all of that is open, but the threshold question is is action needed?

MR. TEMPLIN: It seems since we are talking about pediatric patients, there could be some cooperation with the pediatrician. Maybe some education to the patient of his or her patient about, you’re 15 years old, you might
think about donating blood. If you're thinking about donating blood, maybe we can send you down to the LabQuest or wherever, LabCorp, the hospital or the doctor's office could do it right there, and just do a complete blood count, take some iron tests, and do that. That might be something that would help the blood centers to know what's going on to prevent future problems.

DR. LEITMAN: Let me give my answer to this question, just to make sure that I'm understanding what the panel is being asked to consider here. So the marked increase in simple vasovagals, loss of conscience vasovagals, and injuries, either during or after leaving the blood center, is very compelling to me and I'm not comfortable with it, and I don't think that we should be proceeding as we're doing without implementation and recommendations or guidance to implement strategies that have been shown to at least make a difference and decrease those risks.

We've heard that the decrease is on the order of 20 to 40 or 45 percent, I can't remember the number. So it's not even reducing it by half, but it's reducing it somewhat, which is the most we can do. But not to do anything, I think is wrong. That's my opinion.

DR. JOSEPHSON: I want to echo your opinion. I think I am in agreement with that. There was enough information presented that not only are there that many adverse reactions, but there are things that can be done, and that they should be in some way implemented as a strategy, both from what Dr. Katz said, but just in general, that we should be taking care of these hopefully future donors, but at least taking care of them in the sense that we're asking them to do something altruistic and if we can do something to make their experience better, we should be trying to do that.
DR. LEITMAN: Other comments? Dr. Simon?

DR. SIMON: Yeah, I mean, I think I agree with all of that and I just, as we've heard, I think the Red Cross, Blood Systems, other organizations have been working on this for several years and I think recognize the importance of this, so I would think it's something which there would be a fair amount of consensus.

DR. LEITMAN: That doesn't mean that we don't think more data, more studies should be done, but I think we have enough to say right now, based on what's published and what's known, we should do the best we can, and that should be a guidance or a policy that our standards-setting organizations advise us to do.

Can we vote on this? So the question is does the evidence indicate that adverse reactions and injuries in teenage donors after donation is notable enough to require intervention in the form of strategies to mitigate or decrease such events to the extent possible?

So your lights are shining. Vote yes, plus, no, negative, or abstain, zero. Please vote.

(Vote taken.)

LCDR EMERY: The committee has voted in majority. All yes. I will also read the names into the record. Dr. Brittenham, yes. Dr. Rabe, yes. Dr. DeMaria, yes. Dr. Stapleton, yes. Dr. Templin, yes. Dr. Escobar, yes. Dr. Leitman, yes. Dr. Joffe, yes. Dr. Ortel, yes. Dr. Lerner, yes. Dr. DeV, yes. Dr. Rees, yes. Dr. Sandberg, yes. Dr. Chitlur, yes. Dr. Murray-Kolb, yes.

DR. LEITMAN: There is a correction to that. The first yes was not Dr. Brittenham, but Dr. Josephson. Okay, moving onto the next question, two,
which is also a voting question and has two parts, A and B. Let's read it and see if
we want to continue to reformulate it or use it as it is.

Considering possible mechanisms to reduce the risk of adverse
reactions and injuries in blood donors, A, does the available evidence support
applying donor-specific selection criteria, such as an estimated blood volume of
less than 3,500 mL, as a means to mitigate donor reactions? B, do the available
data indicate that specific measures, such as applied muscle tension, to mitigate
reactions are effective?

Okay, discussion on question two.

DR. ESCOBAR: Well, when you say effective, you said there is some
improvement, but I don't think that it is substantial to say it is effective. I mean,
it's something that might help in some patients. It might not in everybody. So I
don't know if, are effective is the right way to put it.

DR. LEITMAN: To me, effective was a P value of less than 0.01. I
looked askance on 0.05, but less than 0.01 is pretty good for me. It's doing
something significant although the number of subjects in whom it prevents
reactions is not as high as we would wish. We all saw that data. So effective is that
it significantly decreases the incidence of those reactions.

DR. JOSEPHSON: I don't know about the muscle tension in the
kids. I really feel like we didn't see any evidence. We saw potential, so I think it's
a place we should research and see, but I'm not sure that we saw evidence except
for college kids and above, which are more like adults.

Then we're talking about applying that to a 16-year-old or even a 15-
year-old in some states, I mean, I just don't think that we saw that, but I don't
think we shouldn't try to look at that. So I don't know how, but I don't know, it's
effective in certain populations, maybe not this one.

MR. REES: The other thing I think, this is from a regulatory standpoint, is that I've had some discussions with some fellow committee members in that, do the younger-aged donors really follow what the recommendations are? As a regulatory agency, you're supposed to go out and assess a donor drive.

We assess donor centers throughout the state of New Jersey, or outlying states, of all different sizes and variables, and to this day you still tend to see -- I focus my surveyors to go to donor centers and to look, or to go to high school drives, because you see a lot of variability, and one of the things that we still tend to see is, I don't want to say it's a party atmosphere as almost Dr. Katz had said when you get these high school kids together, but you tend to see a very different mentality of these kids and so my concern would be, I'm looking at it as a regulator and the safety of those donors and/or the safety of those products that are going to go to centers to the hospitals.

But are those kids, having two of mine that are a little older, are they aware of the implications of what they're doing and did they really drink the water that they should have been? We tend to kind of see that intermingling and sometimes, as I think Dr. Sandberg and I were saying, it's their mental attitude. Do they really understand and are they at a level where even the interventions are going to work, are they going to be effective? Are they really taking it seriously? I'm not really sure and I'm not sold on that.

DR. LEITMAN: I think one can monitor whether they drink a 16-ounce water bottle, and you can tell them, no drink, no donation, and so they'd really have to lie. They understand lying. So you give that to them, we've done
this in our donor center, and you don't drink it, or the sport drink or whatever the
drink is, and it's done within minus 5 to minus 30 minutes.

They're under observation. They don't leave the center. So the
quicker they drink it, the quicker they can donate and the quicker they can leave.
So I think that's pretty straight forward. The muscle tension, so that's an
intervention that the stuff asks them to do under observation also, at least
initially.

There's something I actually didn't understand. In the Blood
Systems data, three interventions were made at the same time in this age group
and that was the selection criteria, 3,500 in male donors, less than 3,500 were
defferred. There was a water drink given within 0 to 30 minutes before donation,
and the muscle tension exercises were applied.

Then we saw this 20 to 45 percent decrease. It was a retrospective,
prospective study. So they were, I think the retrospective was collected
retrospectively, and the prospectively the intervention data. So we don't have the
ability to separate the effectiveness of either of those three, but cumulatively, they
made a difference that was significant. Is that what everybody understood?

MR. TEMPLIN: Would there be the ability when you're doing a
blood drive to extend the period of time that the individual would have to, like, sit
there, and drink their stuff, and then have their blood donated, and then stay
more afterwards?

Because they're already contained at the school, so they could go to
the gym or go to the auditorium and see a concert or listen to somebody speak,
and then you'd have them there under observation more to potentially prevent,
and then if they are potentially at that threshold for the estimated blood volume,
maybe think of some other approach to maybe replace some fluids or something for those folks, or just say, we appreciate you wanting to donate but come back in six months because you might be ten pounds heavier or two feet taller or whatever. You might have a little bit more blood volume.

It just seems, they're already contained, so it's not like they're coming to the fair and they're going to donate and they're going to go ride the rides. You can keep them a little bit longer. That might help out a little bit as well.

DR. LEITMAN: So it seems that that's part of the strategy that the blood center would implement. As you were talking, I was thinking the message could go out, you will spend at least 60 minutes here, because people think they can donate in 20 minutes, but if you're going to wait 15 to 30 minutes beforehand for the screening and for the drinking of the water bottle, and then 15 minutes afterwards, it takes 20 minutes to actually donate, and then 15 to 30 minutes to observe them afterwards, it's an hour at minimum.

So the message would always be from the time you arrive to the time you leave will always be at least 60 minutes and don't expect to do it -- so that might be one strategy to get them to stay.

MR. TEMPLIN: It scares me looking at Dr. Katz's documentation there. It's like 6,000 units of blood collected and as somebody who may need multiple units at any moment of my life, or my daughter, because of our hemophilia, it'd be nice to know that that 6,000 units wasn't taken out of a pool, and wasn't not available to me or to somebody who is an automobile accident, especially if there's that wall when the individuals go to college or go off to the military.

Especially if there's potential for the topic of tomorrow to be
discussed, Zika in the supply, we wouldn't want to limit any units not going into
the pool if there's a potential for people to be deferred because they end up
travelling to Orlando next month and get Zika virus.

DR. JOSEPHSON: Yeah, I was thinking, so I commented on B, but
on A, I do think donor-specific selection criteria to mitigate donor reactions is
important, and I think as we have smaller people, we should be thinking, and I
think it was the Red Cross data where they had kind of done the blood loss 15
percent.

I mean, we're pretty strict about it for our patients, let alone -- I
mean, all the pediatric patients should be looked at a little bit differently I think
than the adult patients because we don't really know how they're going to react.
So trying to be pretty strict about that I think is a better way to keep people in,
wanting to donate, and try to do that strategy, but also taking care of those
patients.

Then we can actually more accurately know how much blood we
actually took out and maybe that's something that would be transmitted as we do
the iron supplementation. I mean, it just seems that there needs to be more
attention detail in those kids, in those donors.

DR. LEITMAN: That is interesting. So the blood bags have
sufficient anticoagulant to collect as much as 500, but it doesn't have to be 500,
right? It could be less. It could be as low as, someone help me, 450, or what's the
minimum amount in a blood bag? So it could be 10 percent less.

DR. JOSEPHSON: It could be, and I think that also we're so
worried with sickle cell and other things about iron loading, and we are
monitoring how much we're giving, I really think that we need to be monitoring
how much we're taking and to be able to give that back. I think we could be
accurate about that.

DR. CHITLUR: In terms of the vasovagal syncope part, this is also
the age group that is just more susceptible to having this happen to them anyway.
The teenage girls and actually teenagers are just more susceptible to have
vasovagal syncope and I think I was trying to look up what was the incidence, and
they said 22 percent in the general population.

So I think what you're seeing here is sort of a reflection of the
higher incidence that you're seeing anyway in the general population, but that
doesn't mean that we shouldn't institute, that may be more reason for us to look
at this and pay more attention, like Dr. Josephson was saying, that since we've
identified, we know that this is the population at risk, we probably need to pay
more attention to try to see what we can do to mitigate that.

DR. LEITMAN: Additional comments? Seeing as I think we all feel
a little uncertain about how much weight to give to a single intervention, like
applied muscle tension or the 500-mL drink or the video that Dr. France was
showing, that one might advise blood centers to have policies established, to the
best of their knowledge of interpretation of the material they read, to have
policies to mitigate based on best available data, and they can choose what that is.

It could be selection of donors or deferral of donors whose EBV is
less than 3,500 plus anyone of several additional, all applied muscle tension, a
water drink beforehand, waiting for at least 20 minutes after donation,
something in addition or several things in addition, but they must have strategies,
not nothing.

Okay, it sounds like we're ready to vote. A, does the available
evidence support applying a donor-specific selection criteria? Well, this is such
as, so let's vote on such as. Let's vote on estimated volume less than 3,500 mL as
a means to mitigate donor reactions. Let's just vote on EBV. Yes, no, abstain.
Please vote.

(Vote taken.)
We were very impressed by your data.

LCDR EMERY: The committee has voted. I will read the individual
names. They have voted all yes.

Dr. Cassandra Josephson, yes. Dr. Rabe, yes. Dr. DeMaria, yes. Dr.
Stapleton, yes. Mr. Templin, yes. Dr. Escobar, yes. Dr. Leitman, yes. Dr. Ortel,
yes. Dr. Lerner, yes. Dr. DeVan, yes. Mr. Rees, yes. Dr. Sandberg, yes. Dr. Chitlur,
yes. Dr. Murray-Kolb, yes. Dr. Joffe, yes. That is 15 total for 2A and also 15 total
yeses for 1A, and there are 0 noes, 0 abstentions for either 1A or 2A.

DR. LEITMAN: Okay, for B, I am going to ask Dr. Epstein for a little
assistance in this. Do you want me to ask the committee how they feel about
specific measures that we've heard about, applied muscle tension, a 500-mL
beverage of some sort beforehand, a 500-mL beverage afterwards, showing
videos, or thinking about creating them?

DR. EPSTEIN: That would be helpful to us, yes, because if we
simply have the broad answer, then we don't know the specific sentiments of the
committee. So yes, but we highlighted applied muscle tension because we knew
we were going to have data presented on it.

I think how to use water loading and salt loading, there are so many
strata. Again, if the committee feels they can vote upon salt and fluid loading or
replacement, that would be helpful. But I think at a minimum, why don't we do
this, let’s get a vote on applied muscle tension and then just take comments on
other alternatives.

DR. LEITMAN: Thank you very much. So let’s vote on the question
exactly as it exists, but specifically for applied muscle tension. So please vote, yes,
no, or abstain.

DR. JOFFE: I’m sorry, I don’t understand. Are we just voting on
muscle tension?

DR. LEITMAN: Yes. Do the available data indicate that the specific
measure of applied muscle tension during or immediately after donation is
effective in mitigating reactions?

DR. RABE: Is that for the 16 to 18 age group?

DR. LEITMAN: The 16- to 18-year-olds, yes.

(Vote taken.)

LCDR EMERY: The committee has voted. I will read the names into
the record. Dr. Josephson is no. Dr. Rabe is no. Dr. DeMaria is yes. Dr. Stapleton
is yes. Mr. Templin is yes. Dr. Escobar is yes. Dr. Leitman is yes. Dr. Joffe is yes.
Dr. Ortel is no. Dr. Lerner is no. Dr. DeVan is yes. Dr. Rees is yes. Dr. Sandberg is
yes. Dr. Chitlur is yes. Dr. Murray-Kolb is abstain.

DR. LEITMAN: Okay, I am going to take chair prerogative and add
a C. That option C will have everything you see in B except in the parentheses,
there will be fluids/salt supplementation, and by this I mean a fluid beverage,
water or a sport beverage that’s high in salt, either immediately before or after or
both, or salt-containing snacks in addition. So it’s fluid plus or minus salt
replacement.

From the data that you saw presented today, is use of that measure
to mitigate reactions effective in this population?

  DR. EPSTEIN: If I might, Dr. Leitman, I think we heard data that
  water alone had a very different profile than salt or water with salt, so I am a little
  bit concerned about putting them all in one question. If we are going to parse it, I
  think we need to parse more.

  DR. LEITMAN: Okay, so we could we turn off the voting buttons?
  Some people may have already voted. Thank you. Let's rephrase it and just limit
  it to fluid.

  So we saw several fluids, I'm not sure we can differentiate. We saw
  water alone and we saw sports beverages. So I'm not sure I can differentiate
  between those. Most of what we saw, the vast majority, was given in the 5 to 30
  minutes before donation, not after donation.

  So that specific measure, a beverage of approximately 500 mL
  under observation within 5 to 30 minutes before donation.

  DR. ESCOBAR: But again, it comes to the word effective. I guess
  it's, have some effect, not necessarily everybody responded because that's why
  I'm having trouble here. When you say is it effective, meaning maybe nothing else
  needs to be done, that's what we're going to end up saying. So I would say it has
  some effect, I guess.

  DR. LEITMAN: I guess is it compellingly effective enough for you to
  feel that you would say it is effective? No? All right, say that again. How did you
  want to phrase that?

  DR. ESCOBAR: No, I'm just saying because of the word effective, to
  me, means that the majority of patients had a response. When I see the words, it
  is effective, meaning that maybe that's all I'm going to do and I don't need to do
anymore, because it sounds like that it works for most people.

But the data doesn't really show that it works for most people, it's just for some people, it works. So if that's how we want to word it, saying effective meaning it works for some people, then that's fine, but I'm just having trouble exactly with that, the way you're going to phrase it. When you say effective, is it really looking at statistically, or looking just clinically some patients didn't have a reaction, some others did? So I don't know.

DR. LEITMAN: So I would say it's statistically because if some responded and some didn't and there was no statistical significance, you haven't proved anything. I'm not sure, I don't remember if I saw enough data to suggest there was a statistically significant mitigation effect with water beverage alone. So I'm not sure I actually saw that data come by.

DR. CHITLUR: Because I agree with Dr. Escobar. I have the same question. The concern is that if I say it is effective, that means I would give only water, I would not give salt, then I have to say no to one of them. But the question, I'm not sure I can answer like that with the information we have.

DR. LEITMAN: That is fine. Sometimes, as I'm told often by the FDA, hearing your comments is sufficient and I think they're hearing your comments and I think that's likely sufficient since there wasn't a part C here. So I'm glad we went through that exercise. Okay, no vote.

DR. SIMON: Can I make one editorial comment? I think one of the things that relates to all this that we found in trying to deal with donor reactions, not necessarily in this population, is attention to the donors. So when you start giving attention to the people, it's hard to separate that out from the specific measure and I think that's what gets into it, but likely anything you do to provide
more attention and to use some of these measures is likely going to help in some way.

DR. LEITMAN: Thank you. Okay, question 3 is for comment and not vote. Please comment on the need to ensure parental consent material contains adequate information on the increased risk of adverse reactions and injuries in teenage donors.

That's a problematic question because there are states where parental consent is required and states where it's not. I can't remember the chart now, but is it universally required in states for ages of 16 and less? It's not. So there are renegade states where it's not required.

So how can we ensure parental consent in material when in some cases parental consent material is not a necessity? So can we discuss, can we hear comments on whether parental consent should be required or not for subjects, donors less than age 17 or if you want to include less than age 18, whatever you would like to comment on. Comments, please.

DR. JOFFE: Because this includes 18-year-olds and 18-year-olds can, except in a couple of states, don't need parental consent.

DR. LEITMAN: Let's, 17 and under.

DR. JOSEPHSON: So I believe that with the data that we've been shown today and that we just said that we felt like there should be intervention to mitigate these things, I feel like we have enough information to say there are certain risks. We do it with blood donation, I mean, when you receive blood.

I feel like parents should know because these things do happen. I don't think we're ever going to get to zero, and I think that some of those things translate to the parent knowing it's about their insurance, it's about taking care of
them, they're still living under their roof.

I think there are a lot of pieces to this and I think that for these adverse reactions to be called out of the blue and you need dental work done, your face is messed up, or that you've just even fainted at school, and not really know that this happened, I just think there needs to be consent.

MR. TEMPLIN: I would agree. I mean, unless you live in one of those two states that said you're not financially responsible as a parent if your underage child gets hurt, you might be on the hook for some big expenses.

I don't know if there would be a way the federal government could require parental consent or you'd have to go back to each individual state, but I think for at least the 16-, 17-year-old, it might be beneficial for the health of child because they might be peer pressured into donating at the collection center because their friends donated. All your girls or all your boys in your gang or clique or whatever you call it, your pals are donating, you better go there too. That might be a way to get out of it if you don't want to, say my mom won't let me do it.

DR. LEITMAN: I'm thinking of the operational complexity for the donor center. How do they get consent first before a drive is held? Because if we advise that in our comments, it has to be doable. So it might be possible to send material out at the beginning of every year to all parents that's well written that we think provides the appropriate information, and it would be an opt-out, but if you do nothing, you're, by your silence, opting in.

DR. JOSEPHSON: I have two boys, 12 and 14. We have to sign for everything that they want to do. We have to sign for them to be able to go on a field trip. We have to sign for them to be able to do pretty much anything that's
even being done sometimes at the school just so they can go to a lecture sometimes.

So I feel like this is a time where we could be understanding what the school thinks is an important thing. They've said that there's a drive. We as parents might want to talk to them about what it means to donate or how to be altruistic. I think there are a lot of opportunities here by having the parents be involved than it be just a one-off or a peer kind of review thing, all the peers talking to each other, the 10th graders want to do it because the 12th graders are doing it.

I don't know, I just feel like we're missing something and I do think there is a possibility, since we have to do it for lots of other things, this is the way schools work. Just my opinion.

DR. DEMARIA: I think it is hard to argue against transparency, and I think that if the data that was presented to us in terms of the estimate of risk is accurate, that probably reflects somewhat the parents' estimate of risk is as well. So in point of fact, they may have a view of risk that's much higher than it actually is.

I think there's a good reason, both for transparency and making sure they understand the data. It may make them actually feel better about the transfusion, about the donation.

DR. LEITMAN: As the chair, I want to ask Dr. Katz if you'd like to enlighten us on this.

DR. KATZ: Just a tiny bit of context. What Anne showed you was the state stuff. In point of fact, I can't speak for the Red Cross because I've never worked for the Red Cross, but nobody in my association of whom I'm aware
would ever conceive of drawing a 16- or 17-year-old donor without signed parental consent.

The way that consent works is that you send home with the kid a consent form and an information sheet. Now, the quality of the information I am certain is highly variable, but I will bet my job that there is virtually no one who is doing 16- and 17-year-old donors in my association without consent.

DR. LEITMAN: That was helpful, thank you.

DR. EDER: The practice, in fact, is if the state doesn't require 17-year-olds, that parental consent is not obtained. I mean, you're not required to obtain parental consent. I think schools can say if they need it, so it's left to the school. Some schools, it's not common, but in the Red Cross, most 17-year-olds donate without parental permission because it is not required in just about all states except for three.

DR. LEITMAN: I think that's very helpful to hear Dr. Eder's comments on Red Cross policies. It's also helpful to hear that blood centers can implement what we just heard Dr. Katz say they do implement, and they do it. So it's not too onerous. It can be done. It's logistically and operationally not only possible but universal in certain consortiums of donor centers.

DR. JOFFE: I support a lot more parental involvement because I think we've seen enough data. Also, we're living in a new era, and the days when the consent form gets brought home in a backpack, there are lots of different options, email, doing things at the school website and so forth.

And again, until I was at the meeting, I hadn't thought about it, but the thought that a 16-year-old or a 17-year-old could have a vasovagal episode
while they’re driving a car with two other kids in the backseat really scares me, and that would provide parents with an opportunity to say, you’re not going to drive today, or I’m going to pick you up.

MR. TEMPLIN: In the pre-meeting material that we were sent home at our houses, there was this pamphlet or paper from this LifeStream organization, this blood center, and there is a parental permission slip on the back of it, and it says here that 15- and 16-year-old blood donors, but the 17-year-olds don’t need permission.

But because it’s done at the school, the school and the blood center could work together to just require any student at that facility that’s going to donate blood on that particular day to get the permission and send it home and let the parents know what’s going on. So in case the student is driving his or her buddies home, they don’t crash in the cornfield on the way home.

DR. LEITMAN: Dr. Wagner from the Red Cross in the audience?

DR. WAGNER: Yes, in the Red Cross, we get parental consent from the parents of all 16-year-olds, not for 17-year-olds, and I just want to make a comment that the process for getting parental consent for 16-year-olds basically proves that it can be done. It’s operationally feasible.

DR. LEITMAN: Okay, every comment I’ve heard from the committee has stated that the person speaking is in favor of getting parental consent for all prospective donors aged 17 or under. If there is someone who doesn’t, and it’s okay to feel that that’s not necessary, if there is someone who doesn’t feel that it’s necessary, could they comment now?

(No response.)

Okay, so that's part of the answer or comments on three. I think
that if we all agree that there should be consent, then we would agree there
should be adequate information on the consent about real and adequate
information on what the risks are, what the most likely injuries are, and although
one perhaps can't give a percent, point or percent, doesn't mean something, one
can say that they're between 4- and 30-fold more common than in adults and that
gives I think the reader, the parent, an idea of what we're talking about. So a real
explanation of risks.

Any other comments before we move onto four?

Okay, this is number four, a voting question. Considering available
evidence related to iron deficiency in teenage blood donors, does the available
scientific evidence suggest that teenage blood donors are susceptible to
developing iron deficiency?

Okay, why don't we just vote? Yes, no, or abstain. Please vote.

(Vote taken.)

LCDR EMERY: The committee has voted and they voted all yes. So
that is 15 yeses, 0 noes, and 0 abstentions for question 4A. Going back to
question 2B, it was 10 yeses, 4 noes, and 1 abstention, for the record.

I will read the names into the record. Dr. Josephson, yes. Dr. Rabe,
yes. Dr. DeMaria, yes. Dr. Stapleton, yes. Mr. Templin, yes. Dr. Escobar, yes. Dr.
Leitman, yes. Dr. Joffe, yes. Dr. Ortel, yes. Dr. Lerner, yes. Dr. DeVan, yes. Mr.
Rees, yes. Dr. Sandberg, yes. Dr. Chitlur, yes. Dr. Murray-Kolb, yes.

DR. LEITMAN: Thank you very much. So B is a comment, not a
vote. B-1, if so, and it is so since we just voted so, please comment on possible
interventions including further studies evaluating the effect of iron deficiency in
teenaged blood donors. So do we feel that further studies are called for at
evaluating what the effect is of iron deficiency in teenage donors?

DR. JOSEPHSON: I think we need long-term studies about cognitive function. I think this is a time where they're taking their standardized tests, their ACTs, their SATs, I think you've got athletes and I think we should study their performance. I think there are a lot of different things going on, so I think we know that they are iron deficient, we can help them become less iron deficient or replete it to a certain extent, but what is the cost of that? I think we still need to study it.

DR. STAPLETON: That was my point as well, but I think it's a real opportunity to set up a placebo control trial for treatment to see if you can mitigate any cognitive differences you find with iron replacement or supplemental therapy.

DR. CHITLUR: I would have a hard time with a placebo control trial. Knowing that iron would make a difference, I would not want my child to be on the placebo iron.

DR. STAPLETON: Iron deficiency is a chronic disease and I think you have an opportunity to do a placebo crossover, or not crossover, just you have a placebo switched to a replacement, but I think, and this may be my lack of familiarity with the entire field, but the documents that were provided in the briefing documents to me on the effect of cognitive achievement were, I would say, weak.

The reason I'd say that is that it's very difficult to control for compounding variables and cognitive testing. This is an opportunity where you can do a control trial and ultimately treat everyone, but actually to see if there is an effect of iron replacement on testing. So I think it's a wonderful scientific
opportunity.

    DR. CHITLUR: I think there is data in other, not necessarily
donors, but there is definitely data on iron deficiency and cognitive functioning
across the board in pediatric populations.

    DR. STAPLETON: Is that with anemia or is that with -- and is that
controlled for socioeconomic factors that are clearly in the causal pathway for
poor cognitive testing? It's very difficult, if not impossible, to control for
compounding variables that are in the causal pathway. All of the socioeconomic
factors are, so this is an opportunity to really say yes or no and ultimately treat
everybody. So I feel strongly, you might tell.

    DR. LEITMAN: Dr. Murray-Kolb, also, I saw your name as a
coauthor on just this kind of study. Is that correct? Could you comment?

    DR. MURRAY-KOLB: Yes, but in a different age group. I just want
to support what Dr. Stapleton is saying, that I think we need more studies in this
particular age group and I think especially focusing on iron deficiency in the
absence of anemia, I think that's going to be important to really establish how
this population is affected.

    DR. ORTEL: I was just going to say that everything I'm hearing
actually makes the argument that we need further studies in evaluating the effect
of iron deficiency in teenagers, and you just leave off the blood donors.

    I mean, it's kind of that everybody agrees that you need it in
teenagers and outcomes, long-term effects, so the blood donor just seems kind of
redundant to put it in there.

    DR. LEITMAN: I want to end the comments on B-1 there because
everything else will relate to B-2 and B-3 because they're all interrelated. So let's
move on and combine the discussions on possible interventions that include
donor education as well as, right now, without further studies, operational iron
management by ferritin testing, iron supplementation, or limiting donation
frequency.

So we heard that Blood Systems will be implementing routine
ferritin testing this population. So comments on approaches to current
interventions in this population, including what you see in 2 and 3.

DR. ESCOBAR: I mean, I agree with Dr. Ortel. I think we should get
out of the really blood donation, if we're talking about intervention in this
population, it should actually go back to the pediatrician, taking this kind of
information we saw here to the meetings of the pediatrician so they can see, and
they're the ones that see those girls even before they become donors of blood or
they can act and have an effect and maybe it would change if they are able to
identify iron deficiency very early.

DR. LEITMAN: I was speaking to Dr. Joffe on the break and he
would like to see the literature, the data that we saw presented in the CHILL
study. Mr. Spencer, are you listening? He would like to see that, part of that, at
least, submitted for publication in the pediatric literature, because he doesn't
think that pediatricians are aware of that data. Did I paraphrase you successfully?

MR. SPENCER: I would just concur that just as blood centers, there
is clearly a communication gap in terms of what donors need to understand, the
risk for iron depletion, I think there is a very meaningful gap as well between the
donors and their providers and maybe between us and providers.

So there probably needs to be some bilateral and multilateral
communications there to make sure that their antennae are raised for this
potential risk, independent of and perhaps compounded by blood donation, absolutely.

DR. CHITLUR: I support that and I think Dr. Kamel mentioned earlier that they’re going to include the ferritin testing and also include some information about starting iron or iron therapy. I think one important statement in that would be to take this information back to your physician because just telling the mother to start iron I think is not enough.

To go back and find out if there is anything more that needs to be done, any other evaluation that is required, would be just as important, and that's where I think taking it out of just the donation and addressing this as iron deficiency would be important. So I think it's really important for you to add that sentence there, take this back to your physician.

DR. LEITMAN: Thank you.

Dr. Kleinman?

DR. KLEINMAN: Yes, I just wanted to clarify my understanding of the question at least and that is, many people said further studies are necessary, but I'm wondering -- I'm hoping that doesn't mean you need to wait for these results of these further studies because these studies are long-term studies. They will take a couple of years to fund if the funding agencies want to fund them and many years to execute it correctly. I'm seeing people shaking their head, no, that's not what they mean.

But the other point I wanted to make is once people operationalize a program, it costs more if they're going to operationalize it and collect all the data, right? There is a nice paper in the literature by the group from Indiana that actually is one of the two blood centers that provides iron that actually says we
decided to provide it and we decided not to collect data so we could make it cost-effective. So we don't have to set up a whole network.

While I'm obviously involved in research myself and I appreciate the importance of collecting data, I think we don't want that to stand in the way of people actually implementing programs because it could become a roadblock. So I just wanted to get that into the committee's mode of discussion.

DR. LEITMAN: Thank you. There is a program called Iron for Women at the Indiana blood center run by Dr. Waxman that operates like that. It's for premenopausal women. I can't give you the details other than there's not, routine ferritin is not part of that testing.

I'd like to give my comment on sort of linking one, two, and three. From the data I saw today and I was most moved by Mr. Spencer's presentation of first donation, second donation, and seeing those bar graphs move so strikingly to the left towards the iron-depleted and iron-deficient spectrum that I strongly think centers drawing blood from 15, 16, and 17-year-olds should routinely get a ferritin level at each donation.

Unlike that hemoglobin 12.0 to 12.5 in women that we just, premenopausal women, I think it's okay to draw the blood unit because they do meet hemoglobin criteria, even though we know that somewhere between 35 and 40 percent of them, even on first donation, have low iron stores.

But because I know that and I know it's going to get worse from the data that we saw today, I think you have to draw ferritin testing and then you have to have strong messages sent to the subject and I'm not sure it's the subject alone, subject plus parent, not quite sure about that because students have brains and they can listen to your message or they can discuss it with their parent.
I don't think limiting donation frequency is very effective in any of this from data that we saw today. It might help, but that's not the main strategy that's going to have impact. It's going to be the iron supplements.

DR. JOSEPHSON: I think, in combination, I think it should be capped, the amount of frequency that they can donate. I think that other countries have adopted that, as we saw. I think that, I mean, we didn't get to see the breadth of all that data, but there is data and I think that limiting that has made it possible to keep those people in the donor pool.

I think we should look to strategies to not completely shut out people, but I think we should also look to when it's okay to increase the frequencies, but I think we should limit the amount. I know people were talking about doing less drives at different high schools or whatever where they've had -- but I just think capping them at some point, one or two a year or something, may be helpful.

DR. LEITMAN: So you would want to combine both a routine ferritin testing strategy and a message based on those results in addition to --

DR. JOSEPHSON: I would because of how many people were iron deficient to start with, as first-time donors, and you're going to them at their first time, so I think maybe a combination of that, and just keeping their health because we want them to come back. We do want them to be the college donors. We do want them to fill in the baby boomers, and so we want them to stay in there so whatever we can do to do that and keep them healthy is, I think, an investment for all of us.

DR. LERNER: I was a little confused. Do you mean that you wouldn't draw the ferritin before you decided on whether or not to allow the
person to donate?

DR. LEITMAN: I meant I would draw the unit of blood if they met
the current donor eligibility requirements, which is a hemoglobin greater than
12.5. I would have the sample and assess the ferritin later. So you would be
drawing the blood without the knowledge of what the ferritin level is, but I would
have every donation --

DR. LERNER: Even if it was your second or third donation?

DR. LEITMAN: Yes.

DR. LERNER: I think I would probably, obviously you have more
experience, nonetheless, I would be more in favor in actually looking at the
ferritin after that, knowing that it was a multiple donation. I would also agree
that I would limit the number of donations by these particular kids.

DR. JOFFE: As sort of an expansion of this, I would like to suggest
that when blood donation programs occur in schools that they be more integrated
into the school health program. Virtually all schools have a school nurse who
could help relay the information about ferritin levels to the parents or perform a
monitoring function.

There are many schools that have school health centers that may be
staffed by a nurse practitioner or a physician. So I don't know if when a blood
donation program happens, it's totally divorced from the school infrastructure,
but certainly the opportunity for linkages in a public health model would I think
really help address some of the issues of how do you get the information to where
it needs to go.

MR. TEMPLIN: I think there is a multiapproach that you could do.

How much does it cost to do a ferritin test? Is it very expensive? Is it a couple
cents? How much does it cost? If you're doing it at a school, most schools, I know at least at my school, you've got the 9th, 10th, 11th, and 12th graders there. You could get the 9th graders in and explain to them what's going on, work with the school nurse, maybe draw some blood with the kids that are planning to donate at the next blood drive, take their iron levels.

If it's not like a big expense, I mean, obviously, it's more work for the blood collection facilities, but it doesn't take that much to stick your arm on the thing and you get the Luer-Lok or whatever put in, bing, bang, boom, a vacutainer full of blood gets shipped off with a number on it.

Then they can even do it as like a public health thing, they say that the HIV and hep C are potentially on the rise in the schools. It'd be a good way to help the young kids as well.

DR. LEITMAN: Thank you.

Dr. Lerner's comments made me think of what we implemented in our donor center, which is not what I said. If a donor has had a low ferritin, less than 26, let's say, and they merit iron replacement, which they get, that donor has already declared that they are susceptible to iron deficiency.

So we do in my centers on every subsequent donation, we don't assess the ferritin, but we give them a 60 pack of iron, and only that specific donor because of that reason. If their hemoglobin drops below 12.5 on a subsequent donation, then we get lab tests.

Okay, so if we have any more comments on B so that we could move on to five? Okay, number five. Please discuss whether there is enough associated risk in teenage donors to warrant restriction of the donor pool to individuals aged 18 years and over. And it doesn't specify what kind of risks. This could be iron
deficiency risk or adverse events and injury risk.

DR. SIMON: Yeah, I think we have talked about a lot of the things
that can be done to make it safer for the 16- and 17-year-olds to donate in the
school setting and within the blood programs. I think that's where the focus
would be. I think the data we've seen from Dr. Katz I think would argue strongly
against restricting donations to 18 or over at this time. I think we ought to give
the blood banks a chance to use all this information and data and the comments
from this committee to improve the safety rather than wholesale elimination of
the teenage donation.

DR. LEITMAN: Thank you. I would say that I personally agree with
that comment.

DR. JOSEPHSON: I agree with that, too. I mean, struggle. I'm at a
pediatric facility so we're treating kids and we're always struggling for the Os and
for all the different products, and I think there is a healthy balance. I do think
that the people are aging out. I think we need to engage the young people, but I
think we need to do it in a way when we know data.

We need to make it a good experience and a healthy experience
because these are healthy donors. So from a pediatric standpoint, being a
pediatrician, I feel like the burden is do no harm but help people who need it, so
it's kind of this tug, but I think we can do it safely if we let the blood centers do
some of the things we've asked and we think are appropriate to do.

DR. LEITMAN: Dr. Joffe?

DR. JOFFE: I would second those comments. I think all the
strategies that we've talked about I think will help towards balancing the risks
versus benefits of 16- and 17-year-olds giving blood.
MR. TEMPLIN: Yeah, I wouldn't want to restrict any potential of
these folks because if Mr. Katz's female presentation would have been the same
as the male, that would have been 12,000 units that would be pulled out of the
system each year. So we don't want to take 12,000 units out of the system.

DR. LEITMAN: If there are no further comments, we can close
today's meeting. Is that correct, Mr. Emery?

LCDR EMERY: Yes. I would like to take a minute to make a couple
announcements for the committee. Tomorrow, since the meeting is starting at
8:30, the transportation will pick you up at 7:30 instead of 7. 7 o'clock is when we
were going to be picked up tomorrow morning, but it's going to pick you up at
7:30 instead of 7.

I want to thank everybody from the public to the FDA and my
committee members and my guests, as well.

(Recess at 6:00 p.m., to reconvene at 8:30 a.m. the following day,
November 18, 2016.)