



U.S. Food and Drug Administration

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UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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HEMOGLOBIN STANDARDS AND MAINTAINING
ADEQUATE IRON STORES IN BLOOD DONORS

+ + + + +

PUBLIC WORKSHOP

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TUESDAY
NOVEMBER 8, 2011

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BETHESDA, MARYLAND

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The Public Workshop convened in the Natcher Auditorium at the National Institutes of Health, 8800 Rockville Pike in Bethesda, Maryland at 8:00 a.m., Jay Epstein, Director, presiding.

PRESENT:

SESSION 1:
RICHARD DAVEY, MD, Moderator
ORIEJI ILLOH, MD, DBA, OBRR, FDA
BRYAN SPENCER, MPH, American Red Cross
RICHARD FORSHEE, PhD, OBE, CBER, FDA
RICHARD BENJAMIN, MD, PhD, American Red Cross

TOBY SIMON, MD, on behalf of Plasma Protein

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Therapeutics Association

LOUIS KATZ, MD, Mississippi Valley Regional
Blood Center

BRUCE NEWMAN, MD, American Red Cross Blood
Services - SE Michigan Region

LORNA WILLIAMSON, NHS Blood and Transplant

JED GORLIN, MD, MBA, Memorial Blood Centers,
Moderator

SESSION II:

CELSO BIANCO, MD, America's Blood Centers

MINDY GOLDMAN, MD, Canadian Blood Services

JOSEPHINE BAUTISTA, MS, DRB, OBRR, FDA

RITCHARD CABLE, MD, American Red Cross

WILLIAM MURPHY, MD, Health Service Executive,
Dublin, Ireland

SUSAN LEITMAN, MD, NIH Clinical Center

HARVEY KLEIN, MD, NIH Clinical Center,
Moderator

ALSO PRESENT:

STEVE KLEINMAN, AABB

MARTIN RUTA, NIH

BARBARA BRYANT, NIH

ALAN WILLIAMS, FDA

KAREN VACCARO, Independent Consultant

YELENA GINZBURG, MD, New York Blood Center

JANICE SIGMON, NIH

BARBARA ALVING, MD, USUHS

MERLYN SAYERS, MBBCh, PhD, Carter BloodCare

ALAN MAST, MD, PhD, Blood Center of Wisconsin

MICHAEL BUSCH, MD, PhD, Blood Systems Research
Institute

JOE KISS, MD, The Institute for Transfusion
Medicine

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P-R-O-E-E-D-I-N-G-S

(8:01 a.m.)

DR. EPSTEIN: So we have a large auditorium and shall we say compact but dedicated group. I'm Jay Epstein, Director of the Office of Blood Research and Review at FDA CBER and it is my great pleasure to welcome everyone to this FDA workshop on hemoglobin standards and maintaining adequate iron stores in blood donors.

First I just want to note that this workshop was organized in a partnership with a number of sponsors. I want to thank them for their material and intellectual support, Department of Health and Human Services, the NIH, NHLBI, AABB, America's Blood Centers, and PPTA. Thank you.

Now FDA's overarching goal in this forum is to gather ideas how best to achieve a sensible balance between protecting donor health and maintaining a robust blood supply. And as you will hear shortly in greater

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detail, the workshop is going to address the acceptance standards for hemoglobin or hematocrit for a blood donation, measurement methods for hemoglobin and iron level in blood donors, iron loss, iron stores, and iron deficiency in donors, iron supplementation strategies to protect donor health and to avoid donor loss, and the projected impact of changes in hemoglobin standards or the interdonation interval on the blood supply and on blood center operations.

Now as most of you know, probably all of you, the topic of the workshop is not new. Questions about hemoglobin acceptance criteria and iron management in donors date back many decades and they have been the subject of much debate nationally and internationally.

For example, just in the last ten years, there have been multiple public meetings on the subject, including NIH sponsored conferences, a number of advisory

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committee meetings. And Dr. Illoh is going to review these in some detail shortly.

But we are here again meeting on the subject and the reason is good. It is because there are new data available particularly on the relationship between donation frequency, hemoglobin levels, and iron depletion. The REDS II studies which were funded by the NHLBI have generated much of this new information which will be reviewed by several of our speakers.

Now while FDA is concerned about donor health, we are also highly mindful that changes in the hemoglobin qualification standards or the interdonation interval could have a major impact on the blood supply. And again, speakers from blood establishments will address this rather important issue.

Methods to accurately measure hemoglobin, hematocrit, and iron status in donor are important in assessing the donor status. And we will be discussing some newer

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methods in that regard.

Additionally, we are well aware of our international colleagues who have established different donation standards from those that we have in place in the United States and we will hear about some of the experiences in other countries.

Now as with all FDA scientific workshops, the Agency's goal is to obtain current scientific information and to listen to the opinion of stakeholders. While this forum is not a venue either for FDA to seek or to obtain recommendations, or to make policies, we look forward to hearing ideas that might suggest a path forward toward better management of our donors and the blood supply. So we look for everyone's participation.

Our scientific program committee has crafted an exciting day for us or two days really for what I believe will be a highly informative workshop and I am looking forward

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to a lively discussion.

So again, I extend a warm welcome to everyone who has joined us in this effort. And thank you and I will just give the podium to our meeting chairman, Rick Davey.

DR. DAVEY: Thank you very much, Jay and also I would like to extend my personal welcome to all of you who have joined us today.

We do have an interesting agenda. I think the topics that we are going to cover are current and timely, even though they are not particularly new, as Jay has pointed out.

There is a lot of new information that we are going to be reviewing over the next two days.

And again as Jay pointed out, what we would like to find is information that will allow us to find a really a reasonable balance between protecting donor health and maintaining an adequate blood supply.

So we have organized a workshop into three different sessions. Each session

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is going to be followed by a panel of the speakers from that session, along with other experts in the field. Now we anticipate the panels are going to address key issues that have been raised in each of our three sessions.

At the conclusion of the workshop tomorrow, I have asked the moderators from each of the panels to provide us with a synopsis or a summary of their panel's discussions with any thoughts, any overarching conclusions, any thoughts to pass forward that we can perhaps identify to move these topics to some kind of further resolution.

So the three sessions, I will just review briefly. Session 1 this morning is going to address the topic of hemoglobin standards for blood donors in the United States. This afternoon at Session number 2, we will address the issue involving hemoglobin measurement in blood donors. And tomorrow we are going to address the broad topic of iron

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stores and iron deficiency in blood donors.

This is a very full agenda and I encourage the speakers and moderators to really be attentive to their assigned times.

If time permits, we will have questions at the close of each presentation. Another alternative would be to use your three by five cards in your handout to write some questions and hand them in to the panel moderators. And if time permits, again, we can address those questions at their respective panels.

Jay mentioned the thank yous for the people that have organized and supported this workshop. We will have an opportunity to note specific thank yous at the close of this session. But I would like to just second Jay's thank you to the sponsors who have supported this workshop and the steering committee that worked hard to put this agenda together.

Before we begin, there are a few

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housekeeping announcements. There will be refreshments at all of the breaks. It's a good thing. I want to thank our sponsors for that. There is no food and drink in the auditorium, however, so I would appreciate your attention to that.

There is a cafeteria on the floor above here in Natcher. And if you want to take a little walk there is another cafeteria close by in Lister Hill Auditorium. So, lunch will be available.

Keep your evaluations in mind. Evaluations are very helpful to us in kind of thinking about how we have done in this workshop and making plans for any subsequent workshops that might address this topic.

So with those introductory remarks, let's begin our agenda. The first speaker in this morning's session is Dr. Orieji Illoh. Dr. Illoh is a medical officer with the Division of Blood Applications at DBA. She was a transfusion medicine specialist at the

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University of Texas in Houston before joining FDA. She did her training at Howard University and the University of Virginia.

So Dr. Illoh is going to speak to us this morning on the topic of current standards and donor safety and blood supply issues. Dr. Illoh.

DR. ILLOH: Good morning. And today I'll be introducing the topic for today's portion of the workshop. And I will be discussing the current standards in terms of hemoglobin and its relationship with donor safety in the blood supply.

Okay so my outline will include an introduction, very brief. I will then go to the current hemoglobin standards and give you a little bit of the regulatory history, things that we need to consider or I think we need to consider when looking at adjusting hemoglobin standards. And then I will give a little overview of the previous public discussions. Lastly, I will just go over the workshop

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objectives for today.

So what we are here for is to discuss basically today the hemoglobin status that we have in place for our blood donors and address donor safety issues, which is the current hemoglobin standards but also take into consideration blood supply issues, i.e., the impact on blood supplies if hemoglobin standards are changed.

So why are we looking at this in the first place? I think we all agree here that with our current standards, our current standards don't really fall within physiologic norms. So we are going to review that and have discussions on that.

So currently with our hemoglobin standard of 12.5, you know, we are actually collecting blood from donors who are considered anemic and I will go into that a little bit more. And you might also argue that if you look at the physiologic distribution of hemoglobin for females, that

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we are allowing donations -- that if we adjust the standards, we could allow more donations from females who are considered within the normal range. We all know that currently among our hemoglobin deferrals about 95 percent of those come from women. And we also know that hemoglobin deferrals also impact a return of blood donors and therefore, future blood donations.

We are also going to be discussing the hemoglobin measurement. Most of us, we perform hemoglobin measurements on our donors using a simple what we consider point of care test. These test methods vary, sampling vary, something can also vary and affect the results. And the quantitative methods generally measure hemoglobin within 0.2 grams and 0.5 grams per dL.

In terms of relationship with donor health, we will be hearing a lot about that, too. I think we all agree at this point that even though it is used as an indirect

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measurement of iron status, I think studies, some of which will be discussed today show that it is not a good indicator of iron stores.

So what do we have in place in terms of regulatory requirement for hemoglobin? The current requirement is codified in 21 C.F.R. 640.3(b)(3) and currently we say we have a recommendation of 12.5 grams per dL for both genders or 38 percent if you look at hematocrit.

So the purpose of this primarily is to ensure donor safety. You are ensuring that your donor is healthy at the time of donation and also healthy after donation. And second really you want to ensure collection of a potent product.

So in terms of a little bit of regulatory history, this threshold was established since 1958 and basically has not changed. There were previous discussions in the past where gender-specific hemoglobin

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standards were proposed but never finalized. And I think some of you who have been here longer than I have will remember all these discussions. It's just coming back again. And like I said, there have been discussions in the past and you know we are back here to talk about it.

So what do we need to consider when changing hemoglobin acceptance standards? I think one is to consider a definition for what do we call anemia. The definitions of anemia vary depending on where you look at but what I have here is a publication in blood where the authors looked at the NHANES and the Scripts-Kaiser database distribution for hemoglobin among healthy normal individuals in the United States. They excluded those who were iron deficient and they had twice determined what the lower limits of hemoglobin will be considered. So here they defined hemoglobin levels below which five percent of the normal subjects in the population will be found. And

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what we can see here, I think what we all know, is that the hemoglobin levels vary between races and also between the sexes. So males tend to have higher hemoglobin levels and you can see it is higher among Caucasian males compared to black males and the same thing for females. Though it is lower, it is higher among Caucasian females compared to black females.

So if we accept this definition of anemia, let's look at what we have currently.

Now this is another NHANES distribution of hemoglobin and we can see black here represents white males, gray represents black males, and the red arrows here represent basically the levels here. So this is a level at which five percent of the population or less would fall for Caucasians and for black males. This bar here represents our current hemoglobin standard among our blood donors. So this information was published by Dr. Newman in Transfusion.

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Now if we look at women, Caucasian females, African American females, what was considered anemia, this is where we fall in terms of our current hemoglobin standards for blood donors. So that is one consideration.

The second question is okay, we have been doing this for years. Are there any adverse effects of drawing blood from males who have hemoglobin levels of 12.5 grams per dL or 38 percent?

The data in this area is very limited but generally there are concerns that if someone comes in with a hemoglobin level which is considered anemic, there might be an underlying medical condition that may not be addressed. Or if that person already has existing iron deficiency, is there a worsening of that iron deficiency state?

For females, another concern has been if you address the hemoglobin level down to 12.0 grams per dL, we do know that a lot of females, a higher percentage of females are

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iron deficient, especially if they are in the child-bearing age. And so is this really a good idea, bringing in more donors who are potentially iron deficient and causing a worsening their iron deficiency state?

It is very difficult to discuss hemoglobin standards without talking about iron stores. And even though we will be talking more about iron tomorrow, this always has to be kept in mind to kind of work together.

What I am showing here is the experience of Australia where they were transitioning to a higher hemoglobin level and you can see that in '04, this was their hemoglobin threshold for blood donors. And what they looked at was the percent of people who were iron deficient. You can see 6.2 for males, 22 for females. And when they adjusted their threshold a year later to this and looked at the distribution of those who were iron deficient, those are really a significant

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change. So I guess my point here is that changing hemoglobin level alone does not necessarily solve the iron deficiency issue among blood donors. So they both have to be looked at together.

So another thing to consider is what are the other countries doing? We are not alone in having single hemoglobin standards. I have a list of countries that also have this standard, the U.S., Canada, and Switzerland. Other countries have gender-specific standards. So for example I have in this list here, countries that have chosen 13 for males and 12 for females and there is an example of some of them here.

A couple of countries also gender-specific have gone with 13.5 and 12.5 for females: Council of Europe, United Kingdom, Scotland, Germany, and Sweden.

And then finally, there are some other countries that have adopted 13 for males and either 12.5 or 11.5 for females. Now we

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have to remember that the distribution of hemoglobin in different countries may vary. So I think it is kind of difficult to come up with a standard because you have to look at the population you are dealing with. We also have to take into consideration that the donation intervals may vary and also that the collection volumes may vary among these donors and that different programs or different countries might have different programs in place to address iron stores, ferritin measurements or iron supplementation. So, you know, this is going to vary.

So finally we also have to consider how any changes in what we have right now will affect the availability of blood and I am sure we are going to hear a lot about that today but these are some of the things that we have thought of.

You know, raising the standards for males, for example, will obviously cause a loss of male blood donors if the threshold is

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raised. Keeping in mind that African American males have lower hemoglobin levels in the first place, you will be losing a significant number of African American males, for example, and that might also impact the availability of blood for special groups of patients, e.g., sickle cell patients. It may also impact the availability of plasma from male donors, since that is what we prefer to collect at this point. And I'm sure the other speakers will also outline some other potential impacts.

For females, if the standard is dropped to 12, there actually will be a gain of female donors. If it is left at 12.5, I guess things remain the same.

So now I am going to talk, go into the previous public discussions that we have had concerning this issue. Now like I said, this topic has been talked about even before I got into medical school. So, forgive me if this is not new to you.

So in 2007, FDA proposed in the

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proposed rule, asked for comments and supporting data on changing the hemoglobin or hematocrit levels to 12 or 36 percent as acceptable minimal values for female allogeneic donors. They also asked for data or comments on the possibility of adverse effects of a minimum of 12.0 or a hematocrit of 36 percent is used for females.

Finally, we have to ask the possibility of adverse effects if a minimum of 12.5 grams per dL or a hematocrit of 38 percent is maintained for males as we have now. So basically is there any data suggesting that there are adverse effects with this current level?

Some of the comments that FDA received were, at this time, was to wait for the results of the REDS II study, and we will hear a lot about that today on iron stores and blood donors. Some agreed with the proposal to lower the hemoglobin standard in women to 12.0. They are suggesting that a hemoglobin

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of 12 is normal for females and that there was an enormous potential to improve the blood supply by so doing

Some others, however, disagreed with the proposal to lower the hemoglobin standard in women to 12, you know, arguing that it did not make a positive benefit to the donor and that many women were susceptible to iron deficiency or anemia.

And then in 2008, there was a topic of iron status in blood donors, discussed at the Blood Products Advisory Committee meeting.

And here at this meeting there were discussions about iron deficiency in blood donors and alternative strategies to mitigate iron depletion. And one of the recommendations that came up from that meeting was consideration to changing the current hemoglobin and hematocrit acceptance standards. And I will review this slide again tomorrow where it talks about supplementation and the interdonation interval also.

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And then the Advisory Committee on Blood Safety and Availability in December 2008 discussed this issue and made the following recommendations. They recommended once again that FDA should reconsider the donor hemoglobin acceptance standards, they should adopt different gender-appropriate acceptance values, and they commented that the current single value of 12.5 grams per dL permits acceptance of a significant number of anemic males, while excluding many normal females.

And then more recently there was a BPAC meeting last year and the Committee, following a question on whether the hemoglobin standard for males should be changed, they voted ten to zero to increase the hemoglobin requirement for male donors. They however voted against decreasing the hemoglobin requirement for female donors. And their argument was also the iron status of females for that.

The committee recommended that we

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await the final analysis of the study on blood donors, which is a REDS study, basically, before considering any changes in the interdonation interval.

So the key things I think we will be discussing today are donor safety issues, basically blood collection for males who are considered anemic based on their 12.5 grams per dL and also consideration of the blood availability issues when hemoglobin standards are adjusted.

So the objectives of the workshop today are, to one, collect current information on the relationship between donor hemoglobin standards and donor safety, discuss the effects of hemoglobin standards on blood availability, and finally discuss our current hemoglobin measurement methods in blood donors and see whether that is adequate or whether there can be some recommendations on better testing methods.

And that is it for me. And if

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there are any questions, we will take them.

(Applause.)

DR. ILLOH: Any questions? No questions.

DR. DAVEY: Thanks, Orieji for that nice opening.

Our next speaker is Bryan Spencer.

Bryan is a research scientist at the American Red Cross in the New England Region. There he is particularly interested in conducting epidemiologic research related to different elements of transfusion safety. His academic training is in infectious disease epidemiology. And since joining the Red Cross in 2002, he has contributed to research programs in transmissible tick-borne diseases, especially Babesiosis, which as you know is pretty prevalent in his region of Connecticut.

Bryan has been very involved in the REDS-RISE Analysis Group and its efforts to evaluate the impact on blood availability and potential regulatory changes to interdonation

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intervals, and also changes in male or female hemoglobin levels.

And Bryan is going to talk to us today about his work with the REDS ii Donor Iron Study. He is going to talk to us about the REDS II Study, its hemoglobin distribution data and deferral patterns in blood donors.

So, Bryan.

MR. SPENCER: Thank you for the invitation to speak, the nice introduction and to Dr. Illoh for the very nice introduction of the topic. So I will discuss some of the results of from the REDS II program, specifically on hemoglobin distribution and deferrals.

So I'll give a little bit of background. Much of it was covered by Dr. Illoh in her presentation, so I will go through that fairly quickly. We will get some data, both historical and from REDS as well, showing the limited value of hemoglobin as a surrogate for iron status and then bulk of the

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presentation will be showing some of the results on hemoglobin and hemoglobin deferral in the REDS II studies.

We will look at the distribution of hemoglobin values in first-time donors, compare that to a reference population, actually the same population shown by Dr. Illoh, predictors of hemoglobin deferral in our donors, and then look at hemoglobin as a continuous measure. Until recent years, many blood centers relied on copper sulfate, a qualitative standard to accept blood donors. And more recently we now have actual quantitative values and that is very helpful for us in understanding both what our donor population looks like in terms of hemoglobin status as well as assessing what any sort of regulatory changes might have in terms of impact. So we will show some models there, look a little bit at hemoglobin recovery following phlebotomy, and then the impact of raising male donor hemoglobin requirements.

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I will spend a little bit of time discussing some of the uncertainty in hemoglobin measurements, less of the instruments themselves but primarily of some of the operator characteristics that Dr. Illoh mentioned and then a little bit on future directors.

So as both Dr. Epstein and Dr. Illoh noted, this is not a new topic. It has been on the agenda for quite some time and been addressed at many recent public, four of the last ten years, with the committee on blood safety and availability three years ago, giving a clear recommendation for a different gender appropriate acceptance value. So a very explicit acknowledgment that a single standard doesn't fit all donors.

And then of course, the BPAC from last summer, the summer of 2010 where there was a unanimous vote to raise hemoglobin cutoff levels in male donors, albeit without explicitly endorsing a given level as the new

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standard. And then a clear recommendation not to lower it in females. So I think many of us went to that workshop thinking these changes might be offsetting and that the impact on blood availability of a drop in the hemoglobin requirement for females and raising it for men would more or less be net-neutral. The outcome suggested there actually might be a very big impact on blood thinners, on blood availability from changes that might be coming down the pike.

So the REDS II program most folks in the room are probably pretty familiar with it but it ran for six years. It was funded by NHLBI. It included six blood centers, two Red Cross, four non-Red Cross, it included both East and West Coasts, and four centers in-between. Between us, we represent about eight percent of U.S. blood collections and that comes to about 1.2 million donations and a couple hundred thousand deferrals each year. And we collected data systematically from all

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donors, all presenting donors over a four-year period. So, we have altogether a database with about a little bit less than two million donors in five million red cell donation visits.

We don't have quantitative hemoglobin values for the entirety of this time period. Most of the centers began, they operationalized quantitative hemoglobin or hematocrit measures of donors during that time period. So we have quantitative values for about 1.8 million donor visits and sequential values from over 900,000 donors. So this is some of what I will be presenting today.

Within the REDS II study, we did a longitudinal study called RISE on iron status in blood donors that enrolled first-time and what we call reactivated donors, donors who hadn't made a red cell donation in the prior two years. And then at the opposite end of the donation intensity spectrum, frequent donors of both genders, and they were defined

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somewhat differently, two red cell donations in the prior year for females, three for males, and we enrolled roughly a two to one ratio of frequent repeat donors to first-time donors and pretty balanced between the two genders.

We looked at iron status and hemoglobin deferral and characterized that as a function of donation intensity but is well controlling for several other factors, demographic factors, some genetic polymorphisms, behavioral characteristics including smoking, dietary consumption, as well as interval since their last red cell donation.

Our outcome measures aside from hemoglobin deferral, risk for hemoglobin deferral included absent iron stores which is intended to reflect complete exhaustion of storage iron, to find as plasma faired in less than 12 nanograms per milliliter. And then an intermediate level of iron deficiency which we

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called IDE and that represents the log of serum transferrin receptor over ferritin. And this cutoff reflects the upper two and a half percent distribution of first-time or reactivated male donors at enrollment.

So it is defined for this specific population and we chose that population that wouldn't have been subject to blood loss. We will hear more about this, about RISE from subsequent donors. This background was covered very nicely but the main point, we have had the current standard for a long time with a proposed rule change in-between that would have made for gender-specific requirements but that wasn't adopted. During this time period, AABB did actually have standards that had gender-specific donation requirements. So many blood centers were in fact doing that.

And this is data from the same paper that Dr. Illoh showed; the U.S. is not unique in having a single standard for male

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and female donors in terms of hemoglobin requirements, nor an interval frequency of eight weeks. But we are somewhat of an outlier for having both. Some other places, such as Switzerland that has the same hemoglobin requirement for males and females limits donations to fewer than that which you can do in the U.S. Basically in the paper I think the only other place that has the same requirements as the U.S. is the Canadian Blood Services. So again, we are something of an outlier.

But as we consider whether to maintain the current standards that we have or to make changes, it is important to remember that hemoglobin and the intervals are really addressing different questions, different issues. So what question -- I was asked to speak about hemoglobin. So let's ask ourselves, what question are we answering with donor hemoglobin measurement? Dr. Illoh addressed these. Making sure that we are

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getting a healthy donor, that we are not doing any harm to the donor, as well as ensuring minimum potency of the product that will ultimately be transfused to a patient.

Again to repeat what she said, and I think we will hear this in multiple presentations over these two days, hemoglobin is often considered an indirect measure of donor iron status but this is very misleading and I will show some data to that effect, some historical and some more recent.

This schematic from a paper in blood shows that iron depletion is really a process. It is not an event. That a person goes from normal iron status through different stages, with a laboratory profile that changes over a lengthy time period. And ferritin changes fairly quickly in that process with the depletion of storage iron but we see that hemoglobin really doesn't start dropping until pretty late in the process. So, if we are using hemoglobin to tell us about ferritin,

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you know, those changes start to appear pretty late in the game.

And this paper by Toby Simon from 30 years ago in a cross-sectional analysis looking at hemoglobin levels and iron status in blood donors as a function of cumulative lifetime donations shows in male donors a very dramatic drop in iron, such that there are not all that altogether very different from female donors after five to six lifetime donations. Females have a less severe drop because of menstrual blood loss but certainly they are dropping as well. Not much change for hemoglobin over a very broad range, one to two, all the way up to more than 25 lifetime donations. So again, we have known for a long time, hemoglobin levels are a pretty poor surrogate for iron status.

So a couple of slides from the RISE study to reinforce the point that the correlation between hemoglobin and iron is not terribly strong. This is a busy slide so I

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will just make a few points.

One is that so we are using the iron status measures that I discussed before.

Absent iron stores, so depletion of storage iron and then IDE is an intermediate level of iron deficiency at enrollment in RISE. We have already got a pretty decent share of female donors who have at least an intermediate level of iron depletion. In the repeat female donors who had given at least twice in the prior year. We have gone one in four with exhaustion of storage iron and two out of three with an intermediate level of iron deficiency. This is not discussing the clinical impact of this. We weren't -- It wasn't one of our primary objectives to assess that. So we don't have terribly strong data there but we do see in terms of iron depletion that it certainly is present and appears to be associated with blood donation having very different levels in first-time and repeat donors.

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And so as far as the relationship with hemoglobin, we see most of the hemoglobin values for females are in this range, from 12 and a half to 14 and a half, almost 90 percent of females that we enrolled are in this range.

We did not enroll anyone below 12 and a half.

So someone who got deferred at what would have been their enrollment visit did not join the RISE study. So of those who enrolled, most of the females are in this range and we don't see much change in that distribution between the new donors or the repeat donors.

So again, hemoglobin seems somewhat unresponsive to blood donation and the distribution of a proportion of either severe or intermediate levels of iron depletion doesn't seem to correlate all that well with hemoglobin levels in the first-time donors. It may be a little bit stronger in the repeat donors. Certainly this trend here, from 61 up to 69 percent with intermediate levels of iron depletion would be statistically significant.

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But is that a meaningful difference? You know, maybe, maybe not. So that is female donors.

And in male donors, we have got a broader distribution of the hemoglobin values, as we would expect at enrollment. None of the first-time donors had AIS, had complete exhaustion of iron stores. And again, this outcome IDE was defined according to the specific population we had.

So we can't learn much about these folks in terms of iron versus hemoglobin simply to say that the first-time male donors, very few of them are iron depleted. In the repeat males, that has gone up quite a lot. One in six frequent donors, which again were those who had given three times or more in the prior year, have complete exhaustion of iron stores and one in two have an intermediate level of iron donation. The trend perhaps seems a little more clear here but it is not exactly monotonic.

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So again there is no given level where we can say the hemoglobin definitely tells us a donor is iron deficient or excludes the possibility of iron deficiency. So it is not that the correlation is entirely absent but it is, at the same time, not terribly informative. So if we are using hemoglobin to tell us about a donor's iron status, we are getting a very imperfect measurement.

These are data from the same blood paper that Dr. Illoh showed. And let's assume then that with hemoglobin measurement in blood donors, the question we are answering is, is this donor anemic. And we see that in this population, which took too large databases and because the data for hemoglobins are normally distributed, you can find a lower five percent of the distribution by taking the mean and subtracting 1.65 times the standard deviation.

Well there is no population where 12 and a half is a normal level for male donors, male people. And it varies by age,

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race and gender. But even within male donors, there is a one gram per deciliter difference, which is pretty big. And then in female donors or females, we see that 12 is well above the 12.5, rather, is well above the normal level of a five percent lower distribution and even more so for African American females.

So in the REDS donors, we have thousands, if not tens of thousands of donors to look at quantitative values. We are looking only at first-time donors because we want to look at a population whose hemoglobin is completely unaffected by blood donation and in female donors we see an average of 13.4, 13.3 that is pretty stable across the different age groups, less than 20, 20 to 34, 35 to 50. And over 50 in male donors reasonably stable but about a half gram drop from the youngest to the oldest age group.

The standard deviation is one or 1.1 or two grams per deciliter. So using the

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same measures or methods as the paper in Blood, we can define a lower five percent distribution and see that it is not altogether terribly different from that paper. This population does include those who are iron deficient; whereas, the other one excluded those who were iron deficient or had morbidities associated with anemia. But this begs the question really of should we be using the same standard for both genders. And I think the question really answers itself.

So the REDS II studies, looking at hemoglobin deferral, there is a couple of papers published specifically on this. Dr. Mast, in *Transfusion* last year published a cross-sectional analysis looking at demographic correlates of hemoglobin deferral in several hundred thousand REDS II donors. Donation intensity was explicitly included. The RISE study, the enrollment data are already published. The longitudinal data are in press now. I think they are available

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online. It is methodologically stronger and then its longitudinal analysis looking at the same factors we discussed before includes donation intensity, as well as interval.

And then the group that I have been working with over the last year, the RISE Analysis Group has been examining many of these things for 1.2 million donors and three million donor presentations. So again, the RISE data represents a very select donor population of first-time donors or frequent donors. And the RISE Analysis Group is looking at the overall data set.

So to start with age and gender, we see that this is from Dr. Mast's cross-sectional analysis at the reference age group of 41 to 50 years of age, females have 11 times greater risk of being deferred for hemoglobin and within each gender, the relationship between risk for hemoglobin deferral and age is different. During child-bearing years, the risk isn't altogether that

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different from one. The confidence intervals do exclude one but you don't see all that much difference. And then the risk drops after menopause. You do see that it starts to climb but during that time, it is still lower than child-bearing years.

In male donors, you see a very consistent climb from the youngest to the oldest age group. And this graph is from Dr. Mast's paper showing that graphically. And one hears about the anemia of aging and what these data suggest, again these aren't from a randomized trial but it suggests that the anemia of aging perhaps starts at a very young age and continues steadily over a person's lifetime. This is a very clear trend and risk for hemoglobin deferral starts from the youngest donors all the way up to the oldest.

So what physiologically is going on is not answered by these data but it does show that anemia of aging isn't limited to just the older age groups. Here we see age and gender

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results for Dr. Cable's RISE study and then those produced from the overall REDS database.

And we see generally similar trends. The odds -- These aren't explicitly comparable to the data from the Mast study. It is not quite an apples to apples comparison because the statistical methods are different and how the ratios are calculated a little bit different but we do see similar trends. As expected, much greater risk in females versus males in both groups, and more apparent in the larger database, a risk for females that drops after child-bearing years and a risk for males that increases monotonically from the youngest to the oldest age groups, such that we see in the 60-plus compared to the less-than-30s, a six-fold risk for hemoglobin deferral.

So some of the other factors that we looked at. Race, given the distribution in our donors as well as a reference population, it is unsurprising that African American donors have a higher risk between two and two

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and a half times greater-fold risk for hemoglobin deferral compared to white donors.

With respect to weight, someone who has greater body mass and greater blood volume is losing proportionally less blood with each donation. So we see higher risk in the smaller blood donors defined differently across the studies. But certainly clear results there are small donors are more likely to be deferred for hemoglobin deferral controlling for a number of other factors.

Interestingly, after controlling for many of these factors, we still managed to see a two-fold difference across the blood centers. And so that suggests there is quite a bit of the outcome that we can't quite capture and whether that is operational characteristics or procedures or something else.

We don't think that there is any systematic differences between the donor population that would confound this risk but

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for whatever variables that we put into the models, we couldn't eliminate the blood center effect. And the difference is pretty meaningful. Some of the blood centers do physical findings first, some health histories. So that might affect the overall numbers some.

This number of blood centers performing "confirmatory HemoCue reading" is actually more than two. I learned just yesterday that a couple other blood centers perform a second fingerstick on HemoCue. So that may not account for the difference either.

So with respect to donation intensity, we see that there doesn't appear to be in the RISE study any clear trend. These odds ratios are right around unity. So in this population of first-time and heavy contingent of frequent very committed blood donors, we don't see an association between donation intensity and risk for hemoglobin

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deferral. In the larger REDS II database, in an unselected population, a trend does appear to emerge, whereby at higher levels of intensity, the risk drops. And given the large numbers, these confidence intervals do exclude one.

Well intuitively, we would think that the more frequently someone donates, the greater their risk of deferral. So what this data to me suggests is that donors seem to find a rhythm that they can donate at, a frequency that lowers somewhat their risk for deferral. Probably a function of how well they feel donating at a given frequency and ultimately they find a rhythm that perhaps lowers their risk for deferral.

We have some other results that suggests that a lot of donors drop out. They don't come back. And maybe that contributes to what appears to be a lower risk among those donating most frequently.

So with respect to the donation

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interval, we see clear and consistent trends comparing the RISE data to the overall REDS database where if you come back at eight weeks, again controlling for a number of other factors, your risk for hemoglobin deferral is quite a bit higher, twice as great or more compared to those who come back after six months, 26 weeks.

So we see a little bit lower results here but unsurprisingly donors who come back that early are still in the process of recovering their hemoglobin and that process takes quite a bit longer than eight weeks.

So this plot shows risk for hemoglobin deferral as a function of interval.

So the earliest returnees again are around two. And that risk drops. The longer they wait to come back, there is a bit of an anomaly in the data here that we are still trying to tease out, but the trend is very clear. And we are really around 26, 30 weeks

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before that risk is back to zero. It doesn't mean that that is what the most appropriate donation interval is, just that risk for deferral takes a bit of time.

So because we have quantitative values for hemoglobin and hematocrit in our data, we don't have to look only at risk for hemoglobin deferral as a yes or no dichotomous outcome. We can actually look at, in linear models, look at the actual values for hemoglobin, predicted values for hemoglobin in our donors. So we established a reference group in these models. White male, 40 to 49, 150 to 174 pounds, at blood center F, no donations in the last two years. And the model predicts that that donor walking in the door is going to have 15.3 grams per deciliter level of hemoglobin. And the results will show, reflect changes with respect to that level.

So comparing risk for hemoglobin deferral with odds ratios from the logistic

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models with a dichotomous outcome to actual predicted levels of hemoglobin in the linear model, we see that this much greater risk for females correlates to about not quite a two gram difference, lower difference for females as compared to males, and we see that there is not really much change in terms of predicted hemoglobin level across more than two decades of age within females. And then beyond child-bearing years, we see that older women in their 50s and 60s and up, compared to those 40 to 49 have relatively modest higher predicted levels of hemoglobin, which correlates to about a 30 percent lower risk for hemoglobin deferral.

In males, this six-fold greater risk from young to old is associated with about 0.67, 0.70 grams per deciliter. So the affect over these age groups looks fairly modest and the magnitude of that effect from youngest to oldest is not quite 0.7 grams.

So looking at some of the other

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factors, we see with respect to race, again our risk for hemoglobin deferral was about two and a half times greater in African Americans compared to whites. And that is associated with about a half gram per deciliter lower hemoglobin level, again, controlling for all these other factors in the model.

We do not manage in the linear model, either, to eliminate the blood center effect. I mentioned a two-fold difference of risk for hemoglobin deferral, so 0.81 a lower risk compared to a 90 percent greater risk across the blood centers with respect to blood center F. It is associated with a range of actual hemoglobin levels of 0.74.

So what we see here is that the blood center effect is actually of equal or slightly larger magnitude than the effect of age within male donors. So this again suggests a certain amount of randomness and variability in the methods to establish hemoglobin values for our blood donors.

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With respect to donation intensity, these are the odds ratios we saw before. And in our donors we see that even the most intense donors only have 0.2 grams lower hemoglobin compared to those who had given just once or so in the last two years.

So we see really modest changes in hemoglobin as a function of donation intensity. Subsequent speakers will show that donation intensity is by far the strongest predictor of iron status. So that association is very clear. It is not absent but it is very weak with respect to hemoglobin.

So again, to the extent that we are using hemoglobin to tell us about iron status, we are not really doing a good job.

So with respect to donation interval, what do we see here? Again, at eight weeks, twice as likely to be deferred. And what is that associated with in terms of hemoglobin levels? About 0.3 grams per deciliter lower. So again, the magnitude is

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not that great; decreases up to about 26 weeks.

So plotting that, so this reflects that someone who comes back after eight weeks at that point, they are about 0.4 grams lower than they were at their pre-donation hemoglobin measurement that we captured. So we see that there is a pretty quick rise in hemoglobin levels. Again, there is that anomaly in the data but an exponential model fits us pretty quickly where hemoglobin rises fairly quickly and ultimately approaches the level where there is no change from the prior donation. And beyond about 40 weeks or so, we see that the data are pretty scattered around zero, no change. But again, this is a somewhat lengthy process.

So some other studies looking at hemoglobin recovery, there is two studies here; one from very long ago; one more recently. Both studies were in young men and this paper from JAMA from 70 years ago found

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that about 75 percent recovered their hemoglobin levels in eight weeks and that 93 percent would do so if they were given iron salts. More recently in this small study that used very strong methods to measure hemoglobin mass found similar results about five weeks with the standard deviation of one and a half weeks recovered hemoglobin with an upper range of 59 days. So again, these are in young men.

We would expect greater variation in a diverse donor population and in fact, that is what we see.

The initial drop in hemoglobin after fitting an exponential decay model to it and the decay is in the gap between measured hemoglobin from prior to their donation to when they return, we see that the drop varies.

Unsurprisingly, the drop is lower in males who tend to have greater body mass than females. Within females it does differ by age but females of child-bearing years have an initial drop about twice as large as that for

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males. Yet, the speed of recovery, the half-life is different. It is quicker in females than in males and again, within females, it differs by gender -- excuse me -- differs by age. So there does appear to be greater variation compared to those other studies.

So after all that, what do the REDS data tell us in terms of what the impact might be on blood availability with a change in male donor hemoglobin cut-offs of 13 or 13 and a half. This is a very busy slide. They have broken it out by white donors, black donors, and then total. Black donors are a relatively small proportion of the overall dataset, about three percent or so; 848,000 total and most of those are white donors. But we see across all male donors we have about five percent of red cell donations during the REDS II program that wouldn't have been made if the cut-off had been set at 13. If the cut-off were at 13.5, we are looking at 14.5 percent. So that is really a sizeable magnitude.

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In the REDS II dataset, we have more presenting female donors than male donors but male donors are more productive. They contribute about 54 percent of the donations, red cell donations that we observed. And so 14 percent or five percent of that 54 percent is not a negligible sum.

With respect to the specific needs of African American patient population, phenotypic matching is much harder when you are losing upwards of eight percent or 19 percent, depending on the cut-off. So this is just to suggest we should be very mindful what the impact might be if we change it.

So returning to the question of the variability of measurement, we heard that HemoCue, there is a variance associated with use of one of the specific instruments used to qualify donors that allows for a second fingerstick if the first one is not at 12.5 or greater. And I am going to present data from one region that records both measurements,

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both fingerstick measurements for quality control purposes.

So here we have paired samples not from a donor before donation and returning several weeks later but from the same donor just minutes apart. We have 14,000 paired samples and I think that the data support the conclusion that there is a very high degree of variability in the sampling. I'm not saying the problem is the instrument. I don't think that is the question. I think it is a question of the sample from a fingerstick. We will certainly hear more about the fingerstick values and what they tell us from subsequent speakers.

We see of the change of hemoglobin from one measurement to another, a pretty normal distribution. This artifact is because below a certain range you don't get a quantitative value. You get a value that tells you it is out of range on the low end. And if that was the case for both

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measurements, then that gives us zero change.

So we kept them in to show that in fact they are low but that produces this little spike that is an artifact.

But if the change in hemoglobin were simply random, we would expect that the net change to be zero, that there is not really a change, some are below, some are above. And we don't see that. In fact, most of the distribution is to the right of zero and the average change is in fact half a gram higher on the second measurement. The magnitude of the two, taking the absolute value is 0.8 grams per deciliter difference. So again, this to me suggests that the sampling of the fingerstick has quite a bit of variability if just moments apart you see measurements that on average are nearly a gram different.

So future directions. The RISE Analysis Group is modeling the joint effects of potential regulatory changes that

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explicitly take into account feedback on hemoglobin deferral from longer intervals. We see that the risk for hemoglobin deferral is lower with longer intervals and our modeling that we are working on now will take that into account. An R01 that BloodCenter of Wisconsin has called STRIDE is looking at iron supplementation strategies, placebo-controlled arm with two different doses, as well as an educational arm. Hopefully we will see whether simply telling donors what their iron status is following blood donation might be sufficient to encourage them to either take iron or lengthen their interdonation interval themselves such that their risk of becoming iron depleted is lower.

And then the REDS III program, which is underway, is planning a study on iron and hemoglobin in donors that would be randomized. So it would give us even a greater quality data than from simply an observational study.

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So to conclude, I would submit that hemoglobin is a poor surrogate for donor iron status and that there is considerable variability in fingerstick sampling and hemoglobin measurements and there is wide variability in donor hemoglobin recovery times following phlebotomies. So where we might draw the line in terms of establishing intervals needs to explicitly take into account that there is a lot of variability across the donor population.

We should ensure that our donor screening methods, our qualification guidelines, are targeting specific objectives.

Hemoglobin measurement and donation intervals are addressing different questions. So if we are trying to ensure that donors don't become iron depleted, that is a different question than is this donor anemic. Is this a healthy donor in terms of where their hemoglobin level is?

So finally, we should be cautious

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about implementing any measure without making sure that whatever changes we make are actually accomplishing the desired objectives and that anticipated benefits in terms of any donor health gains compare favorably to the likely costs in terms of blood availability.

So the REDS II program reflects the input of lots of people and the RISE Analysis Group has benefitted from their effort and continuing support from NHLBI, FDA and others.

So my appreciation to all of them. Thank you.

(Applause.)

MR. SPENCER: I guess we have time for a few questions.

DR. BENJAMIN: Richard Benjamin, American Red Cross. Great presentation. So much data that I think we could spend the rest of the day talking about it. We probably will, I guess.

Could we go back to Slide 22, which shows you a modeling I think of the odds

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ratios of hemoglobin deferral as a function of return interval?

MR. SPENCER: I'm sorry. Which one, Richard?

DR. BENJAMIN: I think it is 22, it is hemoglobin --

MR. SPENCER: Yes.

DR. BENJAMIN: Can we get that up? That one, right.

Just to clarify, you are showing that it takes 30 to 40 weeks for this deferral rate to return back to normal. But this is the odds ratio of deferral. So this graph doesn't tell us that the average donor takes 40 weeks to come back to normal. It is just that a subset of donors who get deferred may take that long.

So in that subset of donors who might get deferred, it is twice as high. The subset is twice as big at eight weeks as it is at 40 weeks. It is not telling us anything about standard donors, normal donors. Right?

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DR. BENJAMIN: I'm sorry. I'm not getting your question.

MR. SPENCER: It is an odds ratio of being deferred.

DR. BENJAMIN: Right.

MR. SPENCER: So instead of addressing those donors who get deferred, it doesn't tell us anything about the successful donors. This doesn't tell us if the successful donors take 40 weeks -- It doesn't tell us anything about the successful donors.

MR. SPENCER: Well this is telling us for controlling for all of the variables in the study age, gender, weight, blood center, after controlling all of that statistically, this suggests that the lower, the increased risk for deferral doesn't go away until about six months.

DR. BENJAMIN: Okay, but it is only addressing those donors that are deferred. It is not telling us anything about those that are successful, which the other graph, I

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think, does address the hemoglobin change and I think it is graph 27 or slide 27, five slides later.

MR. SPENCER: Yes.

DR. BENJAMIN: The question on this one, is this all donors or is this just first-time donors? And is this effect cumulative? If you come back every eight weeks, do you drop 0.4 every time you come back?

MR. SPENCER: This again is the result compared to that referenced population white males 40 to 49, blood center F, 150 to 174 pounds. Controlling for those at eight weeks, the average donor --

DR. BENJAMIN: But these are all donors not just first-time donors?

MR. SPENCER: It is all donors. That's right.

DR. BENJAMIN: Okay. Is it cumulative? If you come back a second time, do you drop another 0.4?

MR. SPENCER: Yes, that is one of

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the things that we are actually working on in our simulations. As I mentioned, we are trying to explicitly take into account the feedback from a longer interval and to risk for deferral. I don't think that the data show that the pre-donation hemoglobin is necessarily in equilibrium.

So for example, there are some other graphs that we have produced that suggest that the net change becomes positive beyond a certain point such that people's equilibrium hemoglobin was, they were not at equilibrium at the prior donation.

DR. BENJAMIN: Thanks, Bryan.

DR. DAVEY: Thanks, Bryan. Those data are important and comprehensive. I appreciate it.

(Applause.)

DR. DAVEY: Okay, our next speaker is Richard Forshee. Richard is the associate director for research in the office of biostatistics and epidemiology at CBER at FDA.

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Rich works on a wide range of issues related to risks and benefits of blood and blood products, vaccines, and human cell and tissue products.

Before joining FDA, Rich was director for the Center for Food, Nutrition, and Agricultural Policy at the University of Maryland.

So Rich is going to speak with us today about his analysis of the impact of any changes in hemoglobin standards on blood availability. Rich?

DR. FORSHEE: Thank you, very much.

Good morning everyone. I very much appreciate the opportunity to speak here today. And I appreciate that people are taking the time out of their busy schedules to come and discuss these issues with us.

Before I get started, I want to give a little bit of background about specifically what we were trying to accomplish

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with the model that I am going to be discussing today. One of the things that we want to do is we want to build that lets us assess the joint impact of changes in the hemoglobin level and changes in the interdonation interval. Because if we extend the interdonation interval, that is going to allow more time for people to recover their hemoglobin. So some of the people who might have donated on Day 56 and been deferred for low hemoglobin would be able to recover if there was a longer required minimum period of time.

So we are trying to develop a model that lets us look at the interaction between these two affects. And what I am going to be discussing today is going to be focusing on the part of the model that we developed that allows us to predict the probability that someone would be deferred for low hemoglobin as a function of time since their last donation and allowing us to assess different

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cut-off points that might be used for that hemoglobin cut-off.

And I want to start off by acknowledging the great cooperation that I have had with this. I am really just the presenter today but I have been working with the REDS-RISE Analysis Working Group. Bryan Spencer has been providing great leadership for that. And David Wright and his team have helped a lot with the modeling that I am going to be presenting with the data analysis of the model.

Anne Fernando at Norfolk State University worked with some of the development of this model this past summer, when she was an Oak Ridge Institute for Science and Education fellow at the FDA and several of my colleagues within the office of biostatistics and epidemiology have also contributed important work and insight to this model.

So what I am going to be talking about this morning is a regression model that

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we have developed for predicting hemoglobin levels as a function of time since the last donation. The outcome variable that we are going to be looking at is the quantitative fingerstick hemoglobin test when a donor presents to donate. And the independent variables are more limited from what we saw in Bryan's presentation. Here we are going to be looking at time since last red cell donation and we knew that this was going to be nonlinear. We saw on some of the earlier charts that an exponential decay function would model that reasonably well. And so that is what we eventually used for this model. And we also controlled for sex and race/ethnicity.

So this shows what the estimated hemoglobin recovery looks like on the basis of this model. So what this is showing is the two curves for the recovery rate for males and females and the important point to note is this rapid recovery that we see between about

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Day 56 and about Day 100. At some point, this begins to level off. And again I think this was obvious when you saw Bryan's chart of the actual data that this was based on.

The next chart that I am showing is the predicted hemoglobin levels that we have as a result of this model that was fit. This chart is a little busy so let me walk you through what we have here.

The solid lines represent the predicted mean values for males and females as a function of time since their last donation measured at the level of days. I have also included the 95 percent confidence interval for the prediction of an individual donor. So these are wider than you would see if we were talking about the confidence interval for predicting the mean. Here we are taking into account the individual variability. And I did that because I wanted to point out to people just how much variability we are seeing at the individual level in terms of the quantitative

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hemoglobin values that we see. And those are the confidence intervals then for the prediction for females.

So for the model that I am going to be presenting tomorrow that shows the comprehensive estimate of changes in minimum days between deferral and hemoglobin levels, we needed to have a flexible way to predict the percentage of donors who would be deferred for low hemoglobin at alternative thresholds and different days that they present to donate. And the way that we are accomplishing that is we are using the feature of regression models that the predictions from a regression model are going to follow a normal distribution. And from this normal distribution, we can get a predicted mean value for the hemoglobin level for any number of days since last red cell donation and we can get a standard deviation for that. And based on those two, we can calculate the probability of being below any given cut-off

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that we would choose, such as 13 or 13.5 as alternatives for males.

I do also want to mention at this point that the model that we are looking at here is only looking at returning donors. We are focusing at this point on how changes in the interdonation interval might affect returning donors. Those are going to be the ones who are going to be most affected. So we do have that limitation.

So using this approach of using a regression model to get a predicted value for hemoglobin and a standard deviation for hemoglobin we can plot what the predicted deferral for low hemoglobin would be at different cut-off levels. Here we are looking at males and we are looking at the current cut-off level of 12.5, an alternative of 13.0 and 13.5. And as you can see, particularly for frequent donors going up to a 13.5 cut-off would lead to a large additional probability of deferral for those frequent blood donors.

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For females, we are looking at a slightly different set of values here. We are looking at the current 12.5, an alternative 12.0 cut-off, and an alternative 13.0 cut-off. I also want you to note the shift on the scale on the y-axis for the males we were only going up to about 0.17 probability, for females we are going up to slightly more than 0.5. And I think the important point here is that this model is predicting that dropping to a 12.0 cut-off would indeed recover a number of additional female donors and we would see a pretty large loss if we went to a 13.0 cut-off.

Here I have just collected those two graphs onto the same scale so that you can see how they fit with one another. So we are going from the current male 12.0 which has the lowest probability of deferral compared to the current female at 12.5, which has a much higher deferral. And you can see the alternative values on that chart as well.

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So using these estimates of deferral we are able to calculate a weighted average of the predicted percentage of donors who would be deferred under the current 56 Day deferral interval. I think it is important to point out that this is only returning donors and this is based on the modeling estimates. And so in particular, the estimate that we have here for females based on the model is higher than what has been reported in the other literature, the Mast 2010, for example, showed about 17.7 percent of all female donors were being deferred. So we are discussing what it is about the model that is leading to this higher predicted deferral.

But we can still look at the relative values on these two models. And for males we can see that there would be some loss going from 12.5 to 13.0 and a much larger loss than going to a 13.5 cut-off. For females, this model is predicting that we would reduce the current deferral for hemoglobin by almost

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half by going to the 12.0 grams per deciliter level. Going to anything higher, we would see further reduction because of deferral for low hemoglobin.

So as I mentioned, this modeling approach that we are using is intended to be combined into a broader model, which will be discussed tomorrow. Being able to predict the probability of deferral for any given number of days since the previous donation allows us a great deal of flexibility in terms of modeling potential donor loss with combinations of changes in deferral for low hemoglobin and minimum intervals between donations. And so we were really building this to get at that important interaction.

So we think this regression analysis that is based on REDS II data is going to give us a flexible way to predict hemoglobin deferrals at potential new hemoglobin cut-offs and it is going to be incorporated into a compartment model and we

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are going to continue working with the REDS-RISE Analysis Group to refine this model a little further and to make sure we have a better coordination between the different estimates that we have seen for potential reduction because of low hemoglobin deferrals.

With that, I will go ahead and conclude. And thank you very much for your attention. And I think we will have some time for questions.

(Applause.)

DR. BIANCO: Hi, Richard. Thank you for a very interesting sophisticated analysis. Celso Bianco from America's Blood Centers.

Has any of these analyses for you or the other ones, looked at blood groups? I think that there is a distortion there that we are not seeing because the analysis is taking the entire population of donors. But we, for instance, torture donors their own agony to come and donate more frequently. And so these

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are a subset on the side that in a certain way we are not considering. Because when we go to consider the impact, certainly those are the ones that will disappear from our table. So it would be very interesting to have this type of focus.

DR. FORSHEE: Thanks very much for that question. I can make a couple of comments with regard to that. In the model that I am going to be presenting tomorrow, we are explicitly looking at the full distribution of blood donors in terms of the number of days between deferrals and seeing what happens when some of those get pushed back.

But to this specific question about hemoglobin deferral, I think that that is an important -- I think the self-selection concept that Bryan spoke about earlier is something that needs to be explored further in the kind of modeling that we did here. So in this model, we were not taking into account

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that lower probability of deferral that frequent donors seem to have that some other research has shown. So I do think that that is an avenue that we could and should explore with this particular modeling that we are doing.

DR. KLEINMAN: Hi. Steve Kleinman from AABB. It might be a question more for Bryan than for you but I just thought of it. And the fact that -- and maybe it is a question for you also, Rich, because she used the REDS data as a basis of your model. But the fact that there is such a larger center effect in the models, that that effect is perhaps as large as anything else makes me ask the question how then can we pool the data and have generalizability for the whole U.S. if there are something in the models that varies between centers which we can't really capture accurately. Is that a limitation, do you think in using the REDS data as a basis for modeling national trends?

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DR. FORSHEE: Well I think it is certainly a consideration. I think if we are trying to model the overall national average affect to the extent that the blood centers are representative of blood centers across the U.S., then pooling that data to come up with the average, in the case of the model I presented this morning, the average hemoglobin recovery as a function of time since last donation, you can do that to get an overall national average.

I think that the differences across blood centers is very interesting and worthy of some more investigation about why we are seeing that level of difference. But if the question that you are looking at is what is going to be the impact on the national blood supply of changing either the minimum hemoglobin standard or the minimum time between blood donations, I think one could reasonably pool those data to get estimates of the average national affect.

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DR. CABLE: I'm Ritch Cable from New England Region.

Just a thought and I know we will have more chance to discuss this, but we have been analyzing fingerstick data here and that is all we really have. And that is all we really do. But that is not all we could do.

There are proposals in Europe, have been proposals in Europe. There was an article in *Transfusion* a few years ago, I'm forgetting who but they basically used the hemoglobin from the previous donation to qualify the donor for the next donation. This is what we do for plateletpheresis donors, as you know. And it has the advantage of using a venous sample. And now that everyone is sampling pre-donation from sampling pouches virtually 100 percent of the time because of the platelet contamination issue, we also have the added advantage of having an actual sample of the blood that we are actually taking. And auto analyzers are fairly inexpensive. In

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fact, you can even do these point of care tests fairly well on a venous center, if you don't feel like buying an autoanalyzer.

And I just think the paradigm that we have to use a test the day of donation to qualify the donor when the hemoglobin, the value of the hemoglobin is so -- It is almost hard to justify why you would start doing hemoglobin testing now if you were starting to do blood collection in the year 2012 and I will argue this point more in my presentation.

But I think we need break out of the we can only use fingerstick hemoglobin as a means to qualify blood donors. If we are going to use hemoglobin successfully, I think we are going to have to break loose from the fingerstick sample because it is extraordinarily variable. It has this extraordinary center effect which you have noticed, a number of people have noticed, and we know that around the country that the hemoglobin deferral rate among centers just by

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asking people is like two-fold. And the people aren't different by two-fold. So something is wrong with how we are doing hemoglobin. And I think we haven't adequately considered other ways to manage this.

That's all.

DR. FORSHEE: Thank you very much for that comment. I think I would like my colleagues from also Blood Research and Review comment on any of the policy implications there. I know that we will have presentations later that do look at the differences in variability between the venous hemoglobin measure and the fingerstick hemoglobin measure.

In terms of the modeling that we are building, I am using the fingerstick hemoglobin because that is what is currently being considered that was what was discussed at the last blood products advisory committee meeting, for example. So that is where the modeling focused.

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There is no reason that one couldn't use a different means of measuring the hemoglobin qualification for donation in the type of model that I am building.

DR. DAVEY: Well, Rich, thank you.

Rich Forshee and Ritch Cable, thank you for the provocative suggestion of dropping hemoglobin. We will consider that a little bit.

We are just a bit ahead of schedule but let's take a half an hour break. I have 9:30 so let's be back here at 10:00 for the continuation of our morning session.

(Whereupon, the foregoing proceeding went off the record at 9:33 a.m. and went back on the record at 10:06 a.m.)

DR. DAVEY: If we could take our seats, we could get going for the next session. If we could take our seats and get started for the next session, please.

Okay, our next speaker is Richard Benjamin. Dr. Benjamin is the Chief Medical

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Officer of the American Red Cross here in Washington, D.C. Richard has been with the Red Cross since 2002, formerly with the New England Region. He did his transfusion medicine training at Harvard University and his undergraduate training in Cape Town, South Africa. Dr. Benjamin is going to talk to us today about the impact of any changes in hemoglobin standards on blood establishment operations.

So, Dr. Benjamin.

DR. BENJAMIN: Well thank you, Dr. Davey for the opportunity to address this issue. Please note that my title is an industry perspective, not the industry perspective. So I am talking really for the Red Cross and don't claim to be talking for the industry.

Okay, so we have covered this morning quite a lot of ground and just to retread in the first couple of slides, what is on the table is the changes to the

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hemoglobin/hematocrit eligibility criteria and donation interval. The only point I have to make here is our current use of 12.5 for hemoglobin, there is a rationale for it and it is based mainly on setting a lower limit for potency and using a single best approximation, given the variability by race and gender and altitude and smoking, it is an approximation for normal and it does serve that purpose.

But our policy is to now include a gender difference basically to ensure two things. To ensure that we don't do the donor any harm, since clearly some of the males are anemic that we are taking blood from but also to ensure that we don't take blood from somebody who is not in the normal population and there is a risk of patient harm, although I don't know any data along those lines.

Whatever we do is going to be confounded still by the other variation in hemoglobin. So race is still going to come into it. Altitude, smoking, other factors are

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still going to come into it. Whatever we do is going to be an approximation.

And as I said before, this has little to do with iron stores. This has to do about taking blood from a healthy normal population, which we fully support.

On the other hand, the second proposed change is one on interdonation interval. Right now we use eight weeks. It allows six to seven donations a year. And we have always thought that it allows for reconstitution of the hemoglobin and hematocrit of the donors. And we are proposing to go to a varying interval for a number of donations by agenda to allow reconstitution of iron stores. And this is based on the observational REDS II data. It is not based on any prospective study that would show that making this change actually would work because we do need to take into account that frequent donors are very self-selected and they are not really described by

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the REDS II database.

Before we go anywhere in making a decision about making changes to what we are currently doing in blood centers, the industry really has to decide on what basis are we going to make this change. Is this going to be a proportionary change to protect donors from an unknown danger or is this going to be an evidence-based change? And we really need to go into this up-front and make that decision. And there is a great paper recently published from Dr. Wilson in Canada. It basically asks five questions what we should be asking up-front before we make any change.

How large is the population affected? How serious is the adverse outcome such as harm? Is it a reversible outcome? What are the costs to reduce the risks? And what are the negative health impacts of making the change?

If we consider those questions for hemoglobin and interdonation interval changes,

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what we will realize is that number one, how large is the population? Well this is a highly selected subgroup of voluntary blood donors who voluntarily come to us. It is a small subgroup.

How serious is the outcome? I would venture that this isn't life threatening or fatal harm that we are doing to anybody.

It is eminently reversible with iron supplementation. The cost of change in fact is going to be quite high in terms of the cost of making the change, the cost of recruiting other donors to fill the shoes of the donors that we defer.

And negative health impact of removal is one thing that I haven't heard spoken about very much so far. Who is going to carry the can for the donors that we defer?

Because we as blood centers are going to go out there to recruit donors to make up the gap. They are going to carry the burden of iron loss and of the risks of donation for the

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people that we defer. And have we looked at that population and thought about the impact there might be on them? And that is what I hope to spend a little bit of time on.

So I do believe that our decision should be evidence-based and not precautionary. And if we consider evidence base, the evidence we are looking at today and tomorrow really is the lowest level of evidence that one possibly can have, which is laboratory indices of harm. It is a surrogate marker for harm. We have little evidence. In fact I don't think we have any speakers talking about actual donor harm that has been measured in any way in these two days.

We of course would like at least observational studies of harm and all we have really are anecdotes. There is no systematic data that I know of of donor harm caused by iron loss, despite a 50-year experience. And that is a great big gap in our knowledge. I'm not saying there isn't harm because I do

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believe there is but there is a great big gap in our knowledge around our harm to donors.

Again, even if we had the observational data, it would be level for evidence. What we really do need is a prospective risk-benefit analysis of any intervention that we decide upon. And that is highly desirable to rule out any unintended consequences of any change we make. Because I bet there will be, and I will go through some of them now, if we make this change there will be unintended consequences. There will be harm to other donors. And that at least would be level one or two evidence. And I am proposing we should seek that before making major changes.

Since I don't see a speaker talking about signs and symptoms of iron deficiency in non-anemic donors, I thought I would at least have one slide and remind everybody we are talking about donors. We have tiredness and fatigue, reduced effort tolerance, impaired

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cognitive function, depression anxiety. It sounds like me.

Impaired growth and development in children. Well, we don't take blood from children and you will see that the donors that we are planning on deferring are not children.

In fact, they are some of our best and most senior donors.

Pica and I think Bryan Spencer had a great abstract at the AABB concerning the association of iron deficiency and Pica in donors. But that same abstract showed that there was no association with restless leg syndrome. So I discount that somewhat.

Perhaps the biggest dangers are poor red cell recovery post donation, leading to iron deficiency anemia down the road and subsequent deferral. I think that is one thing we are scared of. And we do hear stories of donors undergoing inappropriate GI loss investigations. And so those are adverse outcomes.

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All of these are highly responsive to iron therapy and I will posit they have never been shown to actually, in a prospective study, respond to changes in interdonation interval. That is an experiment that is being proposed based on observational REDS data and doesn't take into account how donors self-select and how the donor population may change if we put the deferral into place.

Okay, so for the hemoglobin hematocrit cut-off change to proposals. Wanted to take the males up to 13. That is endorsed by BPAC. And there is anecdotal evidence that we are missing disease in donors. These are anemic donors. Is the blood taken from those donors any higher risk to patients? I don't think there is any evidence to support that. But taking blood from normal donors with normal values is a good idea so I strongly support that.

Dropping the female crit down to 12 was not endorsed by BPAC because there was an

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assumed risk of harmful iron loss, although no evidence of harm was provided at that BPAC. And in fact I will posit that the evidence doesn't support that at all. If we in fact look at Barbara Bryant's data that was presented to BPAC, she looked at female hemoglobin, fingerstick hemoglobin levels and found iron deficiency -- You know, females 12 to 12.5 at 14 percent iron deficient, greater than 12.5, ten percent, very little change within the normal range relative to iron. But if you graph this out, what you will find that within the normal range of females, very little change in iron deficiency but it does go up as you become anemic. Similarly in males, the normal ranges is up here, 13 and above, very little change. But as you go below the normal change, you see this increase in iron deficiency.

So what is being proposed if we allow the females at 12 to donate and defer the males at 13, is you are going to be

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exchanging this population, the 12.5 to 12.9 males for that population at risk, which is down here. In fact, that looks like a pretty good deal.

So I in fact support the change of going to 12 and 13 for males and females. This is using ferritin levels, the normal levels of ferritin as the cut-offs for these graphs.

REDS II actually used the ferritin of 12 for both males and females and they also looked at, this is the RISE data, and I must acknowledge the help of the REDS II in the RISE Working Groups in analyzing the RISE data for this -- actually this is REDS II data, guess for this graph and their input in making the slides.

The REDS II database shows a more acute increase in absent iron stores with decreasing hemoglobin but this was a population of very frequent blood donors. Nevertheless, we are still talking about

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exchanging males between 12.5 deferring these males and accepting these females, which is a population that is no worse than the current males that are giving blood.

So I would argue very much that the BPAC's reticence in endorsing the female 12 cut-off is really not based on the data at hand. And really, they should reconsider that lack of endorsement.

Okay, so what are the risks and benefits of changing the current deferral criteria? I tell you on the risk side, we have heard about decreased blood supply and I will show you some data, the Red Cross data. There is also this idea that if we go from having a single value to two values, that we are going to make mistakes. So, errors, recalls and withdrawals are going to go up and I have got some data on that.

I will also posit that we will cause increased donor harm by transferring the risk of giving blood from one population to

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another. There is a definite risk that you might cause more harm to that population that takes the risk, that gives blood, than the one it is actually trying to protect. And if there is any shift in the donor pool during this change, you could see an increase in infectious disease and I will talk about that.

We will definitely see increased cost, the cost of change, the cost of dealing with increased errors, and so forth.

On the other side, the benefits are possible decreased donor harm and possibly safer blood. I'm going to first deal with this issue of errors and recalls and withdrawals. So if we go from having a single value for both genders and now we have two different values, our donor interviewers sometimes have difficulty telling males from females. Some of our donors have difficulty with this, too. And so we looked at our database. We used two different blood donation records for males and females or we

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have in the past. And I asked the question, how frequently do we get this wrong. And what happens is the donor comes back for their next donation and you find that the gender is wrong in the database. Well over a two-year period that it happened in the Red Cross 97 times. For us it is important because if you are a male and you are noted to be female, you won't get asked the MSM question. If you are a question and you get marked as male, you get asked about MSM but you won't get asked about pregnancy.

So what we learned from this is that those 97 occasions, it is about one in 120,000 donations in the Red Cross system. It doesn't sound like much; however, they were identified late. The blood had already left the blood center. And therefore, most of them resulted in recalls. On average, 1.8 products.

And we are kind of sensitive about recalls and withdrawals and errors in the Red

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Cross system. This amounted to seven percent of our violative BPDs that we report to the FDA and we felt that this was unacceptable. So we are in the process of switching to a single BDR for both males and females as we speak because we think this is unacceptable.

It is almost certain that by going to different hemoglobins for males and females, we are going to make errors during the donation interview and if they are different QC determinants for minimum hemoglobin in a red cell unit, we will make errors at that point, too. So that is a consequence we need to consider as we go forward.

Let's talk about donor loss. Dr. Forshee has spoken somewhat about that. I think these numbers are higher than we would have expected in the Red Cross system. Nevertheless, Dr. Eder presented this to BPAC last year that if we take men and take them up to 13, we would lose about four percent of our

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donors. If we can take females down to 12, we would gain about five percent and there would be a net no change. That is a really good thing because if there is no change, we won't change our practices in the blood center in terms of recruitment of donors. And so we already know who these four percent are and these five percent are and we can simply look at their characteristics and interchange them.

If however we don't the female down to 12 and just put in a 13 or 13.5 for men, we are going to have to go find those donors somewhere. And the best previous experience with this was CJD, where we lost somewhere between five or ten percent of our donors. What did we do? Well we introduced double red cell collections and they now make up 12 to 14 percent of our donations. Well, that isn't good for iron.

We also had a full-scale attack on high schools and colleges. Right? We basically made up the difference by going to

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high schools and colleges. We don't have, we never measured the effect but that, over the last ten years, is effectively what happened.

If we do the same thing around losing this four to ten percent of donors, I will say we will do much more harm than the potential benefit of deferring these folks. I am very scared that if you set the recruiters loose to go find more donations, they are going to go after younger and younger donors, and many of them will be first-time donors, and we will be doing harm.

Okay so what does, for the hemoglobin deferral, if we just defer the males between 12.5 and 13, what do they look like? Who are these donors? Well this is REDS II data again and it shows that those donors that would be deferred are some of our most senior donors. Okay? They are not young folks. They are not the folks we worry about in high schools and colleges. We are going to be deferring the males that are older.

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If we can exchange that for the females, this is what the female population of 12 to 12.5 looks like by age. Many more younger donors. But these are folks that we are already recruiting and we already know who they are and that won't change.

If we can't do this, if we only have to defer the males, then we have to look at the excluded population and say these are the folks that we are going to have to recruit and make up the donors from. Again, many more young donors and many more first-time donors.

And our recruiters will choose who to recruit. So there is going to be a change in where we go find this blood. We cannot assume that we are just going to get the blood from the whole population. I am really scared that our recruiters are going to go down here where we can cause damage and harm.

Just to show you the numbers, the males 12.5 to 13, these are very frequent donors. Over two years, five times the median

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number of donations. Very few first-time donors. Normal distribution of Type O blood.

If we swap them for females of 12 to 12.5, we will get more black female donors in, which is a really good thing. Also, very few first-time donors, a lower median number of donations.

If we can't take these donors, we are going to go to the eligible population and they are going to be 18 percent first-time donors. Within this population, there are first-time and repeat donors. If there is any change in the ratios, if we change our recruitment and change those ratios and take more first-time younger donors, infectious disease markers are likely to go up.

And if we go for younger donors, remember that younger donors tend to have poor iron stores, especially the females. So if we go for these kids, we are going to end up with more iron damage to those donors who are probably more susceptible in cognitive

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development, etcetera, for iron deficiency.

And if we go for young donors, we are going to have them falling down the stairs and breaking their jaws. I mean, these are the folks who hurt themselves through blood donation. So again, I am really very scared you are going to recruit a different population, we will go for the younger folks, and we will do more damage.

So the options are no change; the product quality remains the determining factor. Do the 12 and 13 change; blood supply neutral. Some increased errors, recalls, and withdrawals but otherwise to my mind, pretty acceptable; we will be talking blood from normal donors.

If we do the male increase only and don't change the females, we are going to have this decrease in supply. We are going to have the increased errors recalls and withdrawals and I fear we are going to after more first-time donors, especially the females. We are

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going to have higher infectious disease risk, and if there is any change in the age group that we recruit, we are going to possibly do more harm than the benefit of the deferral.

Okay, moving on to the interdonation interval change. Right. So we basically want to defer donors and tell them to go away and not come back for longer periods so that they can get their iron levels up. I remind you that the iron level is a surrogate marker for harm and that we have little data actually showing harm. There may be harm and there probably is, but we have little data on that. And in fact if we do put an intervention in place, we won't be able to measure whether it is effective or not because we have no data for a baseline on harm anyway.

So what are our alternatives? Well, we haven't really explored the other alternatives, such as education and iron supplementation in any serious way. Maybe we should be restricting blood loss by collecting

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less blood from donors. Maybe we should be doing what our Australian friends are doing with ferritin assessments. Those are things that haven't been tried because impact is high. Potentially decreased supply, increased errors, withdrawals, recalls; change in the recruitment pattern to young, first-time, iron-poor donors; and infectious disease markers may go up.

This again is from Dr. Eder's presentation at BPAC. And she showed that if we went to a four times a year for men and three times a year for women change, we would be losing an average of about six percent of our donors. And how will we make that six percent up is the question. First of all, who are those six percent? Well, they are our senior donors. The pattern looks very similar to the hemoglobin deferral for males. They are both the females and males, and they are mostly about 40 years old.

And who are we going to go

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recruiting? Well, we are going to recruit a population that I excluded from that deferral that tend to be much younger and have lots of first-time donors hanging around.

If we look at the table, the folks that we are recruiting are highly enhanced for group donation. They have very low infectious disease markers and they have given a median of seven times in every 24 months. These are our best donors that have been giving for years. And now we are going to tell them to go away. We don't want to see you for another three or four months. And we are going to replace these folks with the rest of the donor pool, which are very enhanced in first-time donors; don't give blood very frequently and therefore are not very easy to recruit; and they have four or five-fold the infectious disease marker rate of the donors we are going to be deferring.

This population is a mixture of first-time and repeat donors and again we can

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see that all the infectious risk is residing in the first-time donor pool.

So in conclusion then, deferential criteria for males and females may have unintended consequences. We may see more errors, recalls, and withdrawals. We will place extra burden on the eligible donors. We may lead to increased pressure on young donors. We are more likely to be iron-poor, first-time donors, and susceptible to donor injuries.

And so my recommendation from the American Red Cross point of view is really we should be looking first looking to educate our donors on iron replacement and facilitating the availability of iron to replace the iron that we remove in blood. We certainly need some research on the incidence and prevalence on iron-related adverse events in donors. We really should measure that. I think the change to 12 and 13 makes a lot of sense but it should be piloted so we can actually look

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for any unintended consequences of that change. And I would ask that we don't make any immediate change that is not well thought through, hasn't been studied prospectively, and we do not really fully understand what the unintended consequences of such a change might be. Thank you.

(Applause.)

DR. DAVEY: Thanks, Richard for that provocative talk. Interesting data.

We will move on to our next speaker who is Dr. Toby Simon. Toby is representing PPTA today. Toby's currently the program director for clinical research and development at CSL Behring. He has been there since 2006.

Toby is past president of the ABC, AABB, South Central Association of Blood Banks, and has a long and distinguished career in the field. He has also been the industry rep on BPAC in the past. Most of his career was in Albuquerque at the University of New Mexico and he is still a clinical professor of

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pathology there.

Toby, as you know, published an important kind of seminal paper in this field in 1984 where he identified the link between iron and donation.

And Toby is going to speak to us today on the impact of any changes in the hemoglobin standards on source plasma donations. Dr. Simon.

DR. SIMON: Having done research in this area, as Dr. Davey indicated, I am very appreciative to the FDA for organizing this conference and refocusing us on these issues.

Today I am speaking on behalf of the Plasma Protein Therapeutics Association and you might ask why is the Plasma Protein Therapeutics Association presenting, since the title of the workshop relates to blood donors. Well, historically ever since that 1958 standard at least, the standard for donation of plasma related to hematocrit and hemoglobin for plasma donors has been the same as it is for

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blood donors. We do that by hematocrit, since we also use the capillary tube for a protein check with each donation and so we use hematocrit of 38 to qualify all of our donors.

And we want to make sure that as these considerations continue that it should not be assumed that a change made for blood donors should necessarily apply to plasma donors.

Now our members provide a large amount of plasma, 60 percent of the world's total need, and we collect plasma in approximately 400 centers in the United States, as well as Canada, Germany, Austria, and the Czech Republic. And having been in blood transfusion community and the plasma industry over a number of years, I always get the sense that the blood banking is regarded as the universe and plasma is regarded sort of as the subset like a niche activity. But actually there are more source plasma donations in the United States each year than there are whole blood donations. The last

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year for which we have comparative data, which is 2008, there were 18,817,000 source plasma donations versus a little over 17 million whole blood and red cell donations.

So on the donation side this is very much an activity that is at least equal to the activity in the blood banks. In addition on the therapeutic side, on the treatment of patients, plasma products form a very important part of the therapy that physicians need to take care of patients. And this is a description of the products that are made from plasma donations. The major ones made from normal source plasma, that is donors without any special antibody are albumin, immune globulins that are given intravenously, intramuscularly, and now subcutaneously, and the coagulation factors, VIII, IX, a complex of II, VII, IX and X and various others now that are getting approved for use in patients.

In addition, there is an alpha-1 antitrypsin treatment for patients with certain forms of

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emphysema and liver disease.

For those donors who are either immunized to produce an antibody or have a naturally existing antibody, we have the Anti-D product to prevent hemolytic disease in the newborn, rabies immune globulin, tetanus-immune globulin, cytomegalovirus and so on. So a number of very important products for patients. And for the patients who benefit, we will put them in two categories. Those with inherited problems and those with acquired problems.

The major point I want to emphasize is these patients with the inherited problems to a large extent have an absolute requirement for our products. That is, should there be a reduction in availability of the product, there could be either the death of the patient or a major change in the quality of their life, their ability to go to school, work, and function. These include the patients with primary immunodeficiency disorders of which

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there are about 35 to 50,000 in the U.S.; patients with hemophilia A and B of which there are about 17,000 in the U.S., 8,000 of whom are severe; rare bleeding disorders and we are beginning to see products now available with FDA approval for these patients; and then the alpha-1 antitrypsin deficiency of which there are about 8,000 patients in the U.S.

So the emphasis again here is that should this rather small group of patients lack the products that we produce, it could have enormous consequences for them. On the other hand, in the area of acquired diseases, plasma products are a part of that armamentarium that the clinician needs along with blood products for the treatment of patients with burns, shock and trauma, liver disease, acquired bleeding, angioedema, immunomodulatory treatment, neurological and hematological diseases within transplantation, and then of course as we mentioned prevention of hemolytic disease of the newborn.

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So in the broader medical sense outside of these inherited diseases, our products form a part of what the clinician needs to treat patients who are suffering severe consequences of their illness.

Now the plasma collection for those of you who aren't involved has some differences and some similarities to that of blood collection. The important point, of course, is we are separating plasma from whole blood. We collect the whole blood and then the remaining cellular portion of blood, the red cells, the white cells, and the platelets are returned to the donor. And for the purposes of this conference, the return of the red cells is particularly important. This shows one of the instruments that we utilize to do this, which has a spinning bowl in there to separate the blood components.

To give you a little more detailed look at the process, this is a device made by Fenwal. And from the donor the blood is

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pumped into a separation device, which separates out the red cells which go into a reservoir and back to the donor and then the plasma which is collected for further manufacture. And this is anticoagulated during the procedure.

So there are two devices that are approved for use to collect source plasma in the United States and in most of the world, the Fenwal Autopheresis-C and the Haemonetics PCS2 both work on a generalized centrifugation principle. We collect only plasma and return the red cells to the donor with each donation.

Even in our infectious disease testing, unlike the blood banks, we use plasma samples for the testing. We do not take whole blood from the donor so there is no loss of red cells for testing. And we do not employ a diversion pouch. Therefore, we are making the case that we do not have a significant removal of red cells for these patients.

Source plasma is collected in

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dedicated facilities, not in mobiles. We measure the hematocrit and the total protein prior to each donation, using FDA-approved questionnaire. And then at a distinction to blood banking we have sort of a mini physical that is performed on each donor initially and annually by a physician or a physician substitute. So it is a somewhat more involved procedure.

In addition our donors are tested for protein electrophoresis and syphilis prior to the first donation and every four months thereafter. And in general, plasma donor centers have a significant emphasis on repeat donation. So unlike the situation with whole blood collection, less than five percent of our donations come from first-time donors. And the average donor donates about 15 to 17 times in a year's period. Some of these donors are with us longer, some shorter. They leave and return.

Now a couple of important points

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related to the subject of this workshop. Our donors are younger and they are primarily male. We do have good statistics on that and are running a little over 70 percent male donors. So, this gives us of course less of an issue in terms of iron depletion than would be the case with the blood banks, which is closer to 50/50 as I understand it.

And our age range is different. We do not have approvals in states to draw plasma donations from individuals who are minors. So all of our donors have to be at least 18 years of age and show proof of that when they come to the center. So the problems that Dr. Benjamin talked about with depleting iron stores in these young high school age population, nothing like that could occur at a plasma donation. We don't utilize younger donors.

In addition while not required legally, most of our centers stop donations at the age of 65. The plasma donation is a bit

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of a more rigorous procedure, more consuming of energy and time than is the case with whole blood donation. And our centers generally just as an arbitrary rule stop at age 65. The importance of that for our discussion here is that we are not getting into as much of the issues with anemia of the elderly as would be the case with blood centers that typically collect older donors.

We don't unfortunately have data on the racial proportion but our perception is that we have a more ethnically diverse population that donates than is the case with whole blood donors. So we would have more donors whose normal hemoglobin hematocrit levels are lower than is the case with the whole blood centers. And that means that we would have greater impact should there be a change, a raising of the standard, particularly for males for donations.

Now to get to some specifics, data that we gathered for the presentation at this

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workshop, we analyzed donation data for our member companies which represent about 60 percent of all U.S. source plasma donations, collections. We actually looked at a little bit over 21 million U.S. source plasma donations from July 2009 to June 2010. And we tried to determine how many male donors we would lose if the level would be increased to 39 percent from 38 percent, which we are correlating roughly with 13 grams of hemoglobin, we are assuming the times-three conversion, or if we were to go to 41 percent, which we assume correlates with 13.5 grams of hemoglobin.

We looked at the ratio of male donations to all donations for each hematocrit level and then we analyzed the data to estimate the donation loss if the hematocrit standard were to be raised for males by applying the average percent male donations against the total collections. This therefore was an effort to determine how many donors we

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would lose if there was an increase in the standard for donation to a higher hematocrit or hemoglobin and it were to be applied to us.

So this is the specific data. Looking at a change to a 39 percent from our current 38 percent, the percent of male donors that we would lose would be 1.73 percent, which would translate into 1.22 percent of all donations lost. And while these may seem like small percentages because of the volumes that we are collecting, we would lose over 250,000 donations per year if there were to be even this small increase in the requirement for male donors.

If we were to go to 41 percent, the numbers would be much greater, as you would anticipate; 6.88 percent of male donations would be lost, which would translate into 4.85 percent of all donations and close to a million donations.

And these are donations and one of the points also to make is that we know that

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donors who are deferred become discouraged and often would not return, so that we would have a significant impact on our available donors.

We also have a perception that the situation is somewhat different with source plasma donations than it is with whole blood in the last several years. Our understanding is that the availability or supply has improved with regard to whole blood, whereas in our situation, there is continuing increase in demand for source plasma for the products we talked about, to some extent because of increasing clinical trials, with new approvals for indications or new approvals for products that are found to be useful for patients.

So while we recognize that this workshop is focused on whole blood donors, the hemoglobin hematocrit standard has been the same for source plasma and whole blood over the last many decades. Our data that we have gathered shows that if the limit for male hemoglobin level is raised, it would have a

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significant negative impact on source plasma donations. And as I have indicated, changing the acceptability levels will also have significant impact in temporary donor deferrals for low hemoglobin, resulting in additional loss of donors, since we know that many donors who are deferred temporarily will not in fact return.

We are unaware of any health impact related to the current standard as it relates to source plasma donors. This is in contrast to the issue of iron depletion, which has possible impacts on health and seen in whole blood donors. So we don't minimize the issue for which the conference has been organized. We know that there are issues for whole blood donors related to iron depletion and loss but that issue does not exist with source plasma donors.

And we believe the changes to the male hemoglobin hematocrit standards for our plasma donors are not warranted, since there

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is no significant red cell loss associated with the plasmapheresis procedure. We do follow any red cell losses that occur because of problems with the procedure and defer donors accordingly but in the normal course of the procedure, there is no significant red cell loss and we would not anticipate any issues and therefore believe that the current standard remains applicable and appropriate for source plasma donations.

I would be happy to take any questions.

(Applause.)

DR. KLEINMAN: Toby, Steve Kleinman, AABB. I have one comment and one question. So I will ask the question first.

Do you have any data as to what percentage of presenting donors are currently deferred because they don't meet the hematocrit standard?

DR. SIMON: No, we don't actually have that data. I think that would be an

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interesting additional data for us to provide.

It is obviously than would be the case with whole blood because of number one, repeat donors that we know very well and number two, of course, the smaller proportion of females.

DR. KLEINMAN: Right. And my comment is I think you may have even underestimated the impact on plasma donation if the standard changes because I assume that most of your donors would have no reason, since they don't lose red cells to be changing their hematocrit. So those that are between 38 and 39 percent presumably even if they were temporarily deferred and they did come back, would most likely still fail. I mean because really, why would their hematocrit -- They are at baseline unless they change their diet or whatever. So I don't think you would salvage any of the deferred donors or very few.

DR. SIMON: Well we have that issue. I think as there is going to be discussion I know subsequently of course with

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the fingerstick we do have a day to day variability that you see. So some of our donors will come in and let's say they are at 37 and we can't take them and they might come the next time and be 39 or 40. I think because of that variability and some of our long-term donors recognize that and will return. But otherwise, I think your comment is well taken.

PARTICIPANT: Toby, thank you for that presentation. I have two quick questions. One is there is some red cell loss, obviously. And since these donors come back far more frequently than do volunteer whole blood donors, I am wondering what the actual red cell loss is and whether you have any data on iron in the donors that donate for plasmapheresis.

DR. SIMON: Well to answer the second question first, we don't have any data on iron. As far as I know that has never been studied and obviously, for a number of

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reasons, hasn't been a subject of interest. I do have data on the red cell loss and we have actually taken this from the two companies, what they have measured and have put in their public documents. And if there is saline replacement as one of the procedures, it is three mils with one of them and five mils with the other. With no saline replacement, it is about 11 mil. So relatively small, probably less than most of us lose when we get a diagnostic blood test.

PARTICIPANT: And the other question I had is I know the data for donors who were deferred voluntarily, the volunteer donors and their lack of return, are there similar data for paid donors in plasmapheresis?

DR. SIMON: We don't have that data. I think it depends on the circumstances, how long they have been with us. Certainly people who go through let's say their first visit in the physical and get

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deferred after having spent an hour or more in the center tend not to want to return but others will.

DR. CABLE: Toby, I know some red cell donors are paid. I don't know whether any of them are transfused or whether they are just donating for reagent red cells, for example. To what extent do your centers involve themselves in collecting these whole blood donors? And does that population cross over to plasma? And would that be a source of iron loss in so-called plasma donors?

DR. SIMON: Well we do have some of the centers do collect whole blood donations for two reasons. One is foreign fusion; that is, those are cells that are used to immunize in order to make the NED product. And the second group would be those people whose red cells are used for diagnostic purposes.

So there are a number, a very small number of course compared to the whole blood centers of whole blood donors that are drawn

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by our members. Of course, in that situation, they have to have a license to do that and they would follow all the same rules and regulations that would be followed in the case of a blood center. So that if that rule were to be changed, then we would have that same impact that you would have. But because it is such a small proportion of the whole blood donors, we didn't feel that we should address that as an industry. Does that answer?

DR. RUTA: Yes, hi. Martin Ruta, FDA. So there is data from European studies on harmful effects of serial plasmapheresis donations. I have yet to see anything similar from the U.S. but there were measurements of iron loss and it was very low. It was less than one percent from my memory but it wasn't zero. Of course, there are other parameters that were shown to be changed that were larger. It would be nice to see comparable studies coming out of the U.S. plasma collections.

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DR. SIMON: Yes, there are some differences in the procedures that are done in Europe, depending on the company and the country. So some of them, for example, take whole blood out after the procedure has started and used that blood to do testing. And there are some differences.

DR. RUTA: Yes, I don't think from the papers those related to whole blood but rather from the serial collections. And I can show it to you but it would be nice to see comparable studies coming out from the U.S. collectors on U.S. facilities.

DR. SIMON: Okay, thank you.

DR. DAVEY: Thanks, Dr. Simon, very much.

Our next speaker is Dr. Lou Katz, who as you all know is very active in ABC, AABB, and in the field in general. He has been the industry rep on BPAC. Lou is the Executive Vice President for medical affairs at the Mississippi Valley Regional Blood

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Center. He is an internist specialist trained at the University of Iowa hospitals and clinics. And Lou today is going to talk to us today about the impact of any changes in hemoglobin standards on apheresis platelet collections at a blood center.

DR. KATZ: I hope I will be very brief. This is a quick analysis that we did at my center last summer basically looking at what BPAC had most recently recommended no change in females and raised males to whatever level we arrive at eventually. And I looked at our platelet donors very naively initially as a little bit of a control for our whole blood donors and I think this is maybe an example of the unintended consequences that Dr. Benjamin has referred to. So I am going to show you some data on our whole blood donors and platelet donors with regards to the impact of changes.

So this is our whole blood -- This is donations, not donors. Two year period.

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Total of just under 300,000 by gender and you can see the distributions look as you would expect. When I show you this as a probability plot, this is again the entire 300,000, a change to 13 grams would lead to a loss of 11.8 percent of our whole blood donations. Not terribly informative unless broken out by gender, what you see here. And at the bottom is the impact on male donors.

So from 12.5 to 13 is four percent of our male donors to 13.5 grams would be a loss of nine percent of our male donations.

Not much association with blood type, which surprised me a little bit until I realized how completely we beat up our AB donors for their plasma and if their red cells outdate, that is one of the costs of doing business. There are some statistically significant differences here but clinically I don't think -- operationally probably not terribly significant.

This is plateletpheresis donations.

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Again, the slide is mislabeled. It is not donors. It is donations. And it is as you can see about I think that is 13,000 donations from which we got 28,000 or 29,000 products or split rate getting very substantial. And you can see the distribution of hemoglobin levels.

These are measured with a HemoCue on a fingerstick prior to the donation.

Again, a total of 10.4 percent of our total platelet donations would be loss with a move to 13 if it was for both genders.

Here is the more informative slide. If we leave females alone and just make the change for males, it is six percent at 13 grams, 12.8 percent at 13.5 grams. This is a little bit counterintuitive because these platelet donors are not giving red cells.

Well, in fact, there is 50 mils of red cell loss at each platelet donation when you include a little bit left in the machine and samples for infectious disease testing for which we use whole blood samples.

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And if a donor can give up to 24 times a year times 50 ccs you can see that that is a little over two units of whole blood in a year. Now not all our donors in fact give 24 times a year but the average is eight or nine. So it is a unit of blood anyhow.

That didn't seem to me to explain this difference particularly if it related to iron stores in some way. Again, by blood type not much that is terribly informative.

So then I looked at donors, donations that had either only done platelets during the two-year interval or had done some kind of mixture of red cells and platelets. And there is a typo that I haven't figured out, the N=21000 is incorrect. And I will send slides to Dr. Illoh when I figure it out.

That number is off about I think it is off about a third.

But at any rate, the interesting thing that we saw was that platelet donors have a mean hemoglobin lower than the mixed

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donors and that was counterintuitive. We looked by site and there is a reason that I look by site. And you can see that we have differences. It is sort of a blood center affect but these are our fixed sites.

The estimates, the means in red are sites where we use an automated point of care analyzer in order to select and put donors on machines. So we have a real-time platelet count on a venous sample from those people and the blues are where we use an average of historical counts, both to recruit and to program the instruments.

And to program the instruments. And as you can see, there is a significant difference here that where we use the point of care instrument, these donors are almost a half a gram lower average hemoglobin.

The impact on plateletpheresis of the changes that are being discussed would be substantial, very similar to the impact on whole blood donations at my blood center. The

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observation that I have made here is unconfirmed to my knowledge. And so number one is a plea to centers not to focus only on whole blood donations as we accumulate this dataset. What we think maybe going on here is that the way we recruit our plateletpheresis donors, two things that we do to recruit our plateletpheresis donors is selecting a population that may in fact be iron depleted.

Number one, they are whole blood donors because we know they don't think and we know their infectious disease tests are all negative and that is a good thing before you put somebody on a machine with a very expensive kit, etcetera.

And the other thing is we are selecting people with high platelet counts. And those of you who trained in internal medicine remember that one of the signs of iron depletion is thrombocytosis. So we think we may be selectively recruiting into this population people who are already iron-

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depleted. In addition, there is a continuing loss that is related to infectious disease testing samples, immunohematology testing samples and a small amount left in the machine.

We are doing a study of the iron status of these donors as we speak and to try and see whether my hypothesis with regards to high platelet counts is correct. At the end of the day, I think we need to be very aware that the impact on plateletpheresis donors may be as of a magnitude similar to that of whole-blood donors and be very cognizant of that before we make any changes.

Thank you.

PARTICIPANT: I assume you don't have any iron status measurements on the plateletpheresis donors.

DR. KATZ: A large company A has given me a thousand ferritins to do on a subset of these donors. So hopefully by the end of the year or so we will.

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PARTICIPANT: Lou, this is a pretty pedestrian comment but it has to do with your observation of the hemoglobin -- Let me repeat this pedestrian comment, Lou.

You were looking for a reason to account for why hemoglobin levels were lower in your apheresis donors by comparison with the whole blood group. And I must say from my experience as well when we look at those individuals who are hooked up to the platelet apheresis equipment, they really are the legions of the elderly and they are male. And I'm wondering if that is one of the contributing factors, that difference in the hemoglobin levels and what we are looking at is a group of individuals who do have the anemia of the elderly.

DR. KATZ: I don't know. I don't know how to look at it with our resources.

DR. BRYANT: Hi, Barbara Bryant from the NIH. In our iron replacement trial, we actually did see in our plateletpheresis

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donors that were iron deficient, their platelet counts were much higher. And as I fixed their iron deficiency, the platelet count started to drift downwards. So this is something we are looking at to see how that all correlated out.

DR. KATZ: It is another unintended consequence that if we replace iron in these people we may have a harder time getting the volume of platelets that we have become accustom to. So there are an enormous number of unintended consequences.

DR. BRYANT: We used to judge it like that.

DR. KATZ: We stopped recruiting new female plateletpheresis donors as a trolley mitigation strategy as well, hoping to avoid doing HLA antibody assays and other things that we didn't know how to interpret very well. And so there is an entire cascade of things that we have to rethink if plateletpheresis donors are without careful

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consideration included in a change in hemoglobin standards.

DR. DAVEY: Thank you, Lou. So concluding the morning session, we are going to have a panel. We would like to invite all the speakers of the morning, including you Dr. Katz, up to the front of the podium for a discussion of the data we have looked at and any observations you might have on whether or not we should be changing these hemoglobin standards.

The moderator of the panel today is Jed Gorlin. Jed, I think you know, is the Medical Director at Memorial Blood Centers in Minneapolis. He is very active in setting up one of the AABB tests for us. He is looking at these issues.

We have also asked Dr. Bruce Newman to join us. Bruce has been with the Red Cross for a number of years in the Detroit area and has been very active, published a lot of papers on donor health and donor deferrals.

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Also I am hoping we have Dr. Lorna Williamson, I hope is going to be able to join us. Is she here? Oh, good. Great. We are honored to have Ms. Williamson from the United Kingdom join us to share some of her observations from the U.K.

So if we could have the panel up on the podium, I will turn the microphone over to Jed.

DR. GORLIN: What this is intended to be is an opportunity for the audience certainly to ask any questions. I will try to start on some themed topics just to keep the discussion lively. But please feel free to --

And Richard is reminding me that in our packets we all have three by five cards. So feel free to pose those questions.

And I see Alan Williams is already up with a question.

DR. WILLIAMS: Yes, thanks. Alan Williams from CBER. So a question I guess specifically targeted to Richard but

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potentially for all of you, double red cell collection by apheresis is obviously becoming increasingly common, at least on this side of the ocean. And it complies to normal grams for the apheresis products and involves a 16-week deferral.

And we had a Blood Products Advisory Committee discussion about emergency measures where data were presented in addition to published data showing that double red cell donors actually did quite well.

So I am curious about the statement that double red cells basically compromises iron or is not good for iron. What are your observations with respect to that?

DR. BENJAMIN: I think the comment I made was basically we are removing twice as much iron and the donor has to replace that. I don't have any data around that. But just making the point that when we put in place the CJD deferral, no one has thought about what the consequence might be. And so we should

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repeat that. I'm not casting dispersions on double red cells. We do a few ourselves. But we need to think about those consequences as we go forward.

DR. SIMON: Just one comment on the double red cells. Around the time they were introduced, a colleague of mine in New Mexico actually did a study where people went on the treadmill and went through and exercise process and measured the difference and found that there was no major adverse physiologic effect. So I think your comments are well taken in that respect. And of course, they lose twice the amount of iron and that is why the FDA put in the 16 weeks to make it similar.

MS. VACCARO: Hi. Karen Vaccaro, consultant. I have a question for Bryan Spencer.

I was absolutely fascinated by your slide that showed the two fingerstick data on all of the donor candidates at one side. It

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was a hefty number. And I think you showed that the average difference between the first and the second stick was 0.8 and that was a plus 0.8. And you showed that the distribution was not around zero as random.

So how did you incorporate that data into the totals? Did you use the average of the two sticks, the data from the second stick or the first stick? And what does it make you think about the validity of using only one stick data in all the other sites?

And as a final comment, it seems to me that all of the problems could be solved here by just having everyone do two sticks and take the second higher stick.

MR. SPENCER: My point with that slide was to emphasize the amount of variability in a fingerstick sample. Ideally, to assess that, you would get a double fingerstick from all donors independent of what their first fingerstick value was. We have a second fingerstick only from donors

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whose first fingerstick was below 12.5. So we don't know for someone who was at 12.5 or 13 or 14 what the difference might be were we to sample it again.

So what you have going on there is probably partly a function of regression to the mean but also partly a function of the quality of the sample itself. That curve I showed is a distribution of the differences between the first and second stick. And if it is merely a random process, then I think we would expect that the mean is at zero and we do see that one anomaly notwithstanding, which is a function of what the linear range of the instrument is, we do see a pretty normal shaped distribution.

However, the mean difference between the two samples, and again the first one is drawn by the frontline health historian and the second one is drawn by the supervisor or charge nurse. So someone presumably more experienced, perhaps a little bit higher

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qualifications. The mean change is half a gram higher. So the 0.8 was actually the absolute value of the difference between the two sticks. So up or down, the difference between the two was 0.8 grams in magnitude but the net change is half a gram higher.

MS. VACCARO: Okay, thanks a lot. I misunderstood. I thought it was all the presenting donor candidates were stuck twice. Thank you.

DR. BENJAMIN: Could I just address that question?

The way it was explained to us by the manufacturer of the HemoCue machine was that there are pre-analytical and analytical variables that can lead to an accurate result with that machine. And they were, they claim that they were able to convince the FDA that when the machine fails, it fails low. So that by doing a second stick, and justified by the data, the 0.8 higher result is because there are pre-analytical, analytical issues with the

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machine that the operator may not be aware of, which is why the manufacturer's instructions specifically say you may repeat the test but a different operator needs to perform the test.

So this is the way the machine is approved. So fingerstick I think is important but it may not be the only variable that is a problem.

DR. GORLIN: Ritch Cable is next.

DR. CABLE: If Harvey has a comment on that, I will let him do it because mine is -- I am going to discuss that issue in my talk but I'm not asking a question about it now, the issue of double testing.

I wanted to ask Toby about I am still a little puzzled about iron loss in plasma donors. How many times a year can someone give source plasma?

DR. SIMON: Under the regulations, they can give twice a week every week of the year. So you could get up to 104 donations.

DR. CABLE: And what is the typical

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range of donations?

DR. SIMON: The typical is about 15 to 17 times a year. Most of our donors start donating, stay for a while, usually three to six month period and then, for whatever reason, transition away from donations. Some return at a later time. So it is a very, very tiny group of people that actually donate that frequently.

DR. CABLE: Kind of like our super-donors in the whole blood.

DR. SIMON: Like your super-donors. Right.

DR. CABLE: If you looked at those donors, how much did you say the average loss was with the rinse-back?

DR. SIMON: Well if you look at the -- It depends on which procedure you use. But at the low end it would be about three mil. So you would have about six mil a week.

DR. CABLE: And at the high end?

DR. SIMON: At the high end, it

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would be about 11 mil. So at the high end you could --

DR. CABLE: You could give up to in the high end up to -- And this is red cells?

DR. SIMON: These are red cells. Right.

DR. CABLE: So that would be 1000 ccs of red cells or about five units of blood a year.

DR. SIMON: I'm sorry?

DR. CABLE: The iron equivalent of five units of whole blood a year.

DR. SIMON: Well I don't think -- Well, it gets close to that if you donated twice a week every week.

DR. CABLE: Right. No, I understand that. So I do think it is possible to begin severely iron depleted as a source plasma donor with modern technology and following all the regulations.

So I go back to Steve's comment that, Steve Kleinman's comment that you really

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don't know you don't have a problem until you look for it. And I know you know how to look for it from 1981 in Albuquerque.

DR. SIMON: Right.

DR. CABLE: And I would think it would scream for a study. That was my question that came up.

DR. SIMON: But it obviously is so much less, well it is ordinarily less than what a whole blood donor does.

DR. CABLE: Well you can only look at those tiny fraction of people who give more than --

DR. SIMON: Yes, it would be an interesting study.

DR. CABLE: -- 50 times in a year or 30 times in a year or some number you would work out corresponded to more -- We know from the RISE study that the odds ratios go directly up with every donation over two years. But something like four or five donations over two years or two donations a

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year, you start to get a pretty high rate of iron depletion. So you could translate that amount of red cell loss into a number of donations, given your technologies and do the same study.

I just think you may have a bigger problem in a subset than you stated in your talk and I wanted to basically call you on it.

DR. SIMON: Yes, it would be, as opposed to I think what you see with the donors. In the normal blood center, I think it would be a very small group of people. And there is another, you know, we don't have a lot of the data that would be helpful, I think to inform this discussion. But we do, as you may have noticed in the pictures, tend to have larger males. And that is because they can donate more on the nomogram and they also find it easier to sustain the procedure. And so when you looking percentage-wise at many of our long-term donors, you are going to find the percent is very low. So I think

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everything that we observed would cause us to believe that it is minimal, if it exists at all. Obviously it is always better to have data but that would be our observation.

DR. GORLIN: Dr. Klein?

DR. KLEIN: Yes, Harvey Klein, NIH.

I think Dr. Williamson is the only one up there who actually has experience with different hemoglobin levels and different hemoglobin levels by gender, as well as different donation intervals. So I wonder if she might be willing to comment on whether there are increased numbers of errors in screening or how they look at that, whether she has data on iron or on health of donors or is planning any studies to look at that.

DR. WILLIAMSON: If this sounds like a setup question, I think it is. Thank you.

We have the privilege of having Professor Klein on our R&D Committee and last week we approved funding for a large study in

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donors, which I will say more about in a second if I may.

So just maybe picking up some of the points from this morning. So the situation in Europe as the first speaker very nicely set out is really all over the map. So there are hemoglobin levels mandated across Europe, which are now part of our legal system. So we can't change them without a whole lot of evidence. But the European Union took a unilateral decision several years ago to raise the bar half a gram for both males and females on the basis of no evidence whatsoever. So we went from 13 grams to 13.5 for males and 12 to 12.5 grams for females. And as you might expect, we had to then go and recruit a whole lot of new donors.

Although I think to take Richard's point, the way we tackled that was actually rather than go recruit a whole lot of young donors and new donors was to try and bleed donors a little more often within the rules.

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Because I haven't heard this morning how often donors here actually turn up to donate. It is probably far fewer times than the regulations allow. So we just pushed the marketing a bit harder and hope people return more often. So we did manage to avoid a lot of the issues that you raised. But it got us thinking about the whole question of donor iron on which there is just so little evidence.

So the other observation we had was that we seemed to lose a lot of donors after three or four donations. So they are recruited as a new donor, donate three or four times, and then they just vanish. And of course, we all have the frustration of the vanishing donor and not understanding why people suddenly cease to donate and there are all sorts of reasons.

But if you calculate iron stores and depletion of iron stores, three or four donations might take you to a point where somebody's iron stores just fall off the cliff

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and therefore, they might be self-deferring. And I think these self-deferring donors are just, there must be so much information there but I'm not aware that anybody has gone back to donors who suddenly cease to donate to understand why they have done so and that that would be potentially something very interesting to do. Because I think if Richard has 18 percent first-time donors, you are presumably assuming your demand is reasonably constant. You are losing 18 percent and 20 percent of donors a year, which is twice as many as we lose and I have no idea why that would be.

So given that we are kind of locked into certain hemoglobin thresholds, the -- Oh and in Europe, there is also a standard for the absolute amount of hemoglobin in a bag of red cells, which I believe you don't have here. So we have to do 40 grams of hemoglobin in a bag of red cells.

However, as you heard from the

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first speaker this morning, the interdonation interval is not set within Europe and each country can set their own. And what actually is happening is all over the map. And so some countries lead males and females very eight weeks. Some countries differentiate between males and females and have longer interdonation intervals.

So in the U.K., you can be bled four times a year or every 12 weeks if you are a male and three times a year or every 16 weeks, roughly, if you are female. But we have no idea whether that is correct. And clearly, that is assuming all males and all females are going to handle being bled the same way, which makes no biological sense.

So we have teamed up with an academic institution of public health in Cambridge to conduct a large study, which has a working title of the 50k study. So we aim to recruit 50,000 donors and actually randomize them to donate at different

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intervals.

So males will be randomized between the current 12 weeks, which is allowed versus ten, versus eight. So moving a bit more in your direction. And females from the current 16 versus 14 versus 12.

But we also want to use the study to collect parameters relating to iron deficiency. So a number of markers of iron stores. But in some subsets of people to conduct studies of quality of life, exercise, tolerance, etcetera because I don't think we do understand whether sub-clinic or non-anemic iron deficiency really has any important consequences for normal healthy people and we would like to do that.

The other thing is perhaps to try and look to the future. Because we hear an awful lot about personalized medicine. And applying rules to all men and all women might look a little old fashioned in not so very many more years.

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So we can take the advantage to look at a number of genetic markers of our own handling of things like body mass index, diet, and so on, to see if we can come out with a better way of handling donors that reflects their capability to donate on the one hand versus obviously avoiding the risk of iron deficiency and the anemia. Because it is just this feeling that maybe iron deficiency is a cause of donor loss that we are just not capturing by these self-deferring donors.

So that is the plan. We do, it is very ambitious. We have done large studies using donors for population health studies but not really to answer donor health questions. So we are going to do a big feasibility study over the next 12 months and then rule it out.

So the study if it all works, will report in about three years. And that is I think is where we are in the U.K.

MR. SPENCER: So may I ask how long you intend to follow up the 50,000 donors?

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DR. WILLIAMSON: Yes, for two years, which you might say is a relatively short period of time and it may be that at two years we will try and go on longer, funding permitting =.

MR. SPENCER: Right. I wanted to comment on that with respect to the question of intensity or productivity of donation. Generally a circulated figure one hears here in the U.S. is that the average donor gives about 1.6 or 1.7 times a year. But that is a composite that reflects a tremendous amount of underlying variability. You have people who come in once and they are gone. You don't see them again for years and they have contributed a full donation to that average 1.6 all the way up to the person who is giving two or three times year over year over year. And there is quite a bit of variability. So one of the things we did that didn't present these data today is to classify the donors in the REDS database by their profile the first time

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they appeared in a period of observation by gender the same age groups that we showed and whether they were first-time or repeat donors.

And there were really only of the 16 different groups, only two that are donating at an average, so following up from that first moment through the end of December 2009 that gave it that rate of 1.5 times per year or greater. And that was males in the two oldest age groups. And most of the other groups were half that frequency.

So if you do look at longer periods of time as opposed to a cross-sectional average one and a half times per year, you see quite a bit of variability in the productivity.

DR. GORLIN: The issue of donor interval has now been raised. And Bryan from your data, it would seem that in order to come back completely to baseline hemoglobin it takes half a year or more. But as Richard has pointed out, a relay team is only as fast as

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its slowest runner. And so a small subset of individuals that take longer than average can certainly bias an interval.

What does your data say about what interdonation interval should be. And I leave it to you and Richard to let some fur fly.

MR. SPENCER: Well, I was asked to comment specifically on hemoglobin today. So the interval I wasn't addressing specifically the question of iron. And I think that interval, even while it is related to hemoglobin, recovery is much more important in terms of a donor's iron status than what their hemoglobin level is. Since it does take time for hemoglobin to recover, obviously we care about it at least from an operational point of view and is of less importance asking is this an anemic donor than is this an iron-depleted donor.

That said, wherever we draw that line, you are right, it is an average. So if on average the odds ratio of hemoglobin

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deferral is returned to one at 30 weeks or so, 26 weeks there will be some whose personal risk has reached one at a much shorter interval and some haven't reached it at that point. So whatever that demarcation is, there is going to be people on both sides of it. And if there is a lot of variability in what we are using to measure it, we should be mindful of that in drawing the line in terms of this will have a big impact on our operations, perhaps on availability. So we should be mindful of how much precision there is in a given measurement.

DR. BENJAMIN: Just you brought up the odds ratio again. And the point I was trying to make earlier was from that graph if the odds ratio, if deferral of male donors is at one percent for low hemoglobin, your odds ratio went up to two. So basically at eight weeks you were at two percent deferral and you dropped down to one percent by 40 weeks. It tells you nothing, that graph on odds ratios

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tells you nothing about the 98 percent of males that are acceptable as donation.

And so it is a lie behind our odds ratio. If you don't look at the actual numbers, you should be careful about using those to make decisions.

MR. SPENCER: That is absolutely right. And with respect to what the recovery might be, if we lengthen the interval from eight to 12, maybe we lowered the risk for deferral in males by 30 percent. But you are right, that is 30 percent from a very low number.

DR. BENJAMIN: So let's be more concrete than that. Donors recover because the iron has come. But you know, they take the iron and they metabolize it. It is dependent upon how much iron they are taking in, not the interval. You know, it is a surrogate for how much iron they are taking in over more time. And so I just think we should first address the issue of perhaps they should

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be taking more iron in before we defer a large cohort of donors, most of whom would be eligible to give blood but a subset aren't. And we are penalizing the whole group to get to a small group who could really do with some more iron. So I am clearly not in favor of this at all.

MR. SPENCER: No. I'm not sure that we are arguing different points. I think that you are right.

DR. GORLIN: Dr. Epstein?

DR. EPSTEIN: Thank you. It is a question for Dr. Benjamin.

So you made a strong case that if we raised male hemoglobin and do nothing about female hemoglobin, we create a very difficult situation for blood centers in terms of supply and perhaps also for recipient safety. And you argued also that when you pilot studies to allow unintended consequences but also potentially to study alternatives. So this perhaps fast forwards to the end of tomorrow.

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But do you have current thoughts about what pilots we should be undertaking?

DR. BENJAMIN: I think that perhaps they already are being undertaken. Bryan mentioned the study from Wisconsin around iron. Those are academic studies and those, I believe, REDS should be supporting. And I think they are ongoing. I think REDS III has some plans in this area as well.

So we should be looking at the studies of interventions and then multiple interventions. If the donation interval is one of them and iron, you know, giving iron or education is another and ferritin levels is another, then we should look at all of those and see which make the most sense. It is an academic question and I think it is being addressed at this point.

DR. EPSTEIN: Thank you.

DR. GINZBURG: Yelena Ginzburg, New York Blood Center. I have a question for Dr. Spencer.

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You mentioned towards the end of your talk that female donors both have a larger drop in hemoglobin post-donation as well as that they recover more quickly. And so my question is about that in terms of interdonation interval about if we do switch to a more female population and many female donors start at a lower hemoglobin, you need less iron to go back to a hemoglobin of 12, compared to how much iron you would need to get back to a hemoglobin of 16 hypothetically and what that would mean for the new donors that would be recruited, should we change the interval for both males and females.

MR. SPENCER: So I'm sorry, I didn't get what your question was.

DR. GINZBURG: How do you interpret the idea that a larger drop in hemoglobin that occurs post-donation in females simultaneously occurs with a faster recovery and what that would mean for changes in the blood donor pool if we changed hemoglobin cut-offs?

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MR. SPENCER: Well I think that it is not clear that females and males are recovering, are reaching their prior donation hemoglobin level at altogether different points in time. The females have a larger drop but the slope is quicker such that they are making up ground more quickly than males do. And that graph suggests that controlling for gender, that they are reaching a change of zero, a net change of zero at a given point in time.

The gender affect seems to be, to a significant extent, a function of body mass because we have removed gender and added body mass to the models. And we don't see that much difference. So it is partly a function of a larger donor is losing proportionally less blood. And so you might expect them to recover more quickly.

DR. GINZBURG: Thank you.

DR. GORLIN: Dr. Cable?

DR. CABLE: We are assuming and I

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think it is a good assumption that the slow recovery that Bryan displayed from the 900,000 donors that have paired quantitative hemoglobins by a fingerstick, we are assuming that data suggests that the limiting problem in recovery is iron, iron availability. And I'm thinking that is a very good assumption but we haven't shown it. So you know, it is only an assumption.

Also, I mean there maybe erythropoietic or other issues that we are not entirely aware of. At least in the short run, for instance, autologous donors, when we were trying to get a lot of autologous donors, it was shown to be helpful to give them both EPO and iron if you wanted them to recover fast. Now these are pretty slow recoveries.

The other thing we haven't even begun to look at in the personalized medicine issues is are there people who -- It is said in hematology training that when someone becomes iron deficient, they start to absorb

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iron a greater percentage of their dietary iron. You never absorb more than 25 percent of your dietary iron, according to the training that we have all received, and usually it is more like ten percent. Some people then when they start to give blood go from ten percent maybe to 20 percent but we don't know whether everyone does that or whether some donors just can't turn on to absorb more. And if there are such donors, these are the donors that can't really be good blood donors and maybe they are the ones that disappear after four donations and are not in our donor pool.

So I think the question of getting iron into people is something that blood bankers are going to have to become a lot more savvy on because we have evidence over very, very prolonged recoveries, 40 weeks. Now the good news is that it is not two years because we know from the RISE data that people who haven't given in two years, we called them

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reactivated donors, look almost identical to first-time donors. So after two years, whatever donation lesion has created in your iron is gone. So we got 40 weeks and we got two years. Somewhere in there everybody gets back to normal after they stop donating. But 40 weeks is a long time, given that the studies that allow the eight weeks were five weeks on the upside or five or six weeks on the upside.

Obviously, these were young men and they were first-time. They hadn't been donating and they had plenty of iron. So no one has ever looked at the recovery except REDS III proposes to do so in actual blood donors and how quickly do they recover. And How is it related to iron?

I think these really haven't been looked at and in particular the individual variation might be quite important as we go forward in determining what to do with Sally who is deferred or when Sally can come back to

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donate, which is what we need to decide.

DR. GORLIN: Dr. Mast may want to comment further but certainly in his study of super donors, people that successfully donate every six to seven times a year thinking there might be a higher rate of hemochromatosis donors, I believe he did not find that but in fact there was a higher rate of smokers. I don't think anyone here is suggesting we should be handing out cigarettes and not cookies. Right?

So individual variances are interesting for a study but I'm not sure it is so practical in mass application.

Question?

MS. SIGMON: Yes. I'm Jan Sigmon from the National Institutes of Health. I have a question that kind of goes to all of you.

And you are talking about perhaps taking more of the female donors. I'm in hemovigilance and I look at donor reactions.

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And I will tell you that we see three to one donor reactions in women than we do in men. And in talking to donors after their reactions, I find that most of the time women will come back a second time and if they have a second reaction, they will not come back again. They are afraid to come back again.

So I think that as we look at more female donations, particularly in the younger groups and I have probably more donation reactions in the 20 to 23 age, something like that, than I do in the older donors. But we do have donor reactions in people that have given 15 and 20 times and suddenly these women will stop donating also.

So I just say that we need to look at perhaps when we are thinking about having more female donations and putting the burden on the female population of picking up those donations, that we might look at the fact that in the donation reactions we may see, it may in fact deplete our donor supply again even

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more.

DR. GORLIN: Dr. Kleinman?

DR. KLEINMAN: Yes, well I think she wanted an answer to her question or comments.

DR. BENJAMIN: Shall I just address that?

Certainly gender is a big issue with donor reactions. But I believe that age is even a more powerful determinant and so, especially the young females, the high school kids that I am particularly perturbed about. So this is something that I actually follow in the Red Cross Hemovigilance System. I know other systems have similar programs and are very concerned about it. Any change in recruitment patterns are going to have any unintended consequences on your donors. And my only point really was let's not make changes without understanding what they are.

DR. KLEINMAN: I just wanted to return to the issue of hemoglobin recovery.

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And just make two comments about that. One I think that this hemoglobin recovery out to potentially 40 weeks, it is still a model. You know, it is a model based I think primarily on cross-sectional data. There might be some follow-up data. But still, it isn't a study per se. And I think the model may or may not turn out to be correct.

So because of that, REDS III is actually planning to study this in more detail. And there is a protocol that we are hoping to launch soon. It is a logistically complicated protocol and actually there are people in the room who are PIs on this who could probably comment better than me. But basically it is a study that will ask donors to come back quite -- So a person will give a donation and they will be asked to come back to give blood samples at I think sort of two weekly intervals up to one week, two weeks, four weeks, six weeks, eight weeks, 16 weeks, 24 weeks, to get enough plots on the curve to

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see what is actually happening with the hemoglobin.

In addition, donors will be randomized into, based on their ferritin levels as to whether they are iron deficient or not. And also some will be given iron supplements and some won't. It is really to alert the group that such a study is in the works, we hope. As I said, it will be challenging to carry out, I think, but it is certainly in the planning stages. But this I think will -- and the reason for the study is because we don't really know what hemoglobin recovery is yet. We don't really -- I mean, we are showing data but I think we need to recognize that data is a bit conjectural and it isn't solid yet and we think that a new study will shed some light on something that really hasn't been studied in enough depth.

And I don't know if any of the PIs who are in the audience want to comment any further on this.

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MR. SPENCER: I would just like to point out that you are right in highlighting one of the limitations of observational data.

We have a model that is strong in the sense that it is using repeated measures on individuals so individuals are serving as their own control. But it is not randomized so we can't assume that someone who comes back at eight weeks or ten weeks is equivalent in all respects to someone who comes back at 40 weeks, other than the difference of interval. Is there likely some other factors that come into play for someone who is coming back at eight or ten weeks that distinguishes them from someone who comes back at 30 or 40 weeks and might just barely be approaching hemoglobin recovery? I think there well might be. I would be very surprised if there weren't any significant differences there.

So I think that the randomized study being planned in REDS III is very important, as well as the 50,000 study being

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planned in the U.K. I think those are going to yield very important data that observational data will take you only so far.

DR. GORLIN: Richard, you mentioned the low level of evidence that low level iron depletion is actually causing harm. But Dr. Katz often says a lack of evidence is not evidence of a lack of harm. And Dr. Newman, you have certainly been vocal in the community in talking about issues of iron deficiencies.

So Bruce, if we could hear a little more from you about concerns of the kind of iron deficiency donors are experiencing.

DR. NEWMAN: One of the facts is that iron itself, people who lack it, whether it is anemia or not anemia, have lack of endurance and are more fatigued. So that is one of the items.

It also is going to increase referrals to physicians which are going to require work-ups and expense and inconvenience. So that is part of the iron

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story as well.

There are other factors. I'm just trying to think. Pica is I think more of a minor issue. Restless leg syndrome, the evidence seems to be against it but we need to wait for more additional studies to see if that is a factor.

These are some of the things I can think of off-hand. So we are hearing about some exciting studies to really document objective measures of iron status or iron homeostasis but to any of the group, what sort of studies should we be doing to look for minor effects of iron deficiency. How do you go about measuring it?

DR. BENJAMIN: It seems to me, Jed that if there are ongoing studies where we are following donors in the future, he should at least have a questionnaire of some sort for those donors at the beginning and various times when we see them just to see how things may correlate with iron. That was just the

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most empirical data out there. We haven't done any of it.

And it is hard to think about what the outcome of any intervention will be if you are only measuring a lab parameter.

DR. ALVING: Barbara Alving, Uniformed Services University or whatever.

I think some of the things we have to think about is the dynamic situations of our donors. So if you are thinking about men and iron deficiency, chances are, they will not be losing iron in other situations, unless there is trauma, etcetera, etcetera.

With women of child-bearing age again if one were an OB/GYN person, one would say well they are in a perpetual pre-pregnant state. So I think one of questions might be what is the potential harm for a woman who has iron deficiency is now then conceiving. And it sort of brings back the whole question of deciding on folate supplementation of flour, so to prepare women who would become pregnant.

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So I think that is one of the questions that we have to think about.

Furthermore, women will continue to lose iron during menstrual cycles. So I think that is another aspect that this is a very dynamic type of situation for women.

The other thing I wanted to ask about is as you looked at the differences among blood centers, is there a difference, what is the difference in the approach to counseling the blood donors? And have you looked at that and looked at that in terms of variability? How many of your donors go out and take iron just because they have been told they should be taking iron? So is that a factor in some of the differences that you are seeing? And are you capturing that?

DR. BENJAMIN: Could I just comment? I think pregnancy is a great example of another iron-poor state. I just want to note that our response to that iron-poor state was to education and advise folate and iron.

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We don't defer them from pregnancy.

(Laughter.)

MR. SPENCER: With respect to the way donors are counseled, there is a recent paper that Dr. Mast and colleagues have published that shows some of the practices and variability across different blood centers. But I wanted to speak to the question of what donors are doing with respect to iron supplementation. And we did actually measure that for the RISE donors at enrollment and at their final visit. And we found that about 40 percent, not quite 40 percent were taking iron at enrollment but the proportion was greater in females and greater in repeat donors compared to first-time donors.

The share that were taking iron at the final visit, 15 months to half a year or so later, had dropped slightly but the relative magnitude stayed the same, females more than males, and repeat donors more than females. And by and large, there wasn't much

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change over that time period. Eighty percent of the people at the end of RISE maintained the status they had at the beginning and we don't have a lot of data to work with there but it is one of the inferences that the data suggests to me is that some of the donors appear to be taking iron perhaps incidental to blood donation, not because of blood donation.

I would suspect that certainly some proportion of those taking it are doing it very specifically to support greater donation intensity and I have heard that anecdotally from donors. But in any case, the relatively high proportion of frequent donors already on iron and we are seeing this in the STRIDE study with Wisconsin does suggest that the marginal impact of supplementation programs might be limited by the number who are already on iron or who are reluctant to go on iron.

DR. NEWMAN: I would like to bring up in females, and it is at 12.5, the deferral itself is a negative event. First of all, the

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person comes and is disappointed that they can't be accepted as a blood donor. Secondly, it is a waste of their time and effort that they came. Then they are wondering what is wrong with them. They may make a self-referral to a physician which involves a co-pay and an expense and work-up perhaps. And so that is a negative event. Then there are probably, if they are in this range where they are between 12 and 12.5, they are told they are normal. So they are wondering well why wouldn't they accept it if they are normal. So that becomes an issue.

And so all of these become a very negative events. In addition, we know that we lose about 30 percent of people in terms of coming back if they are deferred for low hemoglobin.

So I think we have to take into account that the setting it at 12.5 causes itself a negative event.

DR. GORLIN: Susan?

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DR. LEITMAN: Hi. Susan Leitman, NIH. I was just going to comment on your previous comment on that, Bruce.

So in our iron study, I just want to give the panel some idea of what happens when the donor center doesn't take prospective measures to mitigate iron loss but leaves it to the donor and the donor's physician refers the donor to their own physician. And it is a very dichotomous event, depending on gender.

So the female, who is less than 12.5 who wants to continue to donate and goes to her physician finds that she has a hemoglobin of 11.5 to 12.4 in the physician's office and the physician says there is nothing wrong. Because it is in the normal range, an iron panel is frequently not done per DRG. And when the donor says but I would like to continue to donate, what should I do, the private physician says don't donate. So it is a negative event for the blood center.

For the male who is about 12.5, the

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opposite occurs and a large GI investigation with invasive studies is done and very commonly the reason for the low hemoglobin was simply a very frequent prior donation schedule. So it is not really a service to the donor who is male to undergo the colonoscopy.

So either way leaving it to the donor seeking advice from the private physician doesn't really work out well for the donor.

DR. KATZ: There is currently a project in its early months in the blood community to develop a standard set of education materials for donors and there will be a module that has to do with this. And I think it is our responsibility up-front the first time a donor walks through the door to clue them in to these issues. The difficulty, of course, is we have all kinds of things we want to tell them. Which are the most critical messages?

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I mean I think this one is a no-brainer in terms of adequacy of the blood supply but it is going to compete with lots of other information that we are trying to provide donors and reeducate them at the beginning of their donation careers.

DR. DAVEY: Rick Davey, FDA. It appears that over the past several years the blood supply has been quite stable and some would even say robust. And our understanding is that some blood centers are actually contracting their donor operations because of difficulty in moving blood. If that is the case and I would like to ask the panel if they would agree with that, should that be considered at all in the timing of any change in hemoglobin standards? Could it be more easily tolerated these days because the blood supply is apparently more stable in someone more robust?

DR. BENJAMIN: Maybe I can address that. It is indeed true that over the last

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two years during the recession we saw a more robust blood supply. And the reaction of the blood centers were basically, I mean I think there probably has been a four to six percent reduction in red cell collections over the last two and a half years.

We have been laying off people and laying off trained people. We have been cutting back. We operate on an extremely thin margin. So we don't have the people anymore to collect that blood and we don't have the recruiters that would have recruited those donors. So to build up again is an expense. It is a serious expense. So it is not like the blood is lying around because we don't waste blood. We stop collecting it if we don't need it.

So I think there is a cost involved which needs to be factored into to any decision.

DR. GORLIN: Steve.

DR. KATZ: Well there is -- Jed I

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think you are aware of some of this data. Amongst the independents, there is a fair amount of benchmarking going on and there are signs over the last quarter that that glitch or oversupply of red cells may be mitigating actually fairly quickly and supply is getting tight again. So I caution against assuming that the blood supply is going to be robust ad infinitum. I'm going to need my hip pretty soon. I guess I'm going to need some blood. And so there are an enormous number of demographic and economic variables at work here and I don't think it would be wise to count on there being a robust supply over the long haul. If you make a mistake, as Richard pointed out, it is far more difficult to ramp collections up than it is to ramp them back. Far more expensive and far more difficult to be successful. So I would be cautious with that approach.

DR. NEWMAN: Just to add to that, we all know that the population is aging and

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that is going to be associated with even needing more blood for them.

DR. FORSHEE: Speaking just for myself and just to the general point that was raised, it certainly seems to me that it is appropriate to consider whether we are in an area where we have a surplus of blood or where we are near the margin when we are considering what the public health value of taking steps to reduce or expand the blood supply. So I think that it is a consideration whether we are in a tight situation or a situation where we have a comfortable margin, it seems to me that that would be reasonable to consider in making some of these decisions.

DR. KLEINMAN: Yes, I have two additional questions. The first is could we consider different hemoglobin cut-offs based on race? Clearly normal hemoglobin levels differ based on race. And I know people generally don't want to go there but it seems like a reasonable question to ask.

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I wonder if panel members have any opinion on that.

DR. KATZ: I think that Richard indicated some difficulties with the more complex we make our donor-room procedures. And I think the answer to your question is directly in proportion to the level of automation you have in your donor-room. And if we build systems, which we are trying to do all over the country that automate those procedures so that when the donor designates their race in the computer it tells you what you can draw and what you can't, you can mitigate that. But we are not quite there yet. It is doable without enormous increases in errors and omissions. But more automation in the donor-room is probably necessary to allay the kind of concern that Richard has.

DR. BENJAMIN: I do think it is probably more socially acceptable to be sexist than it is to be racist.

(Laughter.)

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DR. KLEINMAN: Yes, well I think we have to look at that and I don't think that is racist at all to say we have a different cut-off if we have differing normal levels. So I think that is a dismissive statement and I think we should look, and I know it is a politically difficult question but why should we reject that out of hand that we can't have different population norms?

DR. BENJAMIN: Steve, I don't reject that at all. It was a facetious comment and I apologize for that.

I think what Louis just said in terms of complexity is really the only barrier. And I do think if we are going down the path of having more appropriate normal levels, that that is a natural follow-on from gender would be to look at the racial differences as well because clearly they are quite marked differences.

DR. SIMON: Well the other issue there, though, Steve is we are a melting pot

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and we have more and more people who are not of a distinct race that one could classify. So I think that, and then all the nuances you know, we tend to look at the black or African American and the white but there are a whole host of others that probably have different normals as well. So it gets very complex.

And my feeling is that it is probably not a direction that is going to be --

DR. KLEINMAN: Yes. No, I realize that it is complex. But I think you know if we were to raise the hemoglobin cut-off in males, if that turned out to be the thing to do because of other considerations, then one of the consequences are that we lose more black donors and they are important donors because of their phenotype blood.

So maybe it is impossible. I don't know. But I think again if we don't change the hemoglobin cut-offs, I don't think it matters. But if we do, couldn't we somehow

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give consideration? And maybe this is just a nice theory and impossible in practice.

Well you would also have to look I think we need more in-depth investigation into the reason for those differences. I think there are some that are understood but most are not. Could it be that a larger proportion of the population is anemic and is skewing what the "normal value" is based on statistics? So I think we would need more investigation into that before we did that.

MR. SPENCER: Further to your point and the issue of complexity. Certainly it increases complexity to have two standards by gender and then perhaps to extend that to different requirements based on race. But the transfusion community has certainly responded to what it perceived as significant issues relating to donor well-being.

Previously and specifically with respect to reactions such that in a high school setting at least and for young, low-

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weight, low-blood volume donors, there are different standards that depend on height, weight, gender, and age. So it is without question more complex. But unless we know it is impossible, it may be complexity that we have to work really hard to figure out.

DR. NEWMAN: I think the way we are approaching race today, it is based on self-selection. So you decide what you are. And one could argue that the black African American population is 25 percent Caucasian based on genes, but it is based on self-selection.

To my knowledge, iron depletion hasn't really been the issue for the differences in black African Americans. I have heard, I understand at least alpha thalassemic trait might be an issue.

But it is an issue because any change in hemoglobin for men is going to affect them. Any decrease in women is going to help them.

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DR. KLEINMAN: Well my second question which was along the same lines, a little bit different but on differentiating hemoglobin, it seems to me that a repeat donor who fails hemoglobin is different from a first-time donor who fails hemoglobin, whatever the cut-off is. And that is, you have a potential explanation in a repeat donor, that is he has failed because you have taken blood from he or she in the past.

A first-time donor, that is not the explanation. And I guess it can go two ways.

As Susan mentioned, it could be because that person has a medical problem. But you know these are only normal ranges and as Jed has cleverly in his slide, people are normal but they are two standard deviations from the mean. So you know if we have a first-time donor whose hemoglobin is below -- This goes more to the question of what do we tell our donors. Because I don't think we know -- we are not doing it consistently yet.

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But it would seem to me that if you are a first-time donor, this could just be the fact that you fall -- It is normal for you, in other words but it is a statistical aberration. So I wonder maybe a little discussion of what low hemoglobin means to the donor and if anybody has any reflections on this difference between the significance in a first versus a repeat donor. Not so much from the viewpoint of collecting but what our obligation is to tell -- what information we should give to people.

DR. SIMON: Well, I think you know, having some experience with this, I think it just gets very complicated. Certainly you are right that repeat donation you would have an explanation. But then you have to look at how frequent.

I mean, I have a personal experience because I used to donate every eight weeks and got iron deficient. And I didn't think anything of it. And then my

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doctor diagnosed me as anemic. And at that age group, I had to have a colonoscopy and all that sort of thing, even though I knew it was due to blood donation. So I think it gets rather complex and I think these messages are going to be very carefully worked on. And because every situation is different, it is going to be problematic in the long-run.

DR. GORLIN: Dr. Sayers.

DR. SAYERS: Thanks. Merlyn Sayers, Carter BloodCare and University of Texas, Southwestern.

I must say I am left at the moment with the sense that on the one hand we are talking about interventions like lengthening the interdonation interval or changing the crit. But we are looking at those interventions and we are in search of a justification. I have yet to hear that.

And this comment really harkens back to something that Steve Kleinman said with regard to what do you tell the donors. I

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mean, we know what to tell donors when we defer them with a low hemoglobin or a low crit but so many of them say well when should I come back. And I think it is going to be different for the first-time donor and for the regular donor but maybe there is room for some comment on what is the information that you give to somebody you have deferred with a low crit in response to their question well, when do I come back?

MR. SPENCER: I guess I would ask what do we do now?

Without commenting on what we should be telling them, I can comment on what donors do. And a lot of them come back very quickly and these are data that I didn't show either but a lot of people come back within a week or two of having been deferred. And that may be a recognition of a certain amount of variability in the measuring of hemoglobin as experienced donors. But what we see stratifying by age and gender is that in

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females, who make up most of these deferrals, within a week, those coming back within a week, their average hemoglobin is half a gram higher than the one which caused their deferral.

Now remembering that at that point in the recovery process the recovery is slower, we certainly shouldn't expect physiologically a half gram difference. That can only be a function of a sampling issue or just a lot of variability in measurement. And 50 percent of them, a week later, get accepted.

DR. RUTA: Yes, hi. Martin Ruta. A couple questions. One about iron supplementation. So we kind of looked at that before. And there have been workshops in the past but not a lot of takers. So you know, we have kind of searched around the world and found one person in Denmark a couple years ago who is doing a limited iron supplementation and Dan Waxman here and Harvey. But

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otherwise, it didn't seem like there were a lot of takers in terms of trying iron supplementation. So one question is really is there likely to be a change in perception or willingness to try iron supplementation and there were a whole host of reasons why people would want to do it.

And the second question goes back to a supply. So just logistically, if a supply is contracting now because demand is contracting, is there any way to target the contraction toward increased intervals or toward higher hemoglobin level of 13 for men or is that impractical?

In other words, if you are collecting less because you need less of a supply for the hospitals, is there any way to say don't come back six times a year, come back five times a year? Or is there any way to say that the people we defer will be the males with the levels below 13?

DR. BENJAMIN: I just maybe can

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comment on the contraction that we have experienced in the Red Cross is when we have excess blood on the shelf, we collect less blood. We don't do that indiscriminately. We select which blood we don't collect. So we stop going out on Sundays where we pay the staff double time. We stop doing double red cell collections because the kits are way more expensive than a whole blood collection.

And that definitely is the case that the most expensive blood you collect is the last unit you collect. So you in fact, when you withdraw, you actually save more money than you would because those are the expensive units to get in the door.

So if we have to re-expand, we are going to be expanding on the most expensive blood we have. So another issue with the recession has been tremendous financial pressure on blood centers around the cost of blood. And I know many blood centers have not increased the price of their blood for a

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couple of years and in fact may have even decreased it with the many customers.

So there are these complex pressures. And I think to just say the blood is lying around for us to pick it up is a misconception.

DR. GORLIN: I'm going to ask the panel to hold on iron supplementation questions because that is our entire subject for tomorrow. So if you can wait on that, that will be addressed tomorrow.

DR. KATZ: I just wanted to make one comment. And that is, I looked at the agenda weeks ago and now I am stricken that I missed the point that we really didn't put on the agenda the issue of what happens when people get iron depleted short of anemia. And I think it is important and I think Merlyn was saying this as well, we really need to understand what it is we are doing bad, if we are doing something bad, what is we are doing bad by drawing donors at the levels we are

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drawing them at now.

It strikes me that we are kind of stuck in this rationale it is not nice to fool mother nature. And in general I think that is true that we probably shouldn't perturb physiology but the potential impact of changes in hemoglobin standards is really enormous and perhaps we should be focusing on if we are doing something bad, what is it.

DR. GORLIN: Alan?

DR. MAST: Hi. I'm Alan Mast from Blood Center of Wisconsin. I have a few comments.

So from my -- I don't know where to start. So I don't want to be iron deficient or anemic. And I don't want my family members to be iron deficient or anemic. So it doesn't really matter to me whether there has been any studies to show that these things are harming them or not. It doesn't matter. I don't want them to be iron deficient or anemic.

I think there are good studies. I

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think Pica is a big issue, a lot bigger issue than we recognize. Lots of blood donors get Pica and then they, and I know at least one, they go home and their family thinks they are crazy because they are going to the gas station every day to buy ice.

I think there is good studies in girls, teenage girls showing that they get iron-depleted without anemia. They have decreased performance in cognitive tests. And if they get iron-deficiency anemia, they have decreased performance and they do it more slowly. And I have a 16 year old girl and I don't want her to have decreased cognitive function. So those are my comments about those. Whether or not we are trying to prevent anything or whether or not it is important, I think it is.

The other thing I wanted to say is that we have done, as far as what kind of education to tell donors, it is not rocket science. We did focus groups and these data

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we published these in transfusion a couple years ago. And they basically just want to know the truth. We went to a lot of them and one of the problems with a focus group like this is you get the crazy donors that agree to be in a focus group. Some of them are just crazy. They want to donate all the time and they are trying to find out -- You know, every time they are deferred, they want to know why it is deferred. They want a recount. This is wrong. You know, dah, dah, dah, dah. And none of them knew to take iron more. They were trying the three-bean chili. They wanted everything, no matter how hard you tried to direct their group to what you wanted them to, they went back to what did you eat last time before that allowed you to get accepted. That was the number one thing was what dietary changes could they make to not have a low hemoglobin deferral. And none of them were talking, oh, I just take iron pills.

And the one thing we did do is we

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got out of them pretty clearly is they want to have, and we made a new hemoglobin pamphlet that is not being used anywhere, not even at Blood Center of Wisconsin but I think it is a pretty good pamphlet on how to educate donors about hemoglobin deferral. And it starts out with common things and then it progressively gets worse and worse, you know, more and more severe. You know, it goes from vitamin deficiency to diabetes and rheumatoid arthritis and different causes of anemia, all the way up to colon cancer or other kinds of really bad things that could happen. And they specifically said this in the focus group, don't scare us. Because when we originally made the pamphlet we had it, you know, it could be something bad. You know, don't ignore your anemia.

We also have something in there about donation intervals. So we are not trying to -- but they wanted to have other things before that so we changed the whole

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pamphlet around to have the worse things be last. So we didn't try to scare them intentionally.

And then it has this other experience and this is all anecdotal evidence.

We looked at deferral of 104 people. And the only thing they did to agree to be in this study is we sent them a letter and if they agreed to be in the study, we were just going to get a survey three months later. And when we got the surveys back, one of the people had Stage 4 lung cancer. So three months earlier, they were a healthy person trying to donate blood and now they are Stage 4 lung cancer with metastases to the liver and lung -- liver and somewhere else -- and bone. Liver and bone it was.

And then another person was just deceased. And so there was nothing in the survey. It just said deceased and so we didn't know why this person died. So I figured that since this person officially died

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on our steady protocol and could have died from the stress of knowing there was a survey coming in the mail in a few weeks.

(Laughter.)

DR. MAST: We better find out why they died. And so I called his wife and he had died of acute lymphocytic leukemia. And this first sign that he had disease was when he was deferred for blood donation. And I said in this letter, now that we are trying to work on this, I wanted to tell her we recognize this is a problem and I am trying to help. There is a group of us at least here trying to figure this out and do it better. And I said but we are intentionally trying not to scare donors. And her response was well I think a little bit of scaring would have been good, you know, from her point of view. So that is just one story.

Anyhow, I will be quiet now.

DR. GORLIN: I am hearing grumbling stomachs from the front. So I think we are

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going to cut it off here, if you don't mind, Rich.

DR. DAVEY: I'd like to thank Jed and the panel for their contributions. We will break for lunch. Take about an hour, back here at 1:15 and we will take the afternoon session.

So again, thanks to the speakers and we'll see you after lunch.

(Whereupon, at 12:19 p.m., a lunch recess was taken.)

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A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:16 p.m.)

DR. BIANCO: I think we are on time to start Session 2 that will look at hemoglobin measurement in blood donors. And essentially as the organizers thought, there are several methods for hemoglobin or hematocrit measurement based on a drop of blood drawn through a fingerstick. And these tests produced different results from different sites, the finger or the earlobe or whatever. There has also been a search for noninvasive technologies that would reduce donor discomfort but they appear to have even a larger coefficient variation.

The goal of this session is to perform a critical review of available

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methodologies in the observed variation. And at the end of the presentations, there will be a panel that will be chaired by Dr. Harvey Klein that will try hopefully to address which are the current methods and samples types acceptable, how much variability is acceptable and should decisions and ideal hemoglobin standard in blood donors be taken into consideration the variability of results based on test method and sample type.

And actually the question that we are not specifically asking but that is in our mind is is there a gold standard for hemoglobin? Because I think that even as a surrogate we don't have one.

Our first speaker is Dr. Mindy Goldman from Canadian Blood Services. She is going to talk about measurement of hemoglobin in blood donors: instrumentation and sampling methods. Dr. Goldman has been active in many facets of transfusion medicine in Canada, including optimization of donor eligibility

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criteria.

In 2005, she was the recipient of the Canadian Society for Transfusion Medicine, an award recognizing an individual who has made a major contribution to transfusion medicine in Canada. She is currently the executive medical director of donor and transplantation services at CVS. Mindy, welcome.

DR. GOLDMAN: Thank you very much.

Also I would like to thank the organizers for inviting me.

As also mentioned, I am going to give an overview presentation on the measurement of hemoglobin in blood donors. There will then be other more learned speakers who are going to go into greater detail on instrumentation and sampling methods. So if you have any difficult questions, they should be reserved for those speakers.

(Laughter.)

DR. GOLDMAN: So I am going to talk

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about important factors in hemoglobin measurement and then move on to source of sample, timing of sampling, methods of measurement, a little bit about capillary sampling in general, and the influence of measurement accuracy on donor deferrals.

So what are important factors in hemoglobin measurement? Well obviously sensitivity is key. So we want to defer donors that are below our cut-off. It may actually be more important to defer those that are actually most likely to be anemic. So all the male donors in North America below -- And here is the difference between Canada and the U.S. In Canada, the criteria is 125 grams per liter while in the U.S., it is 12.5 grams per deciliter. So I apologize for the measurement changes but it is the same thing.

So all the males that are below 12.5 and the women that are particularly low, you really don't want to accept those as donors. Then specificity is important. So we

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don't want to defer people who are actually eligible and there have been some nice studies done, some by people in this room showing that these people may never return, especially if they are early in their donation career.

Another point that might be important is actually see over the entire range. Why is this important? Well partly for donor counseling. You may want to have different messaging for a female donor who has a hemoglobin of 10.4 versus one who has a hemoglobin of 12.4. Also for re-booking strategy so we are not currently doing this in our organization but in other countries such as Australia and the Netherlands, the frequency that donors are called to be rebooked does vary, depending on their hemoglobin level and the trending of their hemoglobin.

Donor satisfaction is an important issue. So it is not a very well-liked part of donation in our donor surveys. It is actually

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almost as disliked as the phlebotomy itself. Donors always want things to go quickly, so they don't want to sit around waiting for something to happen. So speed is important. And concordance with other hemoglobin determinations that they may have in their physician's office also contributes to satisfaction or lack thereof. And we have had good examples presented this morning. Donors are not too happy if you send them to their physician because they have a low hemoglobin.

The physician tells them it is normal and vice-versa. They are not happy if they pass your hemoglobin and then they have their routine checkup a month later and it turns out they are anemic. And since I answer complaint letters that come to our head office, I am familiar with both of these donor dissatisfaction issues.

And finally operational feasibility. I mean a lot of our blood is collected on mobiles. We need something that

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is quick and easy to use. We heard from Dr. Benjamin the importance of the KISS principle, Keeping it Simple. So a simple algorithm is nice. And because we are doing it on every donor every time, it would be nice if it was inexpensive.

So, what would be the gold standard? And if you are very observant, you might notice that this is gold. So it would be a venous phlebotomy sample drawn immediately before donation and measured on a laboratory analyzer. That would give us optimal sensitivity, specificity and accuracy. Unfortunately, it would give very poor donor satisfaction, waiting for results and it is not feasible.

So like a lot of other things in life from balancing the national budget or solving the global financial crisis, the optimal solution and the practical one are different. And what we are doing here is basically a compromise.

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So if we move on now to look more in detail at the source of the sample that we are using to measure our hemoglobin, you can use a venous phlebotomy sample from a separate venipuncture site. This is done for example in some European countries that do a donor pre-screen for first-time donors where only samples are taken and no donation. You can take a venous sample from the donation kits. So some people for plateletpheresis donation are taking a sample from the diversion pouch.

From a whole blood donation, you can take a sample either at the beginning of the donation or at the end. This is done in some countries and also is done in some studies, as we have heard about the REDS II study.

And finally, in lieu, I have a capillary sample because that is really the one that most of us are using routinely. The earlobe is no longer acceptable as a site because of over estimation and variability in measurement. And the capillary fingerstick is

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our mainstay.

Finally, noninvasive measurements are becoming available at least on the trade show at the AABB, although I do not believe that any are currently approved.

So the timing of sampling of North America and in most jurisdictions, it is being done immediately pre-donation. However, as was mentioned this morning as well, there are algorithms in some countries, in Germany and in France, where testing will be done on the blood donation. And based on those results, if the hemoglobin is high enough, then the donor may be accepted and not have repeat testing the actual day of their donation. Similarly, some countries do samples only testing and if the hemoglobin is high enough, they will not retest the donor.

So methods of measurement, color comparison, gravimetric method, copper sulfate, microhematocrit, photometers, laboratory autoanalyzers and non-invasive

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measures. I am going to go through these very briefly.

Color comparison more for the sake of completeness just to know that there has been a hemoglobin color scale that was developed by WHO and it chose color shades for hemoglobin levels between 40 and 140 grams per liter and it has been shown to be quite useful in developing countries.

Good old copper sulfate sink or swim method. So the copper sulfate solution has a defined specific gravity. And if the drop of blood sinks in the 15 seconds allotted, then it is assumed that the donor hemoglobin is higher than 125. And if the drop swims, then it is assumed that it is not heavy enough and the donor is considered a failure on that method.

If the specificity is poor, in other words, a lot of failures, actually have a high enough hemoglobin. So it is often combined with the second method to rescue the

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so-called failures.

So it is quick and relatively inexpensive. However, it is not quantitative.

So you are not actually learning anything about hemoglobin distribution in your donors or what their actual hemoglobin level is. It is quite operator dependent and it has a subjective endpoint.

There are false passes that can occur. In other words, it has some poor sensitivity there. And the pass rate in donors with an unacceptable hemoglobin compared to venous sample has been reported to range anywhere from five to 11 percent in studies from the U.K. up to 83 percent in a study from Spain.

Hematocrit systems. I should do a disclaimer that any company name that I am mentioning is just to give an example of that technology. It doesn't mean that I endorse or do not endorse that method and there might be many other companies out there with very

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similar products.

So microhematocrit systems such as ClearCrit and HemataSTAT, they are fingerstick capillary samples drawn into very small capillary tube. The tube is sealed and it is centrifuged for one minute.

More recently, ultrasound technology has been developed. This is the UltraCrit and there is measurement of an acoustic pulse through the sample.

Photometers. Photometers are based on spectrometric measurements in disposable microcuvettes at a given wavelength and path length. The concentration of hemoglobin is a function of the absorbance and the absorption coefficient. And the absorption coefficient is different at each wavelength for different hemoglobin species. So for oxyhemoglobin and deoxyhemoglobin.

So how do the photometers get around that problem? Well either oxy and deoxyhemoglobin are converted to a single

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stable species, such as azide methemoglobin or absorbance is measured at the isosbestic point, which is the point where both forms of hemoglobin have the same absorption coefficient or absorbance is measured and integrated over a range of wavelengths. So it depends on the method which of these is used.

So the first one that was developed and widely used is the azide methemoglobin method and an example of this is the HemoCue 201. So here you have disposal cuvettes that contain the reagents in dried form that will lyse the red cells, convert all hemoglobin species to azide methemoglobin. Then you have measurement of absorbance of azide methemoglobin at 570 nanometers and you also have measurements at 880 nanometers to compensate for turbidity caused by lipids and white cells and other things in your sample.

So more recent methods have been developed that require no chemical reactions on the cuvette. An example of that is the

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HemoCue 301, which measured absorbance at 506 nanometers, which is this isosbestic point.

Another example is the DiaSpect which we are now using at Canadian Blood Services which measures absorbance over a wide range of wave lengths. They both also correct at 880 nanometers and the advantage of these photometers is that the cuvettes are cheaper.

They are easier to store because they don't have reagents in them so they can be stored under a wider range of temperatures. And the readings are much faster. So the readings happen in five to ten seconds, rather than taking approximately 60 seconds.

Laboratory autoanalyzers I think are considered the gold standard so they also rely on absorbance. So they lyse the red cells, they convert hemoglobin to a stable chromogen, hemiglobincyanide. More recently companies have been trying to get away from cyanide which is not a very good agent for the environment and using other reagents. And

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then they measure light transmission at a wavelength of 540 nanometers.

Finally, noninvasive measurements.

They use optical, electrical, or acoustic methods of total hemoglobin measurement and their underdevelopment. Two of them that had booths at AABB, OrSense and Masimo. I believe they work by occlusion spectroscopy. They restrict blood flow in digit with a cuff and then they measure change in optical transmission at multiple wavelengths when the cuff is released. And if you would have made a better chemistry major than me, you can read about some of these methods in this article here.

I think they are quite promising but they are not yet licensed in the North America. Maybe some have achieved their CE mark in Europe and the data I have seen so far suggests still a higher coefficient of variation compared to the other methods that are in current use, but certainly very

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promising.

So what about comparison of methods? Actually when I was initially asked to give this talk, I thought I would put them all in one nice big table, my usual technique of punching a lot of papers into one table.

But it didn't happen for a variety of reasons. And one is that if you look at the individual studies, some of them use different methods but the same sample source.

So for example, they are looking at a portable photometer versus a lab analyzer on a venous sample. However, the photometers are actually designed to use a capillary sample, not to measure hemoglobin from a tube of blood. So you have to prepare the sample from the tube to be measured using the photometer.

And it is quite tricky as I learned when we validated our new method. So differences that you see may actually be due to improper sample preparation for the cuvette filling.

Other studies look at different

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methods with different sample sources. So they are comparing a fingerstick photometer reading versus a venous lab analyzer. So there you are not quite sure if the differences are due to the instrumentation or they are just into the difference in sample source.

And finally, studies use different donor populations that have a different percentage of female donors and use different eligibility cut-offs, as we heard this morning for example, for female donors. Some countries have a cut-off of 120. Others have a cut-off of 125, similarly for males. Different jurisdictions have different cut-offs. So the pretest probability of failure is different and that affects the sensitivity and specificity of the tests. So a test will look very good in a study that has predominantly male donors who tend to have high hemoglobin values and where in your jurisdiction there is a low eligibility cut-

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off, such as 125. The same test can look quite poor if you are looking at a donor population that consists primarily of females and you have an eligibility cut-off that is in the normal range for those donors. So the same test can look quite different, depending on which population you are looking at.

So in general, I would say that the microhematocrit and photometer methods are clearly more sensitive and specific than the copper sulfate method is. And in general, photometers are more sensitive than the spun microhematocrit. There is actually very little data comparing all the methods together and different photometers in studies may vary between them, although again there is no nice study that actually looks at several of them in an ideal fashion.

And it is interesting that in the REDS II study, I think three or four different methods were being used in different centers and maybe were responsible for some of the

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variability seen in the center effect.

So just a little bit about capillary sampling. There is going to be a whole other discussion about this. And we have already heard some of this as well but when you are doing a capillary sample, you are drawing a mixture of blood from arterioles, venules, capillaries, and some interstitial and intracellular fluids thrown in. There was a lot of variability in measurement related to multiple factors. The site sample as I have already mentioned, the earlobe is a higher result than a fingerstick. The anatomic position of the donor may make a difference, whether the donor has been standing for a while or sitting. Hydration level, room temperature, and last but very important, operator training and skill. And in many studies, the coefficient of the variation of the same method will be quite a bit greater using capillary samples compared to the same method being used on venous samples.

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In most studies, the mean capillary hemoglobin is higher than the venous hemoglobin. However, this is not constant for all donors. So this is just one example from a recent publication in transfusion of the distribution of the deviations of capillary from venous hemoglobin on over 9,000 donors. So here you see the percentage of donors and capillary hemoglobin minus venous and so here is zero. And you can see that on average, the capillary hemoglobin is a little higher than the venous. However, there are many donors where the inverse is also true.

And I am just going to conclude by talking a little bit about influence of measurement accuracy on donor deferrals. So, hemoglobin measurement is being used as a screening test in healthy individuals. An accuracy of plus or minus three grams per liter or 0.3 grams per deciliter is really only about two or three percent of the total hemoglobin and it certainly would not

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influence treatment in the patient care setting. We would not consider 12.5 to be very different from 12.8 in a patient. However, it becomes very important in our setting, since a hemoglobin cut-off of 12.5 or 125 is in the normal range for females. So a shift in measurement of plus or minus three grams per liter has a major impact on deferral rates.

This just happens to be some of our data in a couple of our centers. So you can see the hemoglobin distribution of our female donors and it is actually exactly the same as some of the other curves that have been shown.

Here we have 125 and you can see how many female donors are within plus or minus three of the cut-off. And when we changed our screening algorithm from a copper sulfate followed by a HemoCue on failed donors to DiaSpect, which is a newer photometer on all donors, we had a drop in our female deferral rate, due to low hemoglobin which went from

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being approximately ten percent to being approximately eight percent.

So first we got very nervous about this. Of course we didn't know if what we were doing, neither what we were doing before nor what we are doing now can be considered a gold standard and when we rolled out the new method, we also retrained all staff. So it is not clear if it is actually the new method or the increased training that led to this difference. But when we looked at our curve, that difference in our deferral, which is huge actually, and probably the most significant thing I have ever done to increase donor eligibility in my organization and it was unintended consequence was really due to a shift of less than a one gram per liter in measurement, just because we have so many donors that are right near the cut-off.

And if you look at the male donors, you can see that very few male donors are near the cut-off. And so there is very little

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impact or variability in measurement on deferral in male donors because you are at the bottom of the distribution curve.

So in summary, measurement of hemoglobin in donors is a screening test and it is a compromise between the ideal and the operationally feasible. I think that it is clear that measurement using photometers and hematocrit is more sensitive and specific than copper sulfate.

Probably more variability may be related to the fact that we are doing this with capillary sampling rather than to the exact instrumentation that is being used. And small inaccuracies may have a large impact on deferral rates due to the location of the eligibility cut-off of female donors.

And thank you for your attention.

(Applause.)

DR. GOLDMAN: Any easy questions?

(Laughter.)

DR. BIANCO: Okay, our next

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presentation will be about FDA-cleared devices for donor hemoglobin screening and it will be made by Josephine Bautista here from the FDA from OBRR.

Ms. Bautista joined the FDA in October '99 after seven years in the U.S. Navy. She held several management positions in the Center for Devices in Radiological Health, CDRH. And in January 2011, joined the Office of Blood at the Center for Biologics as a senior advisor for In Vitro Device Policy. Josephine is currently completing her doctoral degree.

Please, Josephine. And you can help us by explaining what is a cleared device to start with.

MS. BAUTISTA: Okay. Well, good afternoon. My name again is Josephine Bautista and I am from the Device Review Branch in OBRR. And today I am going to be talking to you just giving you an overview of the regulatory process. So I am kind of

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switching gears a little bit here so we will be talking about the regulatory side of it instead of the clinical side of it.

So the things I will be talking about today will be the regulatory clearance process to involve the regulatory submission, regulatory route, and the statistical analysis. Also, I will list some of the cleared CBER devices that we have already cleared through the FDA and as far as any future type of device submissions.

The intended uses is one of the most important part of the regulatory submission in that we gather a lot of information from this to tell us a lot about the device. The first thing, what type of analyte are we measuring here? In the case of hemoglobin, it would be the hemoglobin. For the next part of this whether or not it is a quantitative, semi-quantitative or qualitative device. Most devices that we will clear, since we need quantitative results are

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quantitative analyses.

Sample type is a very big issue here because of, as you know, we have the issue of venous blood versus capillary blood. So we definitely look at what type of sample you are going to be using for your assay and the condition for use.

The next part of it is the indication for use. What and whom is going to use the device. So we look at the same things or similar things which would be the condition or the disease that we are going to be looking for; how it is going to be screened; what it is going to be screened for; the target population; who is going to be the population that is going to be involved; which would be donors here; the frequency of use; and in this case it would be for blood donations; and the physiologic purpose. What are we testing here? We are testing blood and we are testing for hemoglobin.

Now why these two issues or why

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these two parts of the regulatory process are important is because it helps us to decide the direction of the submission. If the indication or the intended use says that it is for donors, then we know that it is a CBER product. As these devices are reviewed both in CDRH and CBER, the indication is very important because it tells us that the device is coming to CBER.

The other thing that we are looking at basically is intended use and indication for use is what is going on. What are your claims for this device. And this device, if you are making specific claims, then those are specific studies that we want to see in the claim. So, this is very important as well.

And the other thing we want to determine, what is the regulatory route. Is it going to be a 510(k)? Is it going to be a PMA? I mean, what is it going to be doing. So this is very important and it kind of frames what we are looking for when we have a

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submission that comes in-house.

Most hematology, hemoglobin devices are regulated through the 510(k) and this is because they are usually moderate to high-risk or moderate to low-risk and they are Class II devices, most of them are Class II devices. So we regulate them through the 510(k) process.

One other thing with the 510(k) process is that you have to have a predicate.

A predicate is a device that has gone through the clearance process. And so you refer back to the predicate for your studies and the intended use.

Some of the statistical analysis that we look at, first on the analytical side we look at the precision of the device. We look at how accurate the device is, especially over the entire range as well as the cut-off.

We want to make sure the device is accurate.

We want to make sure that it reproduces. When we run a sample over and over again, we

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want to make sure we get the same result or within a certain range of that result.

We look at it over between sites to see if at one site you get one result and at another site you get another result. So we want to make sure how that reproduces over those sites. We look at it over time. We look at it from day to day over a period of time to make sure that the results that you are getting are being consistent over a period of time.

We also look that normal range study, which is something -- We have talked a lot about this this morning, how we are looking at these types of studies and how we are determining the ranges and the sensitivity of the devices. So these are things that we are definitely looking at when we review these submissions.

Another -- We are looking at the specificity of the device. We are making sure the device, there is no interference in the

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device. We are making sure that when we review the information, if there are known interferences such as lipid or icteric samples or things like that, that it does not interfere with the device. If it does, we need to know about this so that when we look at these studies we can determine exactly how accurate the device is and that this information is placed on the label so that you would know exactly what the problems are.

A matrix study is a very important issue that we look at because here most of the devices are comparing or will use capillary blood as well as venous blood. So we want to make sure that when we look at these studies, that they perform these assays so that we can see if there is a difference between these two different matrices. So when we look at the studies, we compare them both and see if there is a difference. And then we want to know how much the difference is between those two types of samples.

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And the linearity, we want to make sure that the device is linear over that reportable range. If it is not linear, then we need to make sure that adjust it and we want to make sure that the ranges that are reportable are within accuracy that is of the device.

Then we look at clinical studies. And the clinical studies is where we compare the new device to the predicate device. And we want to determine if the new device is as accurate or as precise as the clear device. We also, with that we use clinical samples where we compare samples. Usually if it is in a donor setting, we compare donor samples that are in the donor site to compare and see if those samples are accurate

We also can use a reference method for comparison which we used hemoglobin method is used in one of the references we use.

Then the demographic study is one that is really important and it was also

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mentioned a couple times here today, too. Since there is a difference between male and female, we want to make sure that we have the information and it is included in the studies where we are comparing male samples, female samples, over a range of age, age ranges, as well as the order of these samples so that we can collect this information to see if there is any differences.

So once we finish reviewing all of our clinical studies as well as other regulatory issues that we look at in the submission, then we determine whether it is a cleared. I think the question was asked what is cleared and what is not. But we determined that the device is cleared. In 510(k), devices are considered cleared. They are not approved. They are considered cleared. Approved devices are for PMA Class III devices.

So once we finish the regulatory review and we find that it is substantially

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equivalent in the notice requirement according to the regulation, they are substantially equivalent to the predicate, then we issue a clearance letter.

Moving on. I'm sorry, I'm making my transition here.

So the next thing is I have got a list here of the devices that we have cleared from CBER. And we have three photometric devices and one hematocrit device. Now the DiaSpect is not on this list because we just cleared that device. So it is not currently on the list. So the list that we have here I think is pretty much the same list that the other speaker had, Dr. Goldman had. So the list is pretty accurate and up-to-date list of the devices that we have cleared.

Some future devices are currently we talk and we visit trade shows and professional organizations and we talk about current technologies, which basically we have the photometric ones and the hematocrits and

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those are the technologies that we have cleared. Now as far as non-invasive and newer technologies, we have seen them in trade shows and so forth but we have not had a submission in-house. So currently we do not have any non-invasive submissions that we have cleared in CBER.

So that concludes my talk. Any questions?

(Applause.)

MS. VACCARO: Hi. This is a simple one. I didn't quite catch the name of the third photometric system.

MS. BAUTISTA: The DiaSpect.

MS. VACCARO: Diasys?

MS. BAUTISTA: DiaSpect.

MS. VACCARO: Okay, thanks.

DR. GORLIN: Jed Gorlin, Minnesota.

You talked about the importance of a predicate device but what happens when you come up with a new device like the non-invasive? What additional information are you

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looking for?

MS. BAUTISTA: Well if it's a new device, it would depend. If it is a non-invasive then that is a new technology and more than likely, and I say more than likely I don't say exactly because I don't have the authority to make that decision, but normally it would be Class III, which would be maybe the possibilities of being a PMA. And I say that I'm not making that decision.

DR. BUSCH: Hi. If we were to begin to use ferritin in some way to qualify or determine donation intervals, I assume there are cleared assays for ferritin, would they require any further review or claims, vis-a-vis use in a blood center?

MS. BAUTISTA: For -- I'm sorry?

DR. BUSCH: Ferritin.

MS. BAUTISTA: For ferritin? We haven't cleared any devices in CBER for ferritin that I know of. And please correct me if I am not correct here.

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DR. BUSCH: So it would be in CDRH then.

MS. BAUTISTA: It would probably be CDRH and we would probably consult on that submission if it specifically for donors.

DR. BUSCH: But would it need a submission of any nature? Could we just employ it? It wouldn't qualify the donation, per se. It would just be used to guide frequency.

MS. BAUTISTA: For ferritin? Ferritin is a medical device that will require a submission.

PARTICIPANT: I think what Dr. Busch is getting at is if there is already a clear diagnostic indication for a device, would we need to re-review it at CBER for use in the donor setting? I think we can't prejudge that without looking at its characteristics and what it would do in the donor setting.

So the answer is maybe, maybe not.

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DR. BIANCO: Gene, I know you were there and Josephine is here. Where is copper sulfate in all these stories?

PARTICIPANT: Yes, well we haven't banned it yet. I think we raised questions about it in the 2007 donor eligibility proposed rule, did we not?

DR. RUTA: You are asking should it continue to be used? Is that your question? You are asking how was it approved or what are you asking?

DR. BIANCO: Where is it within the regulatory process? Is it a cleared device?

DR. RUTA: Right. I think it would fall into the pre-amendment devices. So it would be grandfathered. So it would be on there because it was before 1976. But raised questions about whether copper sulfate should continue to be used, within our proposed rule as to should people use it or not. Does that help or at least answer the question?

MS. BAUTISTA: Is that it?

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DR. BIANCO: Thank you very much Josephine.

(Applause.)

DR. BIANCO: Now we will address Dr. Richard Cable from the American Red Cross and we will address the REDS II donor iron study, fingerstick samples in blood donors compared to venous samples.

Dr. Cable is the Scientific Director of the Northeast Division of the American Red Cross. He has served as both CEO and Medical Director of the Connecticut Region of the ARC from '82 through 2005. Since 2005, he has been the Scientific Director and Principle Investigator of the REDS II donor study. He is now Co-Principle Investigator of the Yale-Connecticut Red Cross Center for the REDS III.

Dr. Cable has authored several papers on blood donor iron depletion and hemoglobin assessment. And he also Professor of Clinical Medicine and Laboratory Medicine

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at the University of Connecticut School of Medicine.

Dr. Cable.

DR. CABLE: I want to thank the organizers for having me today, particularly Rick Davey who I have worked with since we started on the same day at the NIH Blood Bank with Harvey Klein in 1906, I think it was.

(Laughter.)

DR. CABLE: Let's see, how do I advance the slide? I push the button? Oh. That works.

Well I did want to -- I'm glad we have got some preliminary discussion of capillary testing because I don't want to talk a whole lot about that but I have a couple other points I did want to make. I have brought this up in my questions and I wanted to go through why we test donor hemoglobin again. Some other speakers have done so, so I will make it snappy. But I think in red that as to the recipient, we are trying to make

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sure the unit is of a certain potency.

There are some problems with that theory but I can't come up with another answer for why they would have set the standard the same for men and women back in 1958. I don't think it is to detect hemoglobinopathies and red cell membrane abnormalities and such. You know, it is a pretty nonspecific measure of donor health and I doubt that is why it was implemented.

For protection of the donor, again, it is a pretty rotten general donor health screen. And you know, I think the health care system is going away from screening healthy people for random things like PSA and, in my view, hemoglobin. We wouldn't start doing it now if that was the reason.

I've got two other possible reasons why we are doing it. One that has not been mentioned is to ensure that post-donation, the donor won't have a hemoglobin that is harmful to them, since we know the hemoglobin drops in

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donors after donation. And I have a big question as have several other speakers whether it is a useful screen for iron stores.

And my answer to that question is it is not a useful one and so the last bullet is kind of N/A.

I didn't want to go through just in red what the post-donation hemoglobin projected would be after the plasma volume and the blood volume were equilibrated after a donation and before any erythropoiesis occurs to replace the donated red cells.

And in a little woman who has a 12.5 hemoglobin or 125 gram per liter hemoglobin to be ecumenical about the border, you would end up with 10.4 or 104 result post-donation, say at three days after donation, if you bled them.

A medium-sized to strapping young man who starts out with a 15 gram would end up with 13.7. So this would be quite a bit of variabilities you would expect. I'm kind of

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thinking that 10 grams per deciliter seems a reasonable limit for this post-donation hemoglobin and that would support a slightly lower cut-off pre-donation for women. And the reason I think ten makes sense is that A, it is a round number, everything needs to be round numbers these days, but we allow autologous donors to give it 11 and their post-donation hemoglobins more like can be as low as nine. And they don't seem to have any meaningful harm and many of them are much frailer than our regular donors.

And I don't think anyone claims that someone with a hemoglobin of ten, even acutely, would suffer any significant symptoms. So you know, we could use this as another way to set a hemoglobin level and no one has mentioned it.

I did want to talk about the hemoglobin concentration and how it relates to the size of blood vessels that you select to get the sample from. Mindy talked a little

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bit about this. The reference venous sample is usually taken from a large antecubital vein. I don't think it makes a difference if you got it from another large vein. That is the gold standard for what we usually refer to as the sample for reference to hemoglobin.

If you estimate the so-called total body hematocrit, which is defined as the red cell mass over the red cell mass plus the plasma volume, although there is some trouble with these measurements, Mollison has spent a lot of time and summarized in the '87 version of his textbook some of these data. The total body hematocrit is about nine percent lower than large vein hematocrit, making the inevitable assumption that somewhere else in the body the hematocrit is lower. And presumably that is in smaller blood vessels.

And we think there is a reason for the lower hematocrit and smaller blood vessels, which is the red cells hate to get up against the endothelial cells and there is a

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laminar flow of liquid across the edge of the vessel and the smaller the vessel, the more the laminar flow of plasma dilutes the blood in the vessel. And obviously capillary testing is also influenced by exactly where you took the sample and a mix of capillary, venule and arteriole blood you obtain. Any my theory is that it is not so much the operator that is the problem as the point in the finger where the lancet ends up that is the problem and creates much of the variability.

So you can talk about training your staff but my belief is that capillary blood is inherently variable in this regard.

However, we know that nearly all blood donors in the U.S. are qualified, if not all, by testing capillary blood from a fingerstick. And it has been assumed widely that these results will essentially mirror simultaneously collected venous hemoglobin. There have been all these quantitative retesting of copper sulfate in the past and

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studies that show that if you take the second sample from a different finger, that you have a better recovery rate than if from the same finger or if you take it from the same hole versus the new hole. The new hole is better than the old hole and you can find a lot of publications by blood center medical directors desperate to publish back in the 60s and 70s, looking at various modifications of this.

But it basically is a one-sided Monty system, where you can only accept people, you can't reject people is I think was discussed before. So basically it is an unfair way to end up with a number. Nevertheless, we ended up with numbers.

Once we got to a quantitative method like HemoCue or the others that were mentioned, the culture of the blood center couldn't help itself and it replicated this repeat testing again, even leaning on HemoCue to write a letter and change their package insert to allow a practice that we already

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were doing. To me, that is a little bit shameful. And if we can't do a better job on the hematocrit, we should just stop, which I have already said. But I think we really aren't doing ourselves any favors as laboratory scientists to behave in this manner because obviously we are cooking the books and we shouldn't do that. That, nevertheless is then how we get the numbers that we are dealing with today. And I need to tell you that in full disclosure that several of the REDS centers do this very thing. And those that didn't are now doing it we find in a survey yesterday. So you know, it is the name of the game.

So the number that ends up on the blood donor record is the cook number, the second test number if a second test is done. Usually we record the first number but the second test number is the one that accepts the donor and gets into the records.

Okay, well this is from an earlier

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table. Mindy summarized a more recent study, which I am not going to summarize. But this is data all the way back to 1977, looking at earstick, fingerstick, and venous samples and you can see that there are statistical differences but in general it is pretty close.

In the Avoy study, the fingerstick was higher than the venous, as in the study we did in 1995 but a different study by Coburn in 1977 went the other way. And I won't bore you with information on the last two rows. They are kind of a somewhat unrelated issue.

Dr. Murphy, who is going to speak to you after the break published an excellent review of this in Ireland and I am only going to show you a little part of his, which is quite relevant to the data I'm about to show you. This is a figure from his *Vox Sanguinis* article in 2010 in which on the x-axis we have the fingerstick hemoglobin and on the y-axis we have the venous hemoglobin minus the fingerstick hemoglobin. So what we see is

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that at higher levels of hemoglobin, the fingerstick value overestimates the venous value. That is to say venous minus fingerstick is negative. At lower values, the fingerstick underestimates the venous, which is to say the venous minus fingerstick value is positive.

And there is a crossing point in his study, and this was a small study to support his big study of 155 donors about equally between the sexes. And there was a point, in this case for men at about 15.7 or so where the fingerstick and the venous values all look the same in a regression analysis.

For women, you have the same relationship but a completely different crossing point. A completely different point at which fingerstick and venous values were identical. Not much was made of this observation in his paper but I think you will see it predicts the value, some of the results I am going to show you, which is that the

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relationship between fingerstick and venous samples are different in women than in men, something that has not been appreciated and this was really the first clue until the RISE data was analyzed in the same way.

Now you see I have used My Father's Tie, this is the name of the PowerPoint template, My Father's Tie, which is a favorite of mine, to reflect this part of the talk because I am now going to go to a talk from the RISE group and I am going to present the RISE data. Everything I have said to date was my personal opinion. I am going to go back at the end of My Father's Tie and give you some more personal opinion. But during this part, I am trying to keep Steve Kleinman happy by sticking to the RISE-approved script. Right, Steve?

So this is the logo for REDS and we are presenting data with a whole bunch of folks to be acknowledged working on data as a secondary analysis from the RISE study. Now

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you are going to hear a lot about the RISE study tomorrow. And this is a little bit ahead of itself. So I am not going to tell you a whole lot about the RISE data, except to say it enrolled four cohorts, a male and a female, first-time/reactivated cohort and a male and a female frequent cohort. I believe Bryan Spencer showed a similar slide, totaling 2425 donors. This is the enrollment data.

RISE had a longitudinal component which will be presented tomorrow. And what we saw as one of the analyses we could do is that we had simultaneous fingerstick and venous values on these donors and we also knew a whole lot about these donors. A lot more than you would ordinarily know at a blood center about these donors. So we decided to kind of beat up the data and see what came about.

So just to tell you how this was done, the fingerstick that qualified these donors, and these were all donors who were accepted for donation, we did not enroll any

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deferred donors that day, the fingerstick was performed routinely by the operational staff at all six centers using all the different methods that the six centers used. And I will show you them in a minute. And we enrolled these donors in RISE.

We obtained the venous sample from the sample pouch, pre-sample donation and 76 percent of the time because we were in the process of migrating as a six-center unit from a pre-donation testing to -- I'm sorry -- from post-donation testing to pre-donation testing and 24 percent of the samples were post-donation samples and I will tell you what we did with them in just a second.

We did venous hemoglobin in the research lab using research staff and we actually used the HemoCue 201 that you heard about, after being trained by the HemoCue technical people. We did this because we thought we would have more consistent hemoglobin across six centers than by using

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six autoanalyzers, not because we thought this was better than autoanalyzers but because we thought we could get, by using the same lots of reagents and so on, we could get consistent results across six centers.

We did do autoanalyzer testing at four centers and nothing in this presentation is going to be reversed by the availability of that data. We also did ferritin and soluble transferrin receptor performed on them. And we categorized donors as, I think Bryan already showed you as, iron-replete, having iron deficient erythropoiesis or having more severe iron depletion and having absent iron stores. And I will show you those definitions in a minute.

These were the six centers labeled by letter to protect the innocent. Four of them used a hematocrit device, three of them the HemataSTAT device. This is what they did then. Many of them have switched since then.

One of them used the UltraCrit device, which

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I didn't see on the cleared list so I was a little puzzled by that but we can talk about that. One of them used the hemoglobin, HemoCue B, which I believe they have switched from that since then. And one of the centers used the then newly released HemoCue Donor Checker. So four different methods at six different centers we are looking at.

We converted these 24 percent of post-donation hemoglobin to a pre-donation value by using a regression formula we derived in 278 separate and different blood donors recruited specifically for this purpose. These folks agreed to giving a pre- and a post-donation sample they required an extra stick in the other arm at the time of donation. And we ended up with a formula that was pretty straight-forward. And the only variable other than adding a constant was donor weight. And we found that the bigger donors have less of a drop when you took a unit of blood out of them, which makes sense.

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We defined absent iron stores that faired less than 12 as you already saw today.

And we defined iron deficient erythropoiesis as the log of the ratio over 2.07, which was based on the 97.5 percentile normal range of first-time males, who were presumed not to be iron deficient.

And this is the first group of data we saw, which and I'm sorry it is a little hard to say. I'm PowerPoint challenged so I took this from the paper, which is online now for your viewing at Transfusion. But we have pairs of fingerstick and venous results on three groups of men over here and on three groups of women over here.

So I will start with the women and this first group of women is women with AIS, with the most significant degree of iron depletion. And you can see in these box plots where this is the median, these are the 25th and 75th percentiles and the lines are the 2.5 percentile to 97.5 percentile distribution for

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these folks that people who had -- the fingerstick values for people, women who had AIS is substantially higher than the venous values for the same donors collected simultaneously by about a gram. A little bit less so for donors, female donors who had the less rigorous form of iron depletion, IDE, and even a little bit less for donors, female donors who appear to be iron-replete.

From what we can tell, it seems to be a gender affect but it might be a continuing iron depletion effect that is just we can't sort out, but women even who are iron replete, their fingersticks are higher than their venous values. So of all women, we found this result. These values P-value is 0.0001, so these are highly significant results. And this is for all 2425 donors in the RISE study.

Looking at the male side, when we look at males who have serious iron depletion, AIS, we see the same thing. Somewhat less

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prominent than in the women but a significantly higher fingerstick than a venous in these few iron-depleted males. This represents about ten percent of the males, this group.

In the males with only slight iron deficiency, fingerstick is still higher but barely so. And this is barely statistically significant. When you look at male donors who are iron-replete, and this is like 70 percent of the donors in RISE and there would be much more, maybe 80 or 90 percent of all blood donors, you see it goes the other way. That in male blood donors who have enough iron, the fingerstick actually is lower and underestimates the venous hemoglobin. So it goes in the other direction. So you have a combination of the effects of iron and the effects of gender in predicting what the relationship is between fingerstick and venous.

So we went a little further and we

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decided to develop some linear regression models to basically predict venous hemoglobin from the fingerstick hemoglobin. That is, of course, what we are trying to do when we do capillary testing to qualify donors. And the variables we put in the model were gender, the three levels of iron status, and the fingerstick hematocrit at four centers or the hemoglobin at two centers. We found, as already mentioned, huge variability between centers, which we have already discussed. And so we decided to develop six separate center models. Rather than put model in as a variable, we just developed six different models, one for each center A through F and I am going to show you those models in just a second. And we developed linear regression parameters which I am going to summarize in this rather complex table but I will try to walk you through it.

Here are the six centers. This represents the venous hemoglobin value of a

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donor whose fingerstick is 12.5. And it basically has no adjustments. So an iron-replete male would be 13.5 and so on. There is a coefficient to multiply times either the hematocrit or the hemoglobin for the hematocrit centers it is a lower number than for the hemoglobin centers because hemoglobin and hematocrit are different scales but this is the slope coefficient for the distance you are from 12.5. If you are female, the curve just shifts down by a certain amount. And if you have AIS or IDE, the curve also shifts down by an additional amount, separate and independent amount.

You can see the gender effect in all six centers was that females are, you know, female predicted hemoglobin values are between three-tenths and -- I'm sorry, half a gram and eight-tenths of a gram lower than in men. So the model shows that despite the method used and despite all the vagaries of different donor staff training and so on, all

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six centers show a rather consistent gender effect in their six models. And you can also see a rather consistent severe iron deficiency effect, a little bit more variable from three-tenths of a gram lower to one gram lower.

So in Center A, for example, an iron deficient female with AIS, it is actually more than 1.5 gram difference, which you will admit is a pretty big difference. The IDE slight iron-deficiency model was much less impressive but sort of intermediate in scale.

And there is a little formula here for those of you who like heavy statistics that you can practice doing your linear regression model.

They are going to show it not all the data but to show it in graphic form, this is the regression model for Center F males, you can see three different lines. You can see -- I'm sorry, my vision is going. The iron-replete male is the blue line, the highest line. Very closely attached to it but slightly lower is the male with IDE line and

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then quite a jump down to the males with AIS line, these are parallel lines because of the nature of the regression formula in the model.

And you can see they run parallel and they cross this line, which is the line of identity. This is a 45-degree line from the origin. Essentially this is the same point where they cross that in Tong and Murphy's paper, it crossed that zero point on his graph. He is showing a difference. We are showing prediction one from the other, so the math is a little different.

And you can see that the crossing point for one kind of male at Center F is different than the crossing point for another donor at Center F. And you can see the center variability creeping in. Well, there is the gender effect. You can see that the curves are shifted quite a bit one way because of the gender effect and shifted downward. You can see the center effect by looking at a different center and looking at males and the

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curves are shifted upwards. Again, for the same center, the females are shifted downward from the Center C males.

And then we did have a little bit of an outlier, Center E females and males. Center E tended to have a little bit of what you might call a calibration issue so that their values were shifted considerably below the identity line. And the implications of these, I am going to skip over this, I am going to go right to the implication lines. We took these regression lines and we just plugged in 12.5 grams of hemoglobin for all kinds of different donors. This is what you would expect the venous hemoglobin to be for half of the donors who passed at that center with a 12.5 fingerstick. So half of the venous hemoglobins would be above this and half the fingerstick donors would be below this. For example, at Center E in an iron-replete female, half the hemoglobins would be about 13.26 and half the venous hemoglobins

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would be below 13.26. That is how to interpret this curve. These are predicted not actual but the regression formula suggests that half are above the line and half are below.

You can see we have a little issue with Center E, where it even with iron-replete females, the point of acceptance on average is 12.19 venous hemoglobin, not 12.5 as we would like it to be. You can see the same thing happens with females with a little bit of iron deficiency. But you get to a female with substantial iron deficiency, AIS, at every single center, the predicted venous value for those females is under 12.5 and for Center E, meaningful under 12.5. And half the donors in Center E are below this and half are above this. So half the donors are below 11.7 hemoglobin as predicted.

For males, the story is better and only in Center E was there any problem in that direction in the one group of males with

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serious iron deficiency. One of them was below 12.5. This is the predicted.

Now there is another thing I wanted to show you. These are iron-replete males. These are iron-replete males with 12.5 and what this shows is the predicted venous hemoglobin for those iron-replete males, which is most of the males, is actually somewhere between 13.3, except for Center E, which I think had an issue with calibration, between 13.3 and 13.8. What I take that to mean is we don't need to change the cut-off for male donors because the fingerstick artifact is already done. So the BPAC needs to just go back to the drawing board and come up with a different solution because they don't know this when they made their determination. We have already raised the hemoglobin for males by using the fingerstick, as long as we make sure the donors, male donors have plenty of iron. If the donor has plenty of iron, we have got a different problem like we do with

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the females. So it is complicated but it is very interesting. Isn't it?

Well what does this mean for what we found in the RISE donors when we actually took the venous pre-donation sample, or the post-donation sample converted to pre and we looked at the percentage of those that were below 12.5? They were supposed to all be above 12.5, right, or at least close to it. After all, that is what we are doing this for.

And we noticed that it works really good with males that have plenty of iron. Only 12 out of 791 had a value below 12.5. It really doesn't work so well for women, any women, even women with plenty of iron. Ten percent of those donors had an actual venous hemoglobin below 12.5. And if they had an iron problem, as a lot of the women did, 40 percent of these iron deficient, significantly iron deficient female donors accepted as donors at six different centers in the United States using standard methods had a venous

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hemoglobin below 12.5. So this shows you how useful a fingerstick hemoglobin really is, which is to say not very. And it is the basis for my argument that we ought to stop doing this and start doing something that actually works. And that is my plea to the workshop to think about that.

Okay, so my conclusions -- I'm not going to go through the conclusions. Well, let me go through them.

Fingerstick is considered a useful estimator of venous hemoglobin but in some donor groups, particularly female donors with AIS, fingerstick overestimates venous hemoglobin at the donation cut-off. And this limitation should be considered in setting donor hemoglobin fingerstick requirements.

Current practice results in the acceptance of many iron-depleted donors with venous hemoglobin values below 12.5 as other speakers have mentioned.

The fingerstick-venous relationship

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is highly dependent on the hemoglobin level, as found by Tong and Murphy in the paper I showed you earlier and I am sure Dr. Murphy will speak more about.

Dr. Murphy's study concluded the fingerstick was a useful reflection of venous.

I'm concluding it is not so useful. Not because either study was wrong but he conducted his study in all comers in Ireland and I'm guessing maybe his donors are not as iron-depleted as ours. We don't know because iron wasn't measured. And so I think he didn't tend to see the iron effect in his donors. And although the gender effect was hinted at in his smaller study which I showed you the figure for, it didn't seem to show up in his analysis of accepted donors. So I think the difference is completely different donor populations.

I wanted to briefly talk about use of hemoglobin to predict an iron status. Most of us have said that is probably not a good

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idea and Dr. Kiss is going to talk about the various predictors and ways of measuring donor iron, including hemoglobin tomorrow but we can say that most people think that venous hemoglobin is a poor predictor. But because the fingerstick-venous difference is affected by the iron status, you can imagine that the fingerstick hemoglobin is even a worse predictor of iron than the venous hemoglobin, which is already a poor predictor of hemoglobin.

So I wanted to show you some ROC curves. This is probably the best way to look at the combination of sensitivity and specificity. And the area under the ROC curve is probably the best predictor of the efficiency of a lab test and Dr. Kiss will show you a bunch of those curves tomorrow.

You can see this is to predict IDE from the hemoglobin that the venous curve is well above the fingerstick curve and the area under both curves is not all that good. But

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particularly under the fingerstick curve, you have got a value that is really low and would not ordinarily be suitable for predicting anything.

If you ratchet it up a little and say let me use hemoglobin to predict really serious iron deficiency, as expected, the curves go up a little, although the difference and the degradation in use of fingerstick is actually a little larger. But the area under the curve is a little bit better but still probably not very good.

So we are back to Dad's tie and my opinions. Fingerstick in male donors without AIS underestimates venous hemoglobin. So raising the fingerstick donor is not necessary. I said that already actually. I couldn't help my opinion coming out earlier.

Fingerstick in female donors with iron depletion significantly overestimates venous hemoglobin and it wouldn't be appropriate to consider lowering the female

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donation cut-off to 12, until we have a way to actually measure hemoglobin in our scientifically accurate and vigorous way. We shouldn't even begin to think about that, in my opinion. If we are going to do hemoglobin and we are going to set a cut-off, let's do it on accurate numbers.

Fingerstick hemoglobin is an inaccurate measure of donor iron and deferral results in unnecessary loss of iron-depleted donors -- iron-replete donors. Based on RISE data, which you are going to see tomorrow, we really need to manage iron depletion not up with hemoglobin but on monitoring and controlling donor iron frequency measuring ferritin and iron supplementation programs, as you are going to hear a lot of tomorrow.

And I will skip the summary and thank you very much.

(Applause.)

DR. BIANCO: So what should we be

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measuring?

DR. CABLE: Not hemoglobin. I think we should qualify the donors having a normal hemoglobin once and maybe periodically after that. And we should use a venous sample. We have plenty of venous sample.

I think we should put aside our lancets. We should stop using untrained staff on blood drives and thinking they are lab techs, because they are not. And we just ought to stop this foolishness. That's my opinion.

I really do believe that fingerstick hemoglobins are not only not useful but probably harmful. And it is time that we called it for what it is, which is we have to do it because the FDA requires us to do it. So the way to fix this is for the FDA not to require us to do it anymore. That's really simple. And this is an FDA workshop, so I could speak my mind.

DR. BIANCO: Dr. Goldman.

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DR. GOLDMAN: Hi. Yes, I have a question. The model of the relationship between venous and capillary hemoglobin and iron status, you developed it using a dataset.

I'm wondering if you then tested out the model on another group of donors to see if it works.

DR. CABLE: That's probably a good idea. The problem is we would need a fairly large number and they would have to have been tested by ferritin and sTfR to use the model.

So we would need a dataset that had a fingerstick hemoglobin, a pre-donation venous hemoglobin, and those two different iron measures to test it out. And I'm not aware that anyone has such a dataset.

So I think yes, it would probably make sense for someone to basically confirm this model. And because of the center effect, I am guessing somebody else would do it and find something else but it ought to be in the same direction. The gender effect ought to

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still be there and the iron effect ought to still be there.

What convinces me that it is compelling is it was so consistent across all six centers, the effect of both gender and iron was rock-solid consistent across the centers, even though the general level of hemoglobin was different in the one center. Even in that center, the differences were the same between the male and females, and between the iron-depleted and the iron-replete. And I can't think that would be accidental.

So it basically was tested out in six centers. You might say one center discovered it and five centers confirmed it, if you wanted to. I mean, somebody else should do it but you would need all that data to run the model.

PARTICIPANT: Ritch, how reproducible is venous hemoglobin? And was there a center effect for venous hemoglobin?

DR. CABLE: A center effect for

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venous hemoglobin? Well, it was considered the gold standard. So --

PARTICIPANT: I mean obviously you didn't test the same samples at all the centers but were the distribution of venous hemoglobins comparable across --

DR. CABLE: Yes. Well, they are different populations. And yes, I believe the median hemoglobin levels were slightly different across the centers. Some of the centers have a heavy African-American population. One of them did. One of them had an Asian population. They are all basically at sea level or close to sea level. And one of the centers had a higher smoking incidence than others. So I would expect the hemoglobin, venous hemoglobin range to vary across the centers but because it is the gold standard, there is nothing to check it against, if you will.

PARTICIPANT: If you did it perhaps twice or something like that, you would

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understand the reproducibility of venous hemoglobin. But your premise is that the problem is capillary sampling.

DR. CABLE: Yes.

PARTICIPANT: It is driving all the

--

DR. CABLE: Well, we did look at the model in the four centers that had an ADVIA autoanalyzer hemoglobin on the same sample that was used for the HemoCue, venous hemoglobin, and interestingly enough, the models were virtually the same. In fact, if I have time I can put a table that has the parameters from the HemoCue venous testing model for six centers with the ADVIA autoanalyzer testing model for four centers and the parameters were identical, save the Center E look the same now, as though Center E had a problem doing its HemoCue 201 testing, which is the conclusion I would make.

Because when you actually looked at the four centers including Center E with an

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autoanalyzer, the parameters were within two or three hundredths of a hemoglobin point from each other. They were really impressively the same. We published the six because RISE was a study of six and, well it's a long story but I can show data with the four that had ADVIA as well.

So I don't think it is a problem with venous testing. Perhaps I should show that in the discussion.

DR. MURPHY: Dr. Cable, just a technical question. We know that in health that the relationship between hemoglobin level and hematocrit is more or less linear. But there are data I think that show that doesn't hold up in iron-depleted, in iron deficiency.

I'm just wondering if the relationship between hematocrit and hemoglobin in your iron-depleted individuals might actually be slightly skewed if the relationship might not be linear.

DR. CABLE: Yes. Well, we used a

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different scaling parameter, which took into account hemoglobin and hematocrit. In each center which used hematocrit. If the red cells were slightly different in size, the parameter could have shifted or changed a little but we didn't look at MC -- I mean, we do have MCVs on the four ADVIA centers because the ADVIA did -- We have parameters on reticulocyte. We have got all the reticulocyte indices you would want, 400 measurements or something but we haven't analyzed that yet.

So I can't speak to the red cells getting smaller issue but I think the model would take that into account with a different slope if the cells got smaller in the hematocrit testing centers. The cells also get paler, so the hemoglobin would be down, too. The MCHC would be down, as well as the MCV. I should be building a model, I think.

But Joe you are not going to talk about indices tomorrow, are you?

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(Off microphone comment.)

DR. CABLE: Yes, we probably do need to look more at that. That's a good point. Somebody is going to talk about that later.

DR. GORLIN: Ritch, if I understand from your regression model, being female was about half a gram but the center range was a full gram. Was that mostly associated with a measuring device or what is your thoughts on the center to center variation?

DR. CABLE: Well if you exclude Center E, where my theory is that something was wrong with their HemoCue measurements, although we haven't nailed this down -- If you exclude Center E and you look at the parameters, there was still a fair amount of center variation. And I think the answer is with fingerstick testing, that they are different. Lancets were different. The staff were trained differently. It is colder in Milwaukee than in San Francisco. I don't

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know.

We didn't try to analyze why the centers were different, save I think we have some more information on why Center E was different.

DR. BIANCO: Okay, thank you, Ritch. Thank you very much.

(Applause.)

DR. BIANCO: And now we have 20 minutes for a break. We will reassemble at three.

(Whereupon, the foregoing proceeding went off the record at 2:40 p.m. and went back on the record at 3:08 p.m.)

DR. BIANCO: Well, welcome. We are starting a couple of minutes later but I am sure that we will manage the schedule.

Our next speaker is Dr. William Murphy. He comes to us from Dublin, Dublin, Ireland and he is going to talk about venous hemoglobin levels in healthy blood donors.

Willy graduated from the University

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College Dublin in Ireland, had specialty training in transfusion at Edinburgh Royal Infirmary and in '96 became the National Medical Director at the Irish Blood Transfusion Service. He has many contributions to the literature in transfusion medicine.

In the beginning of 2011, he moved to the Irish Health Service Executive in order to lead a national optimal blood use program.

And so you can help us in that, too. And Dr. Murphy currently the main research focus is in ex vivo manufacture of red blood cells and in particular, in the design of future clinical studies of these cells.

DR. MURPHY: Thanks very much, Celso. It is a great privilege to be allowed to present these data here. I would like to thank the organizers for inviting me. Actually, they didn't invite me. I invited myself but for agreeing to that.

Okay, Mindy referred to this

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earlier on. She in fact had better slides than I did on this. But we know that the capillary sample draws blood from a large number of capillaries. I am going to call it capillaries. It is probably going to irritate you. I apologize. But capillaries of different sizes and position in the capillary bed.

And it was not entirely clear as I think Mindy's slides showed, what we are measuring in the finger pulp and how truly representative that is of the capillary space.

This is a video micrograph or a still from a video micrograph of capillary blood flowing under the tongue in a normal individual and you can see that the vessels are of different size. There is the small ones here with just one or two cells going through this big clumping slow-moving things. This thing is clumping. There is a large venule underneath on some of the vessels so there are different sizes and probably different hematocrits.

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Now Dr. Cable referred to this earlier round. Mollison was actually the second author of this paper in *Journal of Clinical Investigation* in 1953 by Chaplin et al. And they showed, using isotope dilution studies that the whole body hematocrit bore a relationship to the venous hematocrit but it was in fact less by a factor of about 0.91.

Now it is worthwhile pointing out that in that study there were only 28 subjects, although this is more or less taken as the standard relationship ever since. There were 28 subjects, only four of whom were normal. The rest had anemia or polycythemia.

And in fact, if you look at the normal, the whole body hematocrit and the venous hematocrit in the normal, so far as we can derive that from four subjects, it is probably closer to 0.88 rather than 0.91.

What that means is that the venous blood is diluted about one in ten to one in eight, if you take the 0.88 figure throughout

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the vasculature. So there is a dilution factor, compared to what we are measuring in the venous blood.

And this is how it works and Dr. Cable referred to this. These are data taken or a graph taken from the microcirculation laboratory in Penn State. And what they showed is that as blood goes down the arterials, the hematocrit falls compared to the systemic hematocrit. And it thins down to about 50 percent or less of the systemic hematocrit by the time it gets to the smaller capillaries and then it goes back into the venues, it thickens up again. And this is known as the Fahraeus effect and was first described in 1928. That is not to be confused with a similar but quite different thing called the Fahraeus-Lindqvist effect which is much more commonly quoted than the literature.

And this is what it looks like in this fluorescent angiogram from Michael I suppose from this group. And these small gray

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shadows here are the red cells going down a single capillary and you can see they are spaced out. The hematocrit is about 20 percent or so.

So as blood flows down into the arteriole, it thins out to a hematocrit of about 20 percent, about seven grams per deciliter. I hope I got that right, Mindy. That is 70 to you, seven for the rest of -- Seven grams per deciliter. And then thickens up again on the other side.

So let's take that a bit further. So the venous blood is diluted, as we know, about one in ten to one in eight by this Fahraeus effect throughout the vasculature. So there has to be a border zone. Because actually a compartment with a hematocrit of 0.2 compared to a standard hematocrit of about four, so 50 percent hematocrit, there isn't an area where that exists, a large volume of blood where the hematocrit is half and then it goes back to 100 percent again. So there

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isn't one with borders.

So there is a zone with the circulation where the hematocrit thins out down to about 50 percent of the starting hematocrit and then plumps back up again. And that must be greater than 50; 500 to 750 mLs. Considered to be greater probably.

So there is a large physiological space for modulation of the capillary microcirculation, microhematocrit takes place by definition almost, where the hematocrit thins out from 0.4 to somewhere around 0.2, 0.25. There is some shunting takes place there, not every red cell we know goes down to microcapillary and thins out to this hematocrit of 0.25. And then within this area also, you have to have the reversing of the Fahraeus effect. Actually this large space.

And it is reasonable to assume, I think, there is an assumption until proven or proven otherwise, that this is the space that is sampled in the finger pulp. We are not

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sampling the great veins. We know that the hematocrit is different. And I suspect or it is reasonable to assume, that that is the space we are sampling when we sample the finger pulp.

Now what I am going to hopefully show you is that the relationship of the hematocrit within this space, the relationship with that hematocrit with the venous hematocrit based on data that I could show, is a complex and dynamic variable, that it varies with age, with sex, with red cell mass, and know we know with blood center, and also in a chronobiological rhythm.

And the corollary or the exigencies of that is that because it doesn't have the simple linear relationship with the venous hemoglobin level, it should not be used with venous hemoglobin reference ranges. We cannot say that a person is anemic or not anemic based on a capillary hemoglobin level. I think that is much the same as what Dr. Cable

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has told us. And this is a somewhat different way of getting to the same space. Okay?

So the capillary hemoglobin level does not have a simple linear relationship with venous hemoglobin level and should not be used with venous hemoglobin reference ranges. End of story.

Well what is the evidence? Why do I say that? Again, Dr. Cable referred to this study that we published last year in Vox and it was a longitudinal study of over 36,000 paired samples in blood donors where the hemoglobin in the female blood donors or about two-thirds of this group, the capillary hemoglobin was between 12 and 13 -- sorry -- 12 and 12.5 and in the men it was 13 to 13.5.

What we have been doing for the past several years but don't tell our regulators about it is we have been actually taking blood donors whose capillary hemoglobins are below the cut-off. The European legal cut-off is 12.5 for females and 13.5 for males. We have taken the

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position based on preliminary data and I know now from Dr. Cable we probably shouldn't have been doing this but anyway we have been doing it, that if our female donors' capillary hemoglobin was between 12.0 and 12.5, we took the unit of blood. We at the same time measured the venous hemoglobin based on the divert packs that was taken before the unit of blood was collected and similarly with the men. And we compared the data over those and then we published this, as I said, in Vox. And this was more or less what we showed.

So here is the girls up here. They are in -- well they are all in blue and pink I suppose. So the mean capillary hemoglobin for 26,000 females, these are donation not donors so there is going to be some repeats in there, but it is fixed here somewhere between 12 and 12.5. Okay? And the venous hemoglobin taking up the same donation about ten minutes later as they sat on the bed was higher. It wasn't variably higher but these are the means and it

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was higher and similarly for the males. And the gap is about a gram here and just over half a gram there.

And it has this sort of funny Sawtooth picture here, which sort of suggested that there was some sort of seasonal variation. But the main point we were trying to show was that in general there was a large comfort zone, which allowed us to say that the true venous hemoglobin, assuming that the venous hemoglobin is the true hemoglobin, was in fact safely above the regulatory cut-off both for males and fore females. And that is what we published.

Now when we had been -- after we had centered off, it was obvious that the referees would only come back and say well this could just well be an artifact because you are measuring them on different machines.

They are all done the same way so every capillary donation is done one similar machines which are calibrated against the

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venous hemoanalyzers but they were done on different machines.

And so after we sent off the paper and were waiting for this sort of question to be raised, we looked at the data in a slightly different way. And what we did, if you concentrate here, this again is the capillary hemoglobin down here on the x-axis and this is the capillary minus venous down here.

And if you look at these samples here. So in this one which is the females, there are 26,000 data points and we divided them by increments of 0.1 of a gram. So 12.12 to 12.3, we added some earlier data that we had or some data around the same time that we had from people with lower hemoglobins, both males and females. But in here there is 26,000. These are the data that Dr. Cable showed you earlier from the first-time donors that we were doing as a separate study around the same time.

And what we saw to our, I think,

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surprise, was that as the capillary hemoglobin went down, the gap went up both for males and for females. But they didn't approximate one another. There was a clear gender difference between this gap. So the gap between capillary and venous increased as the capillary went down within this small range and with sort somewhat lesser data around the other places. And similarly for males. But to our surprise, they were parallel and they were never going to meet up. That shouldn't have surprised us. There were, after all, differences between men and women.

We have a hemochromatosis collection clinic and these are data from they are almost all males. We looked at similar data, there are 1,700 donations here, comprising in this group about 220, 230 males, which we subsequently have gone on to recruit a lot more males. We have more data. And they show exactly the same thing.

Interestingly, the cross-over here

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for ordinary donors is about here. For people with hemachromatosis it is up here, so there is an interesting story in here. But within this group of males, which allowed us to have no data on a broader range, we saw more or less the same slope. As the capillary hemoglobin goes down, the gap goes up. As it goes down, the gap goes up.

Just quick come back to -- okay. So we now took these data here, these ones and we analyzed them by age of donor because we were looking for the reason for the difference between male and female. And what we showed and this really was an exciting moment, here is the girls in pink. And what we show is that the mean gap, as we knew, was lower for females than for males but as you divided by older females, the gap drifts up towards the males once they go through the time of the menopause here. Okay?

So here is the gap and then there is an age effect. Up it goes. The men drift

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off slowly, as they do over time. The older males had a lower gap than the younger ones. I mean, the differences here are tiny. The only reason you can say that these are validated is that the number of data points here is about 10,000. Here it is about 26,000. So what we were able to show is that the mean gap between venous and capillary in this group, at that level of 13 to 13.5, is about 1.2 in the younger men and goes down to about not much below 1.1 for females, about 0.6 in the younger donors going up to 0.9. So tiny differences but, nevertheless, probably biologically valid observations.

Now we actually published those two curves in *Blood* last year because they were an exiguous as sort of they were the same data, just analyzed in a different way but we put them in a letter to *Blood*.

At that time, and we still do, we thought that this provided a clue as to why females had lower hemoglobin levels than men

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and don't seem to compensate by increasing erythropoiesis. Girls don't want to be boys.

I would like you to know that. Boys like to be girls but that is a separate issue. Females do not try to increase their erythropoiesis to get their hemoglobin levels up to male levels. Now whatever the pause for that may be, what it clearly -- What I infer from that is that females deliver hemoglobin more effectively to the capillaries than men do per unit red cell mass. So they get down to this seven grams per deciliter at tissue level with a lower headspace, lower pressure hemoglobin, of red cell mass behind it for whatever reason, which we can talk about at the bar later.

Now excuse my French. This is a paper that was presented at the ISBT earlier this year from Gilles Follea who knows now I have used his slide. The last time I used it I didn't ask his permission but I did on this occasion. And they showed exactly the same

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thing or more or less exactly the same thing.

There were 85,000 donations in this group. Down at the level of interest, 12 to 12.4, 13 to 13.4, they have more or less the same numbers as we had and they showed more or less exactly the same thing. That in this group of donors, there is a difference of about 12 or 0.8 grams per deciliter between the venous and capillary hemoglobins in our favor. And for men, we know that is -- my French is a bit better than that. That is the men. These are the women. And for the women, it is about half a gram. Slightly less than ours, which I will come back to later on.

So here is another sort of big group who have shown more or less the same thing over the same numbers.

Come back to my hemachromatosis donors. Again, because these are people with hemachromatosis, they come back again and again and we can actually get repeat readings on the same donor in a reasonable time frame.

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This is a scattered part of the data I just showed you, showing the regression line. These are the individual male donors. Of the 172 males that have given more than twice, we were able to draw a line. And what it shows is that within an individual donor, the gap also moves as the hemoglobin moves. So as these guys come back again and again, their capillary hemoglobin shifts and the venous hemoglobin tends to remain the same. That's how that works out.

And these are just a few individual plots from these guys. They will more or less show the same thing. And the black is the capillary hemoglobin level and the white is the venous hemoglobin level. And with a reasonable eye of faith but I assure you the statistics are very robust, the capillary moves much more than the venous. The venous tends to remain much steadier than the capillary as we repeat venous on these guys. These people are replete by definition. We

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don't bleed them down to ferritins below 50. And what we are showing is that in fact the venous hemoglobin tends to be held steady and the capillary moves around it. So as you bleed them, the capillary comes down and the venous tends to remain the same, which is kind of interesting.

And when you do the sums on that for a two gram drop of the venous hemoglobin, on average you get a full gram drop of the capillary hemoglobin, which is quite a large amount.

So in normal subjects if you just accept that they are hemachromatosis, for a rise or fall in the mean hemoglobin level two down to the venous blood, the mean capillary level rises or falls a corresponding four grams.

So this actually, the capillary hemoglobin confers a buffering or storage effect of red cells but move much more laboring while trying to preserve the venous

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hemoglobin. That is my interpretation of it.

This should all have My Father's Tie in here.

And the total storage capacity compared by this effect depends on the absolute volume of the anatomical space, which I believe is where this affect takes place. Now these are my realistic assumptions. So using my assumptions on the size of the arteriole or the size of the capillary circulation, the space where the Fahraeus affect occurs to give you down this mean capillary hematocrit which I put at 0.3, somewhere between 0.4 and 0.2 to get from there to there.

The volume of this hematocrit variable intravascular space must be approximately 1.5 liters for a total blood volume of five liters. Mean normal hemoglobins in males. You will have to sort of take my word for that on the sums of them but it is certainly more than 750 and probably less than half. So the point here is it is a

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substantial volume of the intravascular space has this variable hematocrit.

The capillary space is capable of accommodating about half or more of any rise or fall in the red cell mass within physiologically normal ranges. I think it is important to point out here that what we have got here is a study of normal healthy people.

This isn't about disease or illness. It is really about normal physiology. And this tends to buffer the venous hematocrit. And with it, the whole blood viscosity and the stroke work. So as your hemoglobin goes up and down, you tend to keep your venous hemoglobin start here, your right heart and then your left heart sees more or less static.

So when your red cell mass goes up, you don't in fact increase your stroke work to the extent you might.

What I am implying here and you may or may not agree with that is that this hematocrit variable space functions as a

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physiological storage space for red cell reserve in humans. So we have a capacitance space of about 1.5 liters where we can vary the hematocrit, the amount of red cells within the same volume.

I want you to come back again to the original study that we showed. When we subtracted out the 12.5 from the Sawtooth pattern, this is what we saw from the donors, that in fact the mean capillary, the mean difference between the capillary and the venous hemoglobin level varied between summer and winter quite significantly. There is quite a nice P-value on this. All the lowest dips were in summer and all the high points were in winter. And when our statistician looked at it, he said well I know what that is. And I will tell you what that is in a minute. And it turns out that these are in fact statistically quite significant. That the mean difference in summer for males is less than a gram over a gram in winter and for

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females it was from 0.56 to 0.78.

The notation that there is a summer and winter in Ireland is in fact a complete fiction.

(Laughter.)

DR. MURPHY: The mean temperature for three consecutive winters was 43.7 and we rose to a dizzy 58.64 in the summer. I do not get a bonus from the Irish Tourist Board but if I did, I wouldn't show you those data.

(Laughter.)

DR. MURPHY: So where are we? We now know that we have a gap between the capillary and the hemoglobin levels in large population studies. Not just our data but other people's data as well. We know that it varies with gender and we know that it varies with age. And we now know that it varies with the season of the year.

Okay. Volume of the hematocrit variable space is somewhere around 1.5 liters, anywhere between 750 and two and a half. That

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is the space for sampling in the finger pulp.

The hematocrit within this space is a dynamic variable. It varies with age, sex, red cell mass, and with a chronobiological rhythm. It doesn't have the simple linear relationship with venous hemoglobin and should not be used with venous hemoglobin reference levels. That is what I wanted to show you there.

Now in the next few minutes I am going to suggest to you how it works. But to go back to this, I think there are good data to support that statement. And that is really what I want to get across at this workshop that there are good reasons why, good physiological reasons why the capillary hematocrit is not as useful as it might be and certainly should not be used with simple venous reference ranges. They have their own reference ranges for how does it work. I really put on my father's tie for this.

Okay, we know there is red cell with hemoglobin which I am using as a

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surrogate for red cell mass, which we all do.

We know it varies with the season. We know it varies with gender and we know it varies with age.

Well this is the most striking, I think. This is what kicked us off. The fact that the gap disappears or tends to go off after the menopause in women, would suggest that it may well be estrogen-related. And without going into it in too great detail, is that related to estrogen induction of endothelial nitric oxide synthase?

The more red cells you have per unit volume of blood, the more you have in your capillaries relative to your veins. Is that related to nitric oxide synthase from deoxyhemoglobin vasodilating of the venous capillary hemoglobin or venous capillary circulation?

What we are showing or suggesting is that decreased flow in the venous side of the circulation caused by nitric oxide

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vasodilation will lead to increased hematocrit, a sort of accelerated reverse of the Fahraeus effect. The higher the red cell mass, the greater the effect because of this nitric oxide effect.

Well what about this one? This is where we started off and this was, I think the heart is a mystery to crack. These are all just notions now. I haven't got any data yet to support them but obviously we are designing or looking for funding for studies to address these.

Well if you look at this, it is not 100 percent but here we go. We know there is not much in terms of temperature difference in Ireland between summer and winter but the peaks tend to occur around December and that is a bit iffy down there. And there is a peak coming in December. And the troughs later on in the year around June.

So the question is, is this due to daylight rather than actually to temperature.

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And the only thing that really changes with daylight is melatonin. And it so happens, as you all know, I'm sure, that melatonin inhibits nitric oxide production by vascular endothelial cells, in vivo and in vitro. A paper that came out on it in the last couple of years.

Interestingly, when we look at -- This is a very soft slide. Now if we look at Gilles Follea's data, he showed without any seasonal variation that his mean gap between capillary and venous hemoglobin level down at the 13, 13.4 level for men was less than ours, less than even our winter or our summer. And the women were similarly less than ours, suggesting in fact well the summer they had better weather in France. I hope you know that. I don't get a bonus from the French Tourist Board either but they do have better weather and they have shorter nights.

So the gap between capillary and hemoglobin level in large population studies

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is a physiological quantity of the data of hemoglobin level gender and age, season of the year, and possibly also a nitric oxide effect on the vascular endothelial. There are other possibilities as well. It could well be associated with the renin-angiotensin system and in fact there probably has to be an Angiotensin II affect in here. Because what we are saying is the erythropoiesis can be driven by the venular side of the capillaries rather than entirely by the arteriole side, which is where the EPO kicks in. And we know, or I sort of found out in the process of this that Angiotensin II does in fact have an erythropoietic effect both as an EPO secretor and a direct effect on erythropoiesis itself. So that is another possibility.

Simple variations in blood flow or capillary flow characteristics could account for some of it and maybe even account for all of it. But all these three effects and other effects that people can think of are not

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mutually exclusive.

So that is my final point, which is the point I have made several times all the way through. And thank you.

I made the joke at one stage this is a blood bank. In Dublin, this is the only Irish bank with liquid assets. It is now the only European bank with liquid assets. So thank you very much.

(Laughter.)

(Applause.)

DR. BIANCO: Our last speaker will be Dr. Susan Leitman here from the NIH Clinical Center, the Blood Bank. She is going to talk about evaluation of low red blood cell mean corpuscular volume in an apheresis donor population.

Dr. Leitman is the Chief of the Blood Services Section of the Department of Transfusion Medicine at the Clinical Center. She is a graduate from Brown University, completed her internal medicine residency and

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fellowship at the hospital of the University of Pennsylvania and was a blood banking fellow here at the NIH. She is an active researcher in several areas of transfusion medicine and was recently involved in studies describing the incidence and severity of iron deficiency of blood donors and benefits of routine iron replacement. These studies will be presented tomorrow and were done in collaboration with Dr. Bryan.

And she is going to talk now about mean corpuscular volume.

DR. LEITMAN: Thank you, Celso. Thank you very much, Dr. Bianco. I want to thank the meeting organizers for inviting me to this very interesting workshop. I want to thank Dr. Rick Davey personally for giving me my first job as a blood banker many decades ago when he accepted me into the fellowship at NIH.

So it was unclear in looking at the preliminary program what direction the

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discussion and the presentations were going to go this morning and this afternoon. I found the presentation by Dr. Murphy fascinating so I will converse with that presentation during a couple of my slides, although I did not intend to do that when I put them up. But it is an interesting sequel.

So, I was asked sort of to move the discussion from fine tuning of hemoglobin and how we measure hemoglobin to a related parameter, which is the red cell mean corpuscular volume or MCV.

So, the red cell MCV is simply the average red cell volume in femtoliters. It is a precise, accurate, reproducible measurement of red cell size. It is also inexpensive, standardized, available in an automated manner and reported as part of the standard CBC from autoanalyzers which perform this measurement by one of two techniques. In one case red cells passed one-by-one with a very small aperture and generate a signal proportional to

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their volume. In the other method, the techniques are used in the autoanalyzer that measure refracted, defracted, or scattered light.

Since hemoglobin is a major determinant of red cell size, and since iron is a major determinant of the red cell hemoglobin content, therefore the red cell MCV is actually one of the best physiologic indicators of iron availability for erythropoiesis or red cell protection in the marrow. As an example of this, we noted in the course of treating several hundred patients with hereditary hemachromatosis with phlebotomy therapy that the MCV decreases predictably during the course of therapeutic phlebotomy, reflecting the development of iron-limited erythropoiesis. And we noted that the MCV could be used as a therapeutic target in the treatment of hemachromatosis, as show in this slide.

So what I have plotted here is the

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MCV on the y-axis and phlebotomies from the time of transition from de-ironing or acute iron reduction therapy to maintenance therapy with zero being the point of transition. So these to the left of the zero are the phlebotomies, the number of phlebotomies leading to iron depletion and then in the positive direction, are the phlebotomies during maintenance therapy. And what you can see, this the mean of the first slightly less than 100 patients who entered the protocol for phlebotomy therapy in our program, and as they approach iron depletion and I will show you how on the next several slides we knew they were iron-depleted, the MCV takes a nose dive and drops by three to five percent below baseline. And so at the time it turns out they are sometimes rather profoundly iron-depleted, the MCV was about 88 to 92 and had started at about 95 to 98.

So at the time of the transition to an iron-depleted state, the MCV was still well

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within the normal range of 80 to 99 but was three to five percent below their baseline. And how did we know they were iron-depleted? Well, because at the same time we were getting ferritin assessments and ferritin is the gold standard to the assessment of total body iron stores. And so we can see that at the point of transition from de-ironing therapy in this hemachromatosis donor cohort to maintenance therapy, the ferritin had achieved targeted levels or we had achieved targeted levels of a ferritin of 50 or less. You can see that we got there, it is the last four of these de-ironing bleeds right at the point where the MCV was beginning to decline. And even a decline in MCV of one to two percentage points below baseline correlated very well with a ferritin drop below 50. And this is all interesting. Oh, note please that the ferritin here starts at 900, goes down to 50 and that occurs over the course of about an average of 20 bleeds. What is of interest to

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this group is what the hemoglobin is doing at that time.

And this is the venous hemoglobin.

Of course we obtained capillary hemoglobins but I did not analyze them in this manner. But I will analyze them in Dr. Murphy's manner very shortly to see if I can confirm those effects.

The hemoglobin in the last three to four bleeds below transition to maintenance also drops and drops by an average of one and a half to two grams compared to the subject's baseline hemoglobin before phlebotomy therapy.

But as has been mentioned many times by many people in today's session, at the time that iron depletion and in some cases profound iron deficiency that was unintentional but ferritins of ten to 20 to 30 and saturations of ten to 20 percent in a few of these donors occurred while the hemoglobin was still above 12.5. Since the majority of these donors are used as allogeneic donors and their blood is

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made available for transfusion, the staff are trained to spread out the phlebotomies from every week, to every two weeks, to every three weeks, as we approach transition to keep the fingerstick hemoglobin above 12.5 so that we can use the blood for transfusion.

So if that is your target, you can collect easily blood from subjects with a hemoglobin of 12.5 or above who are relatively profoundly iron-depleted. In fact over time, as you can document, because it was the phlebotomy therapy in the blood bank, that got them there.

Okay. So moving from a hemachromatosis donor population to a volunteer donor population, what are the causes of a low MCV in a healthy donor population? Well there are three main causes: iron deficiency, anemia, thalassemia trait, and chronic disease. And it is so important to be able to differentiate the first two causes of a low MCV that numerous

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investigators have spent a substantial part of their investigative lifetimes devising formulae to predict what a low MCV represents.

And so this is a number of publications in the last many years looking at the other parameters that are obtained with a routine CBC. One gets the indices, the MCV, the MCH. One also gets the red cell count in millions per microliter and one gets the red cell distribution width.

And all these investigators devised numerous formulae looking at the relationship between the MCV and the red cell count. By several investigators more fancy formulae, the MCVs minus the red cell count times some multiple of the hemoglobin, minus some constant from the Coulter counter, the MCV squared times the red cell distribution width, divided by some multiple of the hemoglobin or the MCV squared times the MCH divided by 100, and on and on. I like the Bessman formula best because it looks at the RDW alone, which

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is simple but maybe even better than that, it is simply the MCV alone.

And the reason any of these work is because these parameters reflect what is going on in the red cell with either iron depletion or an inherited hemoglobinopathy and the MCV is, in general, much lower with hemoglobinopathy than with iron deficiency in subjects with a hemoglobin above 12.5.

And the rest of my comments on this slide all pertain to subjects with hemoglobins above 12.5. Their red cell count will be lower in the subject with iron deficiency than in the person with hemoglobinopathy. The red cell distribution, in contrast, will be elevated in the person with iron deficiency but not in the person with hemoglobinopathy.

So you can take a subject for example with a slightly low MCV, 78, 79, a slightly low red cell count, and a high RDW and say with reasonable assurance that that person is iron-depleted, or iron deficient and

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that is the cause of the MCV. In contrast, if the red cell count is normal and the RDW is normal but the MCV is rather profoundly low, 70 with a normal hemoglobin above 12.5, that is the thalassemia trait.

So, that led to an evaluation of something we see commonly in the apheresis clinic, which is a low MCV. And in this study, which I will now review, we looked at the MCV in a normal, healthy apheresis donor population. We have two such populations in our facility. We have volunteer plateletpheresis and leukapheresis donors, and we have paid -- I'm sorry, plateletpheresis and granulocytes apheresis donors, volunteer donors, and we also have paid donors participating in a research leukapheresis program where the cells they donate are used in vitro laboratories by NIH investigators.

All apheresis donors in our facility are routinely evaluated with a CBC prior to each donation. We defined a low red

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cell MCV as less than 80 fentiliters in the presence of an acceptable hemoglobin. So we only evaluated subjects who went on to donate because they had a fingerstick hemoglobin above 12.5 and recognized that this could be due to either iron deficiency or hemoglobinopathy most commonly in alpha or beta chain variant trait.

We also noted, this was important to our operations, that a low MCV due to iron deficiency had a high likelihood of decreasing leukapheresis yields and collection efficiencies because less dense lighter cells, red cells, due to iron depletion flooded at the top in the centrifugal field of the buffy coat layer and would trick the optical detector of the apheresis machine into thinking it had reached a certain layer accompanied by a certain red cell content and the machine would institute a buffy coat collection but the buffy coat layer had not yet been reached. So we saw inefficiencies in

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leukapheresis collection with iron deficient leukapheresis donors.

This is what we found in a 15-month study period. We analyzed 1162 volunteer and research apheresis donors. And of these 1162, 33 had a low MCV below 80 accompanied by a fingerstick hemoglobin of 12.5 or above. These subjects were more likely to be male than the general apheresis population. I will comment on this in a moment. This has to do with the fact that so many of our research donors were male. And were more likely to be African American, 45 versus 14 percent or Asian, ten versus three percent.

Our volunteer donation population is 53 percent male and 87 percent Caucasian but our research donor population which composed one-third of the general group is 68 percent male and 36 percent African American, which probably explains why there was an overrepresentation of males in the low MCV group.

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So, in apheresis donors with a low MCV below 80 and a normal hemoglobin above 12.5, 50 percent of them had isolated iron deficiency and 36 percent had isolated hemoglobinopathy with 15 percent having both iron deficiency and a hemoglobinopathy.

If one looked just at all the iron deficient, 64 percent of these donors have iron deficiency versus 51 percent which had hemoglobinopathy. And again, 15 percent had both. Here is the reference composition in terms of race and here is the race composition of each of these groups. And what is notable is that the increased percent of African American donors in all these groups compared to the referenced population and the increased percent of Asian donors as well.

In the donors who had hemoglobinopathy as the etiology for their low MCV, the MCV was significantly lower, as I stated a few slides ago, than in those who had iron deficiency as the cause for the low MCV

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or who had a combination of iron deficiency and hemoglobinopathy.

In the iron deficient donors, the ferritin as expected was significantly lower, was very low, than in the other two groups. And in fact with this group with a very low MCV below 80, the degree of iron deficiency was profound with a mean ferritin of 15 in males, six in females, and a mean transferrin saturation of 11.8 percent.

Hemoglobin electrophoresis was performed in all 33 of the subjects who had low MCV. And on this slide, it is showing the cause of their low MCV. So 16 or nearly 50 percent had iron deficiency and 36 percent had hemoglobinopathy alone. Again 15 percent had both. The cause of the hemoglobinopathy in this type of population was most commonly alpha thal trait, 14 cases, a combination of a hemoglobin G Philadelphia trait, that is an alpha trait plus an alpha thal trait. It is an alpha globin gene variant plus an alpha

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thal trait was seen in one subject. A hemoglobin Lepore Boston trait was seen in another subject. That is a beta chain globin defect. And in the five subjects who had both iron deficiency and hemoglobinopathy, alpha thal trait alone or hemoglobin C trait plus iron deficiency was seen.

When these subjects were given iron, oral iron, 325 milligrams once daily of either ferrous sulfate or ferrous gluconate, as expected the MCV promptly increased, as shown in subsequent visits and the RDW decreased. Two of the 21 subjects with iron deficiency were symptomatic, highly symptomatic with pagophagia or Pica. They craved ice as if it was an addiction. And within five to seven days of starting oral iron, that craving stopped.

So I will conclude with this slide that the MCV is a useful screening tool to detect iron deficiency and hemoglobinopathy in the healthy blood donor population. It does

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require a CBC and an automated analyzer. It is a particularly useful test in apheresis donors in whom the CBC is obtained as a routine practice prior to each donation.

As I said, 64 percent of apheresis donors with low MCV had iron deficiency and 51 percent had hemoglobin variants. Iron deficiency in hemoglobinopathy may coexist and the combination of the hemoglobin MCV and RDW are often helpful distinguishing factors.

Low MCV values may be treated empirically. There is no harm to giving iron with oral iron in the donor setting, rather than characterizing what is going on with ferritin and iron panels and the response to treatment may be used to confirm the diagnosis.

I want to thank the collaborators on the three studies that I presented, Dr. Barbara Bryant who is in the audience and will be presenting tomorrow, Dr. Charlie Bolan, and the research nurses Yu Ying Yau and chief

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nurses Janet Browning and Julie Hoffman.

Thank you.

(Applause.)

DR. DAVEY: There might be a couple of questions for Susan.

DR. LEITMAN: It's too late in the day.

DR. DAVEY: Too late in the day. Thanks a lot Susan.

Our next order of business to conclude today's session is a panel discussion led by Harvey Klein. I don't have Harvey's CV in front of me. It would be too heavy to carry anyway. But you know Harvey is the director of the Department of Transfusion Medicine here at NIH, a dear friend, a scholar, President of the AABB, many honors, and he is going to be directing our panel.

The panel will be members of the speaking group this afternoon, Ritch Cable, Mindy Goldman, William Murphy, Susan Leitman, and Josie Bautista. And the panel will look

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at items we have discussed in terms of hemoglobin measurement and whether or not we can draw any conclusions or fast forward from what we have heard from the discussants today.

So Harvey and panel, could they come up front?

DR. KLEIN: Okay, while people are assembling, I think for this particular panel we are not going to consider whether hemoglobin is an accurate measurement of health or of iron status, which we have heard it is not, or what venous level is appropriate as the right value, but we are going to concentrate, I think, on the measurement and on the instrumentation perhaps.

And I think I want to start off by asking all of the panel members, I think I heard Dr. Cable say that we ought to totally abandon the fingerstick and use only venous determinations to screen blood donors. And I would just like to know, first of all, did I hear that correctly, Dr. Cable and do our

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other panel members agree?

DR. CABLE: To be provocative, yes, you heard me correctly.

DR. KLEIN: I wonder, we do have a number of individuals who have been involved in donor screening issues. And do you think it is time to abandon the fingerstick as a screening technique or do we need to somehow adjust it?

DR. MURPHY: Well Harvey, as you know, a lot of tests are done to make the doctors feel better. And there is no doubt that the fingerstick makes us feel better about things. So maybe we shouldn't.

DR. GOLDMAN: I think just because something isn't perfect doesn't mean it isn't good enough to do. It is a screening test. We have been giving male donors who fail the hemoglobin screen and females who are a low fail who have a hemoglobin of 11.0 or below a letter and sending them to their physician to have their hemoglobin checked.

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And then we did a study where we called back these donors to see if they went to their physician and what did their physician find. And this was a big initiative, as you might imagine from the medical side, meaning a lot of my hemoglobin went into implementing it and I was a bit disappointed that only about 55 percent of the people who got the information sheet actually went to see their doctors. However, the vast majority of them said that whether they went to see their doctor or not, over 95 percent of them said that it was important for the blood center to inform them of any abnormality that might be of importance to their health, which is a regulatory requirement in Canada, by the way; that they felt that we had adequately informed them of an abnormality; and a significant of those who had gone to see their physician had a finding of anemia confirmed and some of the male donors had had a finding of colon cancer confirmed or found.

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And actually we got a letter from one donor, since we are so used to getting complaints, this one I almost framed and put in my office, saying I had come to donate hoping to save the lives of other people. I feel the staff at your blood center saved my life because my hemoglobin was found to be low. I went to see my doctor. I was scoped.

I have colon cancer. It was operated on. You know, this is an anecdote but I think that a screening test of some sort is of value. We are screening one million donations a year now. And so we are fulfilling some kind of a public health function, whether we like it or not. And I think we owe something to our donors.

DR. KLEIN: Dr. Leitman.

DR. LEITMAN: I would reflect exactly what Mindy Goldman just said. That we are getting a window into a donor's health by doing the vital signs and the CBC and the donor is giving us something and our patients

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something. And what we can give back to them, other than a sense of altruism and happiness that they are helping, is something helpful to them, like knowledge of their vital signs or knowledge of their hemoglobin.

And if you are in this business long enough, you will what Mindy described. We diagnosed two cases of leukemia and one myelodysplastic disorder over the past several decades that I can remember and the donors were very appreciative of that.

DR. KLEIN: But I guess the question is whether our current measurement as looked at primarily by the fingerstick because I think that is what everyone does, is sufficiently accurate. And by accurate I suppose I mean reflecting venous hematocrit, which is the diagnostic test that is usually used to be useful or whether one ought to, for example, try to validate the RISE algorithm and perhaps on our iPhones, measure the fingerstick and then correct for that to get a

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venous hematocrit.

Is that something that is useful or not? Dr. Murphy.

DR. MURPHY: I think there is an important piece of data that I am missing and it was alluded to earlier on. And that is, what about the people whom we pass, collect or use their blood, and pass who are at the lower limit and probably we shouldn't be taking? What happens to them? Do they have even a very mild morbidity associated with that? It might be subfertility. It might be poor functioning cognitive tests. We should not be doing that.

So I accept that for the vast majority of donors who are involved, 12.5, 13.5, it is a very fun test. But there are people who may be slipping through our net because it is not sensitive enough for pre-morbidity or a complication of blood donation.

Remember in blood donation, there is no risk-benefit profile. There is no benefit. There

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is only risk and we should be cognizant of that. So down there we should perhaps be designing a test but that serves the donors better.

DR. KLEIN: Dr. Cable?

DR. CABLE: Well I didn't say that we shouldn't do hemoglobin testing. I said we shouldn't do a fingerstick hemoglobin testing, to be precise. Whether -- Well and we have a venous sample. So my proposal would be to use that venous sample to do whatever hemoglobin testing makes sense.

Certainly you would want to do a venous hemoglobin either before or right after the first donation. Probably in this country, before because of the nature of the conservative. And we have a federal regulation that requires it. It would be hard to get away from it.

So I think a venous sample, I didn't buy a fingerstick sample the first time, to make sure that you are not wildly

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congenitally hemoglobinopathic or something, makes sense. But there have been studies of sequential hemoglobins in annual physicals, I believe. And I don't believe people's hemoglobins changes all that much, unless you make them iron deficient. We do make them iron deficient. And if we could address that issue in a more direct and effective way in this conference and others, then we don't really need to worry about hemoglobin going down. If someone's hemoglobin is 14, it is likely to stay 14 unless they are a woman, in which case when they reach menopause it will go up or if they get into trouble with menses it might go down, getting back to some public health issues. Or if a guy gets old, he used to be 40 and now he is 65, I can relate to that, you know, it will be a little lower.

But I don't see the benefit of an every time you come into donate six times a year hemoglobin test. That is way over the top for public health reasons. As long as you

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are not wildly making donors iron deficient. As long as we are doing what we are doing now and making donors wildly iron deficient, you can make the argument that we should have a hemoglobin every time but it is a very insensitive and ineffective way to prevent iron deficiency.

So I would say and finally to the point of whether we owe it to donors to do a health screen, I just couldn't disagree more with the comments. Why don't we do PSAs? Health people in this country are coming out against healthy screening without evidence. And I would propose that an annual hemoglobin has no evidence whatsoever to support it. And it has been looked at a lot a less than the PSA.

So I think that you would like to make sure the donor is healthy. Maybe do it once. Maybe you do it once every so often. But I don't see doing it every time you donate and I certainly don't see using a fingerstick

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to do it. So I would like to make my position as clear as I can.

DR. KLEIN: That's pretty clear.
Dr. Epstein?

DR. EPSTEIN: Well this is taking us in a different direction but it is a question for Dr. Leitman. So it is a little bit about kinetics.

What you found was that in the apheresis donors presenting with a low MCV, they already had very, very low ferritins. And when you looked at the graphs of what happened to the MCV versus what was happening to the ferritin, ferritin picked up the change much, much earlier than the MCV did.

So my question to you is do you think it is practical to use change of MCV to monitor donors, whether they are getting into trouble. I think what you showed us is once they have dropped their MCV well they are in trouble. You have made them iron deficient. But our goal is to keep from getting there.

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And so do you think at a practical level, thinking of the kinetics, that this would be of practical value?

DR. LEITMAN: So Jay, those were hemochromatosis subjects, not apheresis donors.

DR. EPSTEIN: Right.

DR. LEITMAN: And if you waited, we were finding the value that meant -- It was an observational study. We didn't know whether the change was one percent, or two percent, or five percent, or ten percent from the donor's baseline pre-phlebotomy MCV to the change. And we found that not only did, just as you stated, any change greater than three to five percent was too late. And what ultimately we set as our indicator was an MCV, it is such a reproducible test, an MCV decrease below baseline of one percent on two successive occasions corresponded with a ferritin that was approaching 50 but not there yet.

So it was a good predictor but you

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had to fine-tune it. And I will say as a caveat that about every five years we change our automated cell counter and although we validate one against the other, the MCV on the Sysmex is not the same thing as the MCV on the CELL-DYN 4. So you keep having to change with new sub-counters and that is a real hardship when you are looking so carefully at a one percent change in the MCV.

So it can be used as a harbinger. Again, it is not an absolute MCV value. It is a delta. It is a change from that subject's baseline.

DR. KLEIN: Mindy.

DR. GOLDMAN: I just want to respond a little bit to Dr. Cable's earlier comment about PSA screening. Of course there is a difference between PSA and hemoglobin is that we are going to be dropping the donor's hemoglobin when they donate. So it is a little bit more relevant to provide them with information about their hemoglobin and to

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assess their hemoglobin than to do their cholesterol and their PSA and a whole bunch of other public health screening that we could in theory do.

I also want to point out that although a lot of the talks were really fascinating and interesting about changes that might occur in the relationship between venous and capillary hemoglobin with seasons and with iron status and so on, I mean, none of those changes is as big as just the physiologic differences between males and females. So if a first split was going to be made in terms of a closer relationship between sort of physiology and hemoglobin, to my way of thinking, that is a larger difference than taking into account small variability. That may be very interesting and it would be very scientifically interesting to understand all of that but is less of a big difference than just the physiologic difference between males and females.

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DR. KLEIN: Well let's follow that a little bit. I appreciate Dr. Murphy's comments. And we don't have good data yet on adverse events or problems with slightly hemoglobin whether it is fingerstick or whether it is venous or even mild iron depletion. But do we have the technology or do we need the technology, and I'm thinking about mechanical technology now, to be able to look at functional changes. For example, we heard about MCV but certainly the most rudimentary cell counter these days can give you all of the various parameters we saw, red cell count, MCV, RDW, as well as hemoglobin, which could tell you that there has been a physiologic change for the worse in a normal individual volunteering to donate blood.

Do we need a new technology to do that or is that overkill? Jump right in.

DR. GOLDMAN: I'll jump right in. On our plateletpheresis donors, we were doing a false CBC because our machine would do a

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false CBC. And then we were calling, had the physician be called every time there was a flag or there was a high this or a low that. And you know, a lot of these people were being sent to their doctors. And I think the problem when you do more sophisticated things on healthy people is that you get into people that have really nothing wrong with them but are a couple standard deviations out or you know, any false positive that machine can have, you are going to fish for that by doing it on basically a healthy population. So that is my experience, based on having a lot of fancy indices on plateletpheresis donors.

DR. KLEIN: Dr. Leitman?

DR. LEITMAN: I think Harvey know that we do that in our center. So, on the apheresis donors, we get a complete CBC and we write computer programs to evaluate changes in the CBC. And the computer sends an alert to a nurse manager of that program if the MCV drops by a certain percent or the hemoglobin drops

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by a certain percent compared to the start of the program for that donor. And then that precipitates a review by the nurse of the donor's entire record and a review with the physician. And in many cases, we detect the beginnings of iron depletion and we treat. We notify the donor. We ask them to come in or we send them iron and they are most appreciative of it. And I think it keeps them active in the program.

So it is easy to do in an apheresis population because you have that data. I feel strongly that since we all have that data in our populations, we should establish computer programs to evaluate that. They are easy. One can have a nurse manager run such program.

And it keeps donors active. It keeps them retained and they are very appreciative of that.

DR. KLEIN: Easy to say for fixed centers. Not so easy to do it for mobile drives, I guess. Right?

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Dr. Kiss.

DR. KISS: Yes, thanks, Harvey. Joe Kiss, Pittsburgh. I just wanted to make a comment about that approach.

Having been part of the RISE study, we did do sensitive measures on the ADVIA instrument made originally by Bayer and now I believe by Siemens. And I am going to talk about this a little bit tomorrow but we looked at percent hypo M and we looked at reticulocyte hemoglobin content on donors followed for two years.

The differences though, you can certainly if you are following an individual patient, you can see these changes over time with that kind of scrutiny of the donor, which is a very different model from the current practice in blood centers.

Again on a smaller blood bank scale, you have apheresis donors are coming in frequently and so forth. But when you are drawing several hundred thousand donations on

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donors a year, you have a very sophisticated tracking mechanism and I am sure we could build that into it. You can't see these changes longitudinally in a donor over time and pick up on the medical model of interpreting this as if you are looking at a patient.

However, even in the RISE study getting this data and looking at it, what we basically had as population on the enrollment, population maybe interim, population data at the end, and the data, you know, the false positives, false negatives are not as clear. But on an individual donor basis, yes, you probably could develop a model like that but it is a very labor-intensive medical response-intensive model.

DR. KLEIN: Thank you. Dr. Kleinman?

DR. KLEINMAN: Yes, a different question and it comes back to the venous capillary difference.

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If I understood correctly, I think the Irish data still goes, I mean the data of venous even at the lower hemoglobin levels goes opposite to what Dr. Cable reported in the REDS study but I am a little confused because the axes weren't marked, you know that clearly on the slides. At least I couldn't see them from where I was.

So my question is down at hemoglobin levels of about 12.5, are you guys finding the same thing or not? It is unclear to me.

DR. MURPHY: Yes, we are for iron-replete donors. So I think what Dr. Cable showed is that for iron deficient donors, are marginal, their relationship reverses, which I haven't been aware of before this.

DR. KLEINMAN: I see. And you weren't able to look at your data that way because you didn't have any iron measurements. Is that correct, Willy?

DR. CABLE: I'm sorry. Data on

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iron-replete donors was spot-on with that data. I didn't know about the age affect and that was very interesting. We didn't put age in our model. Maybe we should have. Maybe we will. But we didn't see the age data and we really didn't go a whole year so that I think it would be difficult for us to look at seasonal data, particularly with six centers across. We don't even know if it is temperature apparently or whether it is daylight. But it would be difficult for us to look at seasonal data.

So I think our data looks very similar, the difference being that the RISE dataset was greatly enhanced in iron deficient donors who we knew about because that was the purpose of the study. Whereas, your data didn't look at that at all.

DR. MURPHY: No, we didn't. These were all donors who had passed. But yes, there would have been iron deficient donors among them but they didn't pick them up.

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DR. CABLE: I was going to ask about the iron effect. I mean, we saw an iron effect in addition to the affects you saw. You postulated nitrous oxide. Iron is known to be a nitrous oxide scavenger. We have seen in blood donors other vasoactive effects that are thought to be nitrous oxide mediated, namely a dilatation of the brachial artery after a vasal occlusion. We did a study in which severely iron-depleted donors had much greater vascular reactivity to hypoxia and vasal occlusion than did non-depleted donors of the same age and otherwise health status.

So we postulate in the article that is just now in press that it was a nitrous oxide effect, citing these articles. I was intrigued that your articles were a different set of literature but again relating to nitrous oxide.

So I am wondering whether the iron effect in this could well be nitrous oxide based on all that data.

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DR. MURPHY: Sure but as I was sort of putting that talk together, I thought I am just making this a little bit pat. I am just sort of, you know, if something sounds too good to be true, it probably is.

So there may well be a lot more to it but certainly it is very interesting.

DR. KLEIN: There are several noninvasive devices that are being promulgated as donor screening tools. They seem to have a wider coefficient variation than even what we are using now. I'm just curious as to what coefficient variation is acceptable. Or how do you look at these?

DR. CABLE: We did some studies with them and I wouldn't buy any stock, if I were you.

DR. KLEIN: Well you don't have to worry about that. I'm a government official. I can't afford any stock.

DR. CABLE: I think the major selling point was getting rid of the ouchie.

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And the way that I would propose getting rid of the ouchie I think you already know. And it is not noninvasive hemoglobin screening. Just don't do the fingerstick. And we already have the sample as I said.

So I don't mean to repeat myself but I think that is not the direction we should go.

DR. KLEIN: Dr. Murphy?

DR. MURPHY: I would just like to make a quick point about the second stick. If in fact the space, the hematocrit within the capillary space is a physiological variable, then I would have thought terror. And I don't know how many of you have had a second stick but you greet the second stick with even more trepidation than you did with the first one. And even a deep break might change your capillary hemoglobin level, let alone an adrenaline rush.

So I would -- I think the test needs to be done for the second stick, as do a

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third stick, and a fourth stick, and then see what you get.

(Laughter.)

DR. KLEIN: I thought you were going to recommend a tongue stick, having seen a tongue slide. That would be certain to inspire terror.

Are there any other questions for the panel or any other issues on measurement or technology? Dr. Leitman.

DR. LEITMAN: I have to comment on Dr. Cable's suggestion that we not do a fingerstick assessment. If I understand you correctly, you would assess hemoglobin but you would do it on the venous sample obtained in the pouch prior to the donation. So you would have a record of what we all agree is probably the best methodology, a venous sample. But you wouldn't know that before you drew the unit. And we know what percentage of units that we -- We can predict how many would be drawn from donors who have hemoglobins of

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nine, ten, eleven, male, and female. And then if you find a hemoglobin is really low enough to be of major concern, you wouldn't use the unit because you are not sure why. Would you use a unit from a person who has a hemoglobin of 9.5? Would you want to give that to your patient? I'm not even talking about the hemoglobin content on whether it is 50 grams or greater but what is the illness in that subject?

So you have both probably harmed the donor, removed 500 mL of blood from someone with an impaired hemoglobin and then discard the unit.

DR. CABLE: Let it be said that I don't want to harm the donor.

I would propose that if we did a venous hemoglobin, that we do it with a point of care instrument at the blood drive. They are certainly designed for that. That is how we did our venous hemoglobin in RISE. And you just use a venous sample rather than a

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fingerstick.

Now, it does requiring sticking the donor in one arm versus the other. I propose to do it once, not every time. Just once for first-time donors. Granted, it is not ideal.

It has got its own problems and we can debate those problems. But I think we are fooling ourselves to use a fingerstick as a sample source for hemoglobin and pretend we are practicing medicine. I said that in my talk and nothing I have heard changes my feeling.

If it is important, we should get a proper sample. If it is not that important, we shouldn't do it. That is pretty clearly where I am. And I do care about donor's health and will not be put in a position of not caring. Let the record be clear.

Thank you.

DR. KLEIN: Dr. Kleinman?

DR. KLEINMAN: Yes, so you know I understand if we have a first-time donor we would like to have a venous hemoglobin

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determination before drawing a unit. But in a person who is a repeat donor, what about the plateletpheresis parameter paradigm where most people use the post-donation count from the prior donation to determine whether they can put the person on the machine? And essentially, I think that is an accepted paradigm. If hemoglobin doesn't change that much over time, other than I mean it could be some catastrophe that the donor has encountered, why not use the venous hemoglobin obtained after the donation as a screening requirement for the next -- You could even build in a buffer zone. If it is above a certain amount you are confident that you can draw the donor subsequently. And maybe you would have to build in a time frame within six months. And if it is below that amount, yes, you will do a capillary hemoglobin before you accept the donor.

Now I realize there is a lot of problems with that suggestion that you would

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have to individualize what you do and where obviously that is very difficult to handle each donor differently. But the general concept of using a venous hemoglobin from a prior donation, I would just like to see what people think about that.

Well, it is sort of common practice in Europe. What they do is they use the venous hemoglobin from this donation. So you come along and the French do this in some places and the Belgians do it and maybe some other places do it as well. They don't take a pre-hemoglobin. They take a hemoglobin from the donation. And if it is too low, whatever too low is, they contact you afterwards and send you a packet of iron through the post.

Now that is that they do and it seems to work. They would also withdraw the unit if it is too low and they will sort of tell the donor to become a patient if they are definitely anemic. I'm not sure how effective that is but it certainly it is a common

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practice across hundreds of thousands of millions of donations and donors.

I personally have misgivings about sending iron tablets through the post to people. All you need is one kid opening their mommy's mail and eating the Smarties. And you have undone any good that you may well try to achieve. But nevertheless, it is a common practice.

DR. KLEINMAN: And in that practice, Willy, when they do that, they don't do a capillary hemoglobin? They do that in lieu of a capillary, instead of?

DR. MURPHY: Yes. Yes, they don't do a capillary hemoglobin.

DR. GOLDMAN: Yes, I think in France they have actually quite a complicated algorithm. And I think almost anything you do in male donors will be okay because they are so far from the cut-off.

There is also some studies from Germany that I listed the references in my

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talk where they usually do have some pre-hemoglobin because they often did a sample of testing only and then they have rather complicated algorithms, depending on what your hemoglobin was, your gender, and maybe the time between your donations, whether you need another hemoglobin done, or you don't at the time of your pre-donation.

I think there is a lot of complexity in those. So it sort of depends on are you in a very simple manufacturing model where you have difficulty distinguishing male from female donors or do you use, as they do in physicians, to screen donors, and are individualizing more your approach to the donor. It is two very different systems.

DR. KLEIN: I think we haven't put Ms. Bautista on the spot yet. So maybe we should do that before we end this session.

Hemoglobin determination as I understand it, you can correct me if I am wrong, was really never designed to be a

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screening test. You came to a doctor's office and they thought that you were ill and so they did a diagnostic test, really. It was originally licensed as a diagnostic, I believe. What would it take now if we had a small instrument that was capable of doing a CBC on site to license that as a screening test? Is that a -- Well what is it and how do you do it?

MS. BAUTISTA: Well I guess the issue would be more or less whether or not it would be the complexity of the lab to do the test. Because at a point of care setting that would be a little bit more difficult than in a regular professional laboratory.

I'm not sure that answers your question.

DR. KLEIN: So it depends on how we use it and what the technology is. It is not equivalent to say an instrument that we now have in a fixed site that is perhaps being used as a screening test?

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MS. BAUTISTA: Well, it is based on interpretation. If you have a nonprofessional doing the test itself, that nonprofessional cannot analyze the results. So it would have to be analyzed by a physician or someone that has the ability to analyze your results.

So it would get down to that. In a donor site, I'm not sure what the level of education or training a person has in doing the assay.

DR. CABLE: Wouldn't that be a medium complexity test under CLIA probably?

MS. BAUTISTA: It would be a moderate complexity test.

DR. CABLE: I mean moderate complexity, yes. Which would require a medical technologist on-site, I believe.

MS. BAUTISTA: A medical technologist or a physician to interpret the results.

Does that answer your question?

DR. KLEIN: It does. I think that

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is a full employment for those physicians among us who are looking for other things to do.

Are there any other questions or comments for the panel? If not, I want to thank them both for their presentations and for their performance as a panel.

(Applause.)

Dr. Davey, do you have any words you want to say to close this session?

All right, 8:30 tomorrow morning, bright and early we are going to be doing iron. Thank you all.

(Whereupon, at 4:30 p.m., the foregoing proceeding was adjourned.)

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