

U.S. Food and Drug Administration  
Center for Biologics Evaluation and Research

Blood Products Advisory Committee

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P R O C E E D I N G S (8:03 a.m.)

**Agenda Item: Opening Remarks**

DR. FREAS: Good morning. I'm Bill Freas. I am the acting designated federal official for this morning. I would like to welcome the committee members. I would like to welcome the public and the guests as well.

This is the 96<sup>th</sup> meeting of the Blood Products Advisory Committee. Today's sessions will be open to the public for the entire day. At the end of tomorrow's session there will be a short closed session.

I would like to go around and introduce the members that are seated at the table for this morning's topic. I'll be starting at the right-hand side of the room -- that's the audience's right -- and the first person there -- will the members please raise their hand when I call their name?

Dr. Simone Glynn, Branch Chief, Transfusion Medicine and Therapeutics Branch, National Institutes of Health.

The next is Dr. Oralee Branch, Assistant Professor, Department of Medical Parasitology, New York University School of Medicine.

Next, Dr. Kenrad Nelson, Professor, Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University.

Next, Dr. James Allen, physician, Raleigh, North Carolina.

Next, Dr. Ann Zimrin, Associate Professor, Division of Hematology/Oncology, University of Maryland School of Medicine.

Next, Colonel Francis Rentas, Director, Armed Services Blood Program, Falls Church, Virginia.

In the vacant seat we will be joined shortly by Dr. Willarda Edwards, whose is a partner, Drs. Edwards and Stephens, Baltimore, Maryland.

In the next chair is Dr. William Bower, Office of Blood, Organ and Other Tissue Safety, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention.

In the next chair, Dr. John Adams, Professor, Global Health Infectious Diseases Research Program, University of South Florida.

Next, Dr. Mark Ballow, Chief, Division of Allergy and Immunology, Department of Pediatrics, State University of New York at Buffalo.

Next is the chairman of our committee, Dr. Frederick Siegal, Medical Director of Comprehensive HIV Center, Saint Vincent's Catholic Medical Centers, New York.

Next is our acting consumer representative, Christopher Templin, Public Policy Advocate for Hemophilia,

Factor Health Services.

Next, Dr. Maureen Finnegan, Associate Professor, Department of Orthopedic Surgery, University of Texas Southwestern Medical Center.

Next, Dr. Blaine Hollinger, Director, Eugene B. Casey Hepatitis Research Center, Baylor College of Medicine.

Next is Dr. Andrea Troxel, Associate Professor of Biostatistics, University of Pennsylvania School of Medicine.

Next, Dr. Thomas Fleming, Professor, Department of Biostatistics, University of Washington.

Next, Dr. Roshni Kulkarni, Professor and Director, Pediatric and Adolescent Hematology/Oncology, Michigan State University.

Next is the non-voting member of this committee, Captain Monica Parise, Division of Parasitic Diseases, National Center for Zoonotic, Vector-borne and Enteric Diseases, Centers for Disease Control and Prevention.

Next, Dr. Katherine McComas, Associate Professor, Department of Communications, Cornell University.

Next is our non-voting industry representative, Dr. Celso Bianco, Executive Vice President, America's Blood Centers.

Committee member Donald Trunkey could not attend

today's meeting.

I would now like to read into the public record the conflict of interest statement for this meeting:

"The Food and Drug Administration is convening the November 16<sup>th</sup>-17<sup>th</sup> meeting of the Blood Products Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all participants of the committee are special government employees (SGEs) or regular federal employees from other agencies and are subject to the federal conflict of interest laws and regulations.

"The following information on the status of this advisory committee's compliance with the federal ethics and conflict of interest laws, including but not limited to 18 US Code section 208 and section 712 of the Federal Food, Drug, and Cosmetic Acts are being provided to participants at this meeting and to the public.

"FDA has determined that all members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 US Code section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of

interest.

"Under section 712 of the Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts of interest when necessary to afford the committee their essential expertise.

"Related to the discussions at this meeting, members and consultants of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 US Code 208, their employers. These interests may include investments, consulting, expert-witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents, royalties, and primary employment.

"For Topic I, the committee will discuss blood donor deferral for malaria risk associated with travel to Mexico. This is a particular matter of general applicability.

"For Topic II, the committee will discuss the design of a new phase 3 study of pathogen inactivation of human platelets using Cerus INTERCEPT Blood System. This is a particular matter involving specific parties.

"For Topic III, the committee will discuss blood



pressure and pulse as blood donor eligibility criteria. This is a particular matter of general applicability.

"For Topic IV, the committee will discuss the public health need and performance characteristics for over-the-counter home-use HIV test kits. This is a particular matter of general applicability.

"In addition, the committee will hear updates and informational presentations on several topics. These updates and presentations are not for discussion by the committee, and therefore committee members were not screened for financial interests relating to these presentations and informational updates.

"Based on the agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 US Code sections 208(b)(3) and 712 of the Food, Drug, and Cosmetic Act.

"Dr. Simone Glynn is employed by the National Heart, Lung and Blood Institute at NIH. She has asked to be recused from Topic II to avoid any appearance of issues due to her work responsibilities as a federal employee at the National Heart, Lung and Blood Institute.

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

employees and they do not vote.

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

"This conflict of interest statement will be available for review at the registration table."

"We would like to remind consultants and participants that if discussions involve any other products or firms not already on the agenda for which the FDA participant has a financial or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

"FDA encourages all other participants to advise the committee of any financial relationships that you may have with a sponsor, its products, and, if known, its direct competitors."

That's the end of the conflict of interest statement.

Before I turn the meeting over to Dr. Siegal, I

would like to ask everybody to take a second to check your cell phones to make sure it's in a vibrate or silent mode.

Dr. Siegal.

DR. SIEGAL: Thank you, Mr. Freas.

Before we start, I would just like to take this opportunity to thank the FDA and Dr. Epstein for inviting me to come back and chair this meeting. I appreciate the opportunity. We have a lot of other "hang-overs" here from previous meetings who are still around. So let's start.

The first thing we are going to do is go to committee updates. We are going to hear from Jerry Holmberg updating the HHS Advisory Committee on Blood Safety and Availability. Dr. Holmberg is the executive secretary of the Advisory Committee on Blood Safety and Availability.

**Agenda Item: Committee Updates**

DR. HOLMBERG: Thank you and good morning.

Since you had your last BPAC meeting, we have not had an additional meeting of the Advisory Committee on Blood Safety and Availability. We will have our meeting at the end of this week and will be talking primarily about the tissue and organ safety.

But there have been quite a few things that have taken place over the last several months that I wanted to provide an update to the Blood Products Advisory Committee.

The first item that I would like to update you on is our new assistant secretary for health, who is Dr. Howard Koh, who is the 14<sup>th</sup> assistant secretary for health. He comes from Harvard. He also was the commissioner of public health in Massachusetts for 6 years.

Our next addition to the assistant secretary for health's office is Dr. Regina Benjamin, who is now the surgeon general. She was just confirmed by Congress last week. Dr. Regina Benjamin will fill the post of surgeon general. This has been a position that has been vacant for the last 2 years.

We also have a new principal deputy assistant secretary. That's Dr. Wanda Jones, who comes from the Office of Women's Health.

We have also established a new office within the Office of Public Health and Science, and that is the Office of Health Care Quality. This office has primarily taken the charge on healthcare-associated infections, and that will be headed by Dr. Don Wright.

I did want to give you a little update on some of the things that we've been doing with biovigilance. When we look at biovigilance for the Department, we really look at it in different aspects, and I'm going to be showing you a Venn diagram of how I perceive the biovigilance and the responsibilities of the Department really breakout out as

far as the way we look at biovigilance.

First of all is the public health policy, which, hopefully, the assistant secretary for health is making, with the assistance of the operating divisions within the Department and also based on scientific evidence and also scientific evidence provided by comparative effectiveness. But also many times some public health policies are viewed upon with at least the public or the societal impact also being considered.

Once those policies are established, then we do have the regulatory oversight, which for you here at the Blood Products Advisory Committee is the FDA, but also CMS and HRSA, HRSA having the oversight on organs.

We then have research, which is the Agency for Health Care Research and Quality, National Institutes of Health, FDA, and CDC. Then we have surveillance, which is primarily CDC, but also a certain amount of surveillance is taking place by FDA and most commonly with the postmarketing surveillance that is required once a product is approved.

So you can see that we do have many agencies that are involved in the biovigilance aspect. Really, where we overlap and the Venn diagram comes together is really where we have to make sure that we have a lot of interoperability and collaboration.

A lot has been said about biovigilance and, within the federal government, the shared responsibilities and capabilities. Let me just say that we cannot do anything without the private sector, and we look very heavily to the private sector to provide a partnership with the biovigilance.

But I do want to present biovigilance in different aspects of capability. First of all is the surveillance part, the sentinel identification, the traceability, the interoperability which I put as the foundation for a biovigilance program, and then also, as the roof of the structure here, is the collaboration that must take place within the federal government and then also through the private sector.

About 3 years ago, the Advisory Committee for Blood Safety and Availability made a recommendation to the assistant secretary and to the secretary that the Public Health Service develop a task force and to look at the critical gaps in patient safety and donor health as it related to biovigilance. Although it took us almost 3 years to complete, this was completed this last year, and we did put -- I should say the entire Department, the public health activities and also some of the other non-PHS organizations such as CMS really collaborated with us on this. We had this document released to the Advisory

Committee on Blood Safety and Availability on the 4<sup>th</sup> of October.

The title of this white paper is "Biovigilance in the United States: Efforts to Bridge a Critical Gap in Patient Safety and Donor Health." This will be a topic of our discussion this week as we convene the Advisory Committee on Blood Safety and Availability.

I know that at the last session that you had in July, which I was unable to attend, some of the biovigilance aspects were talked about. As far as blood, there were eight gaps that were identified with the biovigilance, and that is that we do have a patchwork and sometimes fragmented system of various adverse events, there is likely underreporting of transfusion adverse events, challenges with FDA-required reporting, need for accurate recipient denominator data, no national surveillance for donors' serious adverse events, no accurate donor denomination data, and need for accurate tracking of donor identification, infectious disease test data, and need for timely analysis of reported data.

In tissue there were six different gaps. These gaps will be discussed on Thursday and Friday: limited information on the potential of tissues to transmit infectious diseases; ability to ascertain the reported infections; infectious agents in tissue recipients can be

attributed to the tissue is limited; regulations concerning tissue adverse reaction reporting do not extend to the level of the healthcare facility and healthcare provider.

Current mechanisms for tracking tissue grafts to the level of the recipient are limited; adverse reaction reporting of tissue regulated solely under the section 361 of the Public Health Service Act is limited to infectious diseases; and information about adverse reactions in other recipients of tissues from an implicated donor may not be readily available.

In organs there is definitely a lack of nationwide common organ and tissue donor network systems for real-time reporting, data collection, communication, and analysis of donor-transmitted diseases in organ and transplant recipients. There is also no requirement to retain donor and recipient samples for potential lookback.

In summary, what I would like to do -- this is my last slide -- is just give you an update of some of the activities also that we have been involved with over the last couple of months.

The first topic is really an issue that you will be addressing this afternoon, but on October 26 of this year the assistant secretary for health, Dr. Koh, requested that the Department form a task force to explore the advisory committee's recommendations and possible paths



forward on pathogen reduction technology.

There was also a reorganization of the Department's internal Blood Safety Committee. This is a senior executive council for blood, organ, and tissue safety. As Dr. Williams will be talking in just a few minutes, we have also been active in re-revising and relooking at the guidances that we would have for a pandemic. This guidance is specific for H1N1.

Then also, as we talk about dengue and some of the other issues in the updates, I just want to remind the committee that there will be an arbovirus workshop on December 14 and 15.

That's all I have. If there are any questions?

DR. SIEGAL: Are there any questions for Dr. Holmberg?

(No response)

Okay, thank you.

Next we will hear from Kay Tomashek, M.D., from the Centers for Disease Control on the dengue virus outbreak. Dr. Tomashek.

DR. TOMASHEK: Thank you so much for inviting me to give you an update today. I was also asked to give you a bit about the background of dengue, as I did this summer, risk of transfusion-associated dengue, and then a summary of the current dengue transmission patterns in the United

States and its territories, and then to touch on intervention and prevention efforts that are under way.

So a little bit about dengue. Dengue is a single-stranded RNA virus. It is related to other viruses that you are aware of: West Nile virus, Japanese encephalitis virus (JE), and yellow fever virus.

There are four different serotypes of dengue. We call them dengue virus-1, -2, -3, and -4. They are all capable of causing a full spectrum of disease from undifferentiated fever to severe disease with shock and hemorrhage.

Dengue is a mosquito-borne disease, and *Aedes aegypti* is the most common vector in America, but also *Aedes albopictus*, the Asian tiger mosquito, can also sustain transmission.

The virus replicates within the mosquito for 8 to 12 days. This is what we call the extrinsic incubation period. Then the mosquito remains infected for her life, which is about a month.

Then the mosquito bites human beings and transmits dengue virus with as little as  $10^2$  virus particles per secretion.

The virus then replicates within us humans for about 3 to 14 days, and that is the intrinsic incubation period, before symptom onset. Viremia, though, begins

slightly before onset of symptoms. This has implications, of course, for blood safety. The viremia is thought to last for about 5 to 6 days.

The majority of infected people remain asymptomatic. They have no symptoms, no fever, they do not feel ill, and that also has implications for your panel. The viremia in asymptomatic blood donors we know can be as high as those in symptomatic blood donors, which is usually in the range of  $10^5$  to  $10^9$  viral copies per mL. So viremias in dengue are higher than that of West Nile.

But there are other routes of transmission that have been documented. There has been evidence of transmission through blood products. Recently there was a paper in *The New England Journal of Medicine* detailing a case in Singapore where a symptomatic donor was asymptomatic at the time of collection but became symptomatic one day after donation. The two recipients got dengue-like illness, PCR-confirmed dengue-2, and a third recipient, although that person seroconverted, he had IgM antibodies, he remained asymptomatic.

Then, of course, there were also documented in Hong Kong, in ProMED, a symptomatic donor, again one day after donation, and the recipient of a unit of RBCs developed dengue-like symptoms.

There have also been other routes of transmission

documented. There has been transmission by receipt of donor organs or tissue. There was one case following bone marrow transplant in Puerto Rico and another after renal transplant, and there has also been occupational exposure in healthcare settings. There have been several reports of percutaneous transmission after needle-stick injuries, as well as two published reports of mucocutaneous transmission after laboratory workers were actually splashed in the face with contaminated blood.

In terms of dengue, what does it look like? I think this is important for general awareness. As I said before, the majority of infections are asymptomatic, no symptoms. But in terms of the clinical spectrum, the majority of the cases are undifferentiated fever, meaning the person could have a high fever and then not quite meet the criteria for dengue fever.

Dengue fever is defined as acute fever plus two or more of the following symptoms: headache, retro-orbital pain, muscle ache, joint or bone pain, rash, bleeding, and a low white cell count. So as you look at that, you can see how dengue could be -- the clinical diagnosis of dengue is very difficult. This could be a case of influenza H1N1 or leptospirosis or many other nonspecific flu-like illnesses.

Then the more severe forms of the disease, and

this is, of course, what everybody fears and what everybody reads about, is dengue hemorrhagic fever. There are four criteria for DHF: It is fever, 2-7 days of duration; hemorrhagic manifestations; thrombocytopenia, which means just low platelet count; and then plasma leakage, which can result in pleural effusions and ascites.

In the past we have graded dengue hemorrhagic fever into four grades. The two more severe grades are dengue shock syndrome. It is defined as meeting the criteria for dengue hemorrhagic fever but also, in addition, having circulatory failure evidenced by either rapid, weak pulse and narrow pulse pressure or hypotension, cold, clammy skin, and restlessness.

In terms of the diagnosis and treatment for dengue, the standard of care is supportive management. There is no antiviral for dengue. So there is no curative treatment and there is no vaccine currently available.

It can be fatal, as you know, upwards of 20 percent case fatality. But with timely identification that this is actually a dengue virus infection, close monitoring and judicious use of IV fluids, the case fatality rate in most countries is less than 1 percent.

But the clinical diagnosis, as I said before, is difficult because of the nonspecific symptoms in many of the cases. Then laboratory diagnosis also is difficult

because it often relies on paired samples for a seroconversion of IgM antibodies or early samples for viral RNA.

So what is the risk of transfusion-associated dengue? We know in Puerto Rico that 40 percent of blood donations are made to the American Red Cross sites. The remaining 60 percent are collected by other centers and hospitals. The American Red Cross blood products from Puerto Rico are not only used for patients in Puerto Rico but also in the continental United States, the U.S. Virgin Islands, the British Virgin Islands, Antigua and Barbuda. About 12,000 to 20,000 American Red Cross donations are sent to the continental United States each year.

In the 2005 dengue season, there was a collaborative research project conducted by American Red Cross' Dr. Susan Stramer and the CDC Dengue Branch. All donations from the time period that is not shaded in -- so September 20 through December 4 -- were tested. What was found was that 12 of 16,521 blood donations from that time period were TMA repeat-reactive, for a prevalence of one positive donation per 1,376 blood donations. Four were PCR-positive for dengue virus, and dengue virus was cultured from three of these. Then there was only one IgM positive.

Of the four positive PCRs, the viral load was

between  $2 \cdot 10^3$  to  $8 \cdot 10^7$  viral copies per mL. But there were no donor follow-up studies or recipient tracings in 2005 to see if anyone became ill after receiving these blood donations.

Also, in addition, you could see that we began collecting the blood after the height of the outbreak, so it is believed that this may be an underestimate of the prevalence from that year. So in 2007 we notified Susan Stramer at the American Red Cross that this looked like it was going to be a large year, and we called the outbreak actually the last week of May, and samples were then collected and tested.

The units that were transfused in the United States and those that were used in Puerto Rico were tested. Twenty-five positive donations out of 15,325 were found. These were the TMA repeat-reactive. So that is one positive donation in 614 blood donations, so considerably lower than that which was found for West Nile before we initiated the West Nile testing.

There were 12 PCR positives, and of those 11 were infected, the mosquito cell lines. Six were IgM-positive. As you can see from the little stars, that's when the positive donations were identified. So they are clustering around the height of the outbreak in that year.

Just so you know the magnitude of this, in that

year there were 10,508 cases reported to us at the Dengue Branch. Of those, about 30 percent were confirmed to be positive, or about 3,300 samples.

Also in the 2007 season, of those 11 PCR-positive samples, the viral load for those individuals was  $10^5$  to  $10^9$  viral copies per mL. Eleven, as I said before, were infected, the mosquito cell cultures. There were six IgM positive, but, interestingly enough, two had quantifiable virus at  $10^6$  and  $10^8$  viral copies per mL.

Of the 12 TMA-positive donations that were distributed in the United States and 13 distributed in Puerto Rico, the American Red Cross identified one recipient who received one unit of packed RBCs from a dengue virus serotype-2-positive donor. The individual then, 4 days after the transfusion, developed dengue fever and went on to have dengue hemorrhagic fever. The sequence between the donor and the recipient was a 100 percent match. Thus far, we don't have any other cases that they've identified. They have two recipient samples, and antibody results are pending on those.

So what is happening currently in the United States and its territory? This year has been a very challenging year, to say the least. At the end of May, beginning of June, we called a regional outbreak, which means it wasn't throughout the island but there were four



sites within Puerto Rico that had transmission above what is typically expected. Thus far, as of October 1, we have 4,500 suspected cases and about 1,450 lab-positive dengue cases and 52 DHF cases reported.

There are ongoing regional outbreaks. The last 4 weeks has definitely -- there has been an increase in reporting, but many of our samples are pending so I did not present those results to you. The outbreak this year is all four serotypes, but in the last 4 weeks it has been serotypes 1, 2, and 4.

We expect that 2009 will have similar numbers to 2005, so we will probably be at a prevalence for positive blood donations at about 1:1300.

Other things that are happening this year that you may be aware of from reading the newspapers: There has been an outbreak of locally acquired dengue in Florida, in Key West. As you can see, Key West is right there in the top map. Sorry I don't have a pointer. There was an outbreak identified from an index traveler from New York who visited Key West in the first week of August, returned home, and after three visits to her healthcare providers was diagnosed with dengue in August.

So we were invited to come in and do a serosurvey in the third week of September. We found that eight of 240 participants had evidence of acute, meaning they had a PCR-

positive serum drawn, or recent, which means they had IgM antibody, which you may remember only remains in your body for 3 months. So we know it was recent infection. They had no travel history in 3 months, so we know it was acquired in Key West. Seven of eight reported being ill with dengue-like symptoms.

Ninety-one of 240 had past flavivirus infection. What does that mean? Well, they had an IgG that was positive. Of course, there can be cross-reactivity with West Nile, and we are currently in the process of doing PR&Ts to see how many of those were dengue versus West Nile. One hundred forty-one of the 240 were negative for IgG, meaning that they had not had a past flavivirus infection.

In addition to those people that were identified in the serosurvey, there has been an additional 12 lab-positive locally acquired cases since July. So the outbreak has been going on since July, and they are confirmed positive either by PCR or IgM in our laboratory in San Juan.

Nine of those cases live in Old Town, so you can see they are all clustered in the old village, which is a population of about 6,000. What is interesting is the more recent cases are up here in Stock Island, where the last three cases were identified as late as the third week of

October, and our laboratory has more samples pending. So stay tuned, it is continuing to evolve.

Intervention and prevention efforts. Well, one thing that our laboratory is involved in: As soon as the outbreak was called, we called up the local blood bank, the Key West blood bank, the community blood center of South Florida and Susan Stramer, and started collecting blood donations. My laboratory is currently testing those blood donations that were collected in August and September, so during the outbreak, for dengue virus. I don't have results to present to you today, so I don't know how prevalent dengue virus is in the blood supply in Florida.

In terms of some other points, these remaining points are actually interventions that Dr. Susan Stramer of the American Red Cross has been involved in. Because there is no TMA available for use, the American Red Cross studied another test. It's a nonstructural protein 1 antigen test by BioRad. That was done this summer, and they found one positive donation per every 1,467 blood donations from the 2007 data from my laboratory, which of course is about threefold less sensitive than what I just presented to you from the TMA results, but it was found that nonstructural protein 1 does detect high-titered viremia.

Then the American Red Cross plans to use this test under a 2009-2010 IND in Puerto Rico. However, non-

American Red Cross sites in Puerto Rico refuse to pay for the screen unless it is required. This study also may involve Monroe County in Florida if we find positive blood donations from that area.

Two other prevention efforts that American Red Cross instituted this year are, in order to protect U.S. citizens residing in the continental U.S., American Red Cross discontinued imports from Puerto Rico into the continental U.S. in May of 2009, so at the beginning of our outbreak. Also, for the U.S. citizens who reside in Puerto Rico, like myself, American Red Cross implemented an enhanced post-donation callback information sheet in July, and they also began asking pre-donation symptom questions about recent dengue infections.

In summary, as you can see just from these limited slides, there are several thousand cases reported annually in Puerto Rico. We have a high season, usually from June through December, sometimes through February, as may be the case for this year.

The risk of local transmission in the United States probably will increase with increases in the vector and international travel, as well as our new immigrant population with ties to endemic countries of origin.

Dengue, as you may know from the news, became a nationally reportable disease in June of 2009. It is not

reported, however, in seven states which have the vector, and there is limited awareness of dengue. For example, in Key West, many of the first cases were diagnosed as flu-like syndrome or viral syndrome or something like that. So there is not a lot of awareness that dengue is a risk in many of our southeastern states where the vector is present and there is an international population that could potentially introduce the virus into a highly susceptible population.

Of course, as you know, there are no sustainable effective vector-control interventions at the moment. That's why we have this problem. And there is no vaccine that is readily available for use.

Dengue infection is associated with high viremias, as I showed you. The high viremia is present before symptom onset as much as 2 days but definitely the day before. The viremia in asymptomatic individuals can be as high as those in the symptomatic individuals.

There has been donor viremia demonstrated in Puerto Rico, like I showed today, but also in a nice paper by Linnen et al in *Transfusion* in 2008 showing viremia in Brazil and also in Honduras. There has been transfusion-associated transmission documented, as I pointed out earlier, although this is very difficult to assess, especially in dengue-endemic countries. So we don't know

exactly how commonly this occurs.

So why is there a risk? There is a risk because donors are screened for fever, but most infections are asymptomatic and viremic, and infected individuals typically are viremic prior to symptom onset.

The second point is that donated blood is currently not screened for dengue, even though we have evidence that the prevalence of positive blood donations in populations such as Puerto Rico are at the levels that they were when West Nile screening was initiated.

There is no rapid sensitive screening test available. That is one of the issues. An NS1 antigen assay may be a good alternative. We will have to wait and see.

The U.S. blood supply is at risk? Yes, I think it probably is at risk. As we documented, there is potential for importation of dengue RNA-positive blood components from hyperendemic areas such as Puerto Rico, and that is what I showed you today, and also from infected U.S. travelers with asymptomatic viremia or, as in the case of Key West, locally infected individuals who may unknowingly donate blood when they are infected with dengue virus.

So we may need to screen the blood supply not only in Puerto Rico but in cities with a large population

of international travelers, either locals that go and travel or international travelers that come and visit us and bring the virus to us unknowingly, especially from communities that have the vector or communities that have sporadic outbreaks such as the South Texas outbreak -- they have had about seven or eight outbreaks since 1980 -- Hawaii and now Florida.

Thank you very much for your time.

DR. SIEGAL: Thank you, Dr. Tomashek. Are there any questions for Dr. Tomashek from the committee?

DR. NELSON: How extensive is the dengue epidemic in the other Caribbean islands? Can we assume that it is present everywhere?

DR. TOMASHEK: That's a very good question. We know that it is on many of the Caribbean islands. We don't have good surveillance data from places like Haiti, for example, although we get reports from travelers who go to Haiti to do volunteer work that come back with dengue, and that is as much as we know from that island.

This year there are large outbreaks in the Dominican Republic. We are testing a lot of their samples for them to confirm the serotype. There are many very large dengue-1 outbreaks throughout Central and South America. In fact Guatemala just announced an outbreak last week.

So it is pretty much throughout the Caribbean, Central and South America. Some of the Caribbean islands do not have surveillance, and so we hear about cases through U.S. travelers mostly.

DR. BRANCH: How secure are we that there is no transmission of dengue, say, one month after an asymptomatic infection? So is there no chance of carriage for more than 2 weeks, more than a month? How long would you have carriage of an asymptomatic dengue infection?

DR. TOMASHEK: In terms of the viremia, the viremia lasts about 5 days, 7 days max, within the individual. What we don't know because we don't do surveillance for this is when a person is febrile or a symptomatic person is not febrile, so they have this viremia, when mosquitoes bite you, if it is an *Aedes aegypti* mosquito or *albopictus* if you're in a state with *albopictus*, that mosquito is able to then take the virus into their body, and the virus is replicated within the body of the mosquito. She, the mosquito, is able to transmit the virus for her lifetime then.

So what is happening in Key West and what happens in Puerto Rico, what happens in many dengue outbreaks, is we have interclustering of cases in households. So you will have little Susie get sick, and that same mosquito that got her sick or the same little group of mosquitoes



will then get someone sick a week later, 2 weeks later, 4 weeks later. The whole lifetime of that mosquito, she can transmit the illness. Mosquitoes, thankfully, usually last only a month, survive a month, but in research settings they can live up to 3 months. So you can have these outbreaks that kind of smolder.

That is why, when we have been working with the states, and the states have a number of travel-associated cases a year that are not reported because it has only recently become a reportable disease, but they are very watchful and they visit the home of the index case to see if there is an interhousehold spread.

I think that answers your question. The viremia is a week and then what happens after that is that the mosquito, if there are mosquitoes in your home and you're bitten during this time, then it's capable of transmitting the disease to other people within that household or that community.

One thing we do know about the mosquito is that it is a mosquito that likes to live in our house. It requires our blood to produce young. So it is usually interhousehold spread or intercommunity spread.

DR. SIEGAL: Anyone else? Thank you very much, Dr. Tomashek.

Now we are going to hear from Dr. Alan Williams

from FDA updating us on the influenza H1N1 epidemic and the impact on the blood supply.

DR. WILLIAMS: Good morning.

2009 H1N1 influence is widespread, of course, throughout the world and the United States. It's a predominant influenza-A strain circulating in the United States.

A look at the CDC influenza Web site reports that there have been over 22,000 hospitalizations and, tragically, 877 deaths, 179 deaths in pediatric cases.

The purpose of this report is to summarize some of the activities that have taken place in planning for any pandemic, but specifically H1N1. What I would like to do is first visit a guidance document, an interim guidance, issued near the end of last week by the Centers for Disease Control summarizing some infections-control methods.

Following that I will review some of the preparation activities that have taken place really over the last 4 years involving cooperation both within government and the blood community, and then end by pointing out some key points from the FDA draft guidance, which also was issued near the end of last week.

So from the CDC guidance, this will be of a lot of help to blood centers but also potentially a lot of help to those of us who are going to huddle for 4 days in

advisory committee meetings this week.

The symptoms of seasonal and 2009 H1N1 flu virus can include fever, cough, sore throat, running or stuffy nose, body aches, headache, chills, and fatigue, and there might also be vomiting and diarrhea associated with infection. The symptoms are highly variable from mild to severe.

2009 H1N1 is spread the same way as seasonal flu, from person to person through coughing or sneezing by people with influenza; i.e., droplet spread. Sometimes folks can become infected by touching something such as a surface or an object with flu virus contamination on it and then touching a mucosal membrane.

Notably, measures that will reduce spread of 2009 H1N1 flu will also help prevent the spread of seasonal flu viruses in any season. These viruses may also circulate along with 2009 H1N1 during this season, although H1N1 is clearly the predominant influenza-A strain this season.

Specific to blood establishments, CDC recommends that phlebotomy staff should wash their hands with soap and water between contacts between different donors, and when gloves are used they should change their gloves and cleanse their hands between contacts with different blood donors.

All other staff and volunteers in a blood setting should also wash their hands frequently and especially when

visibly soiled. Alcohol-based hand sanitizers, those ubiquitous little pump jars that you see around, may be used as an interim measure when soap and water are not available and hands are not visibly soiled. Environmental surfaces should be cleaned and disinfected in accordance with standard facility protocols after each donor has vacated the station and before setting up for arrival of a new donor at that station.

I should mention that this guidance has numerous hyperlinks throughout it which reference other CDC materials and recommendations and is really a rich source of information about H1N1 and public health preventive measures.

As far as staff illness in the blood establishments, staff and volunteers should self-assess for flu-like symptoms and remain at home until at least 24 hours after they are free of fever. That is lack of fever without the use of a fever-reducing medication.

Staff who develop symptoms of influenza-like illness while at work should cease collection-facility activities, be separated from other staff, notify their supervisor, and most likely go home promptly. They can also be given a surgical mask to wear before they go home when that is possible and if they cannot be placed in an area away from other staff members.

All staff should adhere to routine infection-control procedures, particularly those related to cough etiquette. When you cough, cover it, preferably turn away as well, and dispose of the material that you coughed into.

Additionally, anticipating that 2009 H1N1 could become even more widespread or more severe, CDC made recommendations if this should happen, and I think it's important to point out that if social-distancing recommendations are put out from CDC or other government entities, it is most likely going to be necessary to continue blood drives, because blood is certainly necessary and a certain amount of getting folks together for a blood drive is critical to maintain that capability.

So, in that situation, CDC recommends that there could be adjustment of the physical configuration of collection sites as well as donor scheduling to reduce interpersonal exposures. There could be active evaluation of staff, volunteers, and prospective donors for influenza-like symptoms at the site entry for the blood establishment so that ill individuals would not even come into the facility. As with all other measures, advance planning and pilot-testing of these measures will help with the implementation if they should be necessary.

Now I am going to move into FDA-specific activities. When 2009 H1N1 first appeared last spring, FDA

put up a Web posting with some statements that were based on available knowledge at that time and for the most part have held true. Blood establishments should pay particular attention to existing SOPs for donor health. Those SOPs in all blood centers include identification and deferral of donors who are not healthy and well on the day of donation and those who have any respiratory illness.

In the event that there is post-donation information, the medical director should make a decision regarding product withdrawal, and industry practice is that typically when PDI is reported with fever 48 hours post-collection, units are commonly withdrawn, although that is not an FDA requirement.

Plasma products, because of the inactivation and removal steps inherent in the fractionation process, are generally viewed to be safe based on studies with model viruses similar to influenza.

Overall, from the first recognition of the outbreak to the present, there has been somewhat limited information regarding viremia associated with H1N1 infection, especially relevant to a blood-donation setting, viremia that would be associated with an asymptomatic period.

There are also no reported cases of transfusion-transmitted seasonal influenza or H1N1 influenza, and there

has been no isolation of H1N1 from blood or serum of asymptomatic infected individuals.

Again, because H1N1 is a large lipid-envelope virus, and viruses with similar structures and characteristics to H1N1 are effectively inactivated or removed by plasma derivative manufacturing, derivative products are viewed as being safe from this virus.

There is really no precedent for influenza-related donor deferrals other than routine deferral for respiratory illness or not feeling healthy and well today.

Just to reemphasize, the current donor health history does include questions that defer donors with symptomatic influenza illness. One of the key questions is the "Are you feeling healthy and well today?" and, as far as respiratory illness, there is a standardized uniform donor history questionnaire used throughout much of the country. This is a series of questions which includes any problems with your lungs, which would reflect respiratory illness.

There have been a lot of preparations for what was at first felt to be a threat of an H5N1 pandemic and now-recognized H1N1 pandemic flu. There have been 4 years of planning discussions between the AABB Influenza Task Force and numerous other stakeholders with FDA, with CDC, with HHS and other HHS agencies.

There is a standing emergency blood-shortage response protocol in place. This involves active real-time assessment of any blood availability or safety threat in coordination with the AABB disaster task force. It is also sanctioned under ESF #8 of the National Response Plan.

Under this disaster task force, within an hour, DHHS and all of the Level 1 agency liaisons can be on a phone call and help to assess and mitigate any blood-shortage situation that becomes known.

Within FDA, beginning in the spring, FDA assembled a pandemic incident management team. It actually involved ten teams with all aspects related to pandemic flu that had regulatory involvement. There were twice-daily telephone calls to review the situation, including status of the blood supply, and very actively Dr. Sharfstein, who was acting commissioner at that time, participated in the spring and continues to as the calls continue. So very high-level involvement throughout the relevant HHS agencies.

I wanted to say a word about messaging because this is important with any stressful situation involving the blood supply. We learned a lot of messaging lessons from 9/11 and some of the events subsequently.

Generally, it is felt in the blood community and throughout that blood on hospital shelves will generally



meet the immediate need in most disasters. So a lot of media attention to donation of blood can result in too many collections at one time when they may not be needed, and such an event would both waste resources and it might actually jeopardize donor eligibility 8 weeks down the line when one again might still need blood supply but some of your most reliable donors might not yet be eligible.

So donors should contact the blood center for appointments for donation rather than just appearing. Donation appeals, particularly those related to any sort of crisis, really need to be carefully coordinated, and the AABB pandemic flu task force and disaster task force has a big role in this.

Ad hoc reports of shortages viewed as being associated with H1N1 should be very carefully considered, because reports of what is simply a local shortage that could be covered from elsewhere can create unnecessary concern and confusion and potential disruption.

Within the blood-collection community, blood establishments during this H1N1 pandemic are closely monitoring transfusion service supplies and they adjust their collections accordingly. Should the H1N1 pandemic become particularly severe, it is expected that as much as a 30 percent reduction in blood demand will be realized because of delay of elective surgeries and other protocols.

The blood community has options to preserve the available supply: proactive planning, increased recruitment, local appeal, national appeal, and provisions for emergency actions or changes in procedures under existing regulations, which include the emergency use regulations and the provisions for variances from existing regulations.

Within the U.S. government, DHHS closely monitors blood-establishment and transfusion-service blood supplies. This is done primarily under the umbrella of the Blood Availability and Safety Information System, or BASIS, which is run out of the Office of Public Health Science under Dr. Holmberg. Major blood organizations and collection facilities provide summary reports to BASIS daily, and BASIS also collects data from 90 transfusion services. So it provides both a blood center and a hospital basis for available inventory. The reports are both quantitative and qualitative, so that if a blood shortage is reported, there is some indication of what the impact is, whether they had to go to an alternate supplier or delay a surgical procedure or some other events to get a measure of the impact of any shortage.

This data reporting goes to FDA when on alert status as we are now. There are some advantages to having both blood-center and hospital-shortage reports because

they have slightly different implications in terms of long-term versus acute shortage concerns.

As far as blood supply observations, the U.S. blood system does move quickly to fill local supply gaps. These are common in the summer, during holidays, in times of excess demand. Throughout the spring H1N1 outbreak, blood remained abundant. Red cells never wavered from a 10-day red cell supply nationwide.

Currently BASIS reports, as mentioned, are shared daily with FDA. As of last week, the current blood supply is adequate to meet needs with over a 9-day supply of O-positive blood, a 3-day supply of O-negative blood available at blood centers across the nation. No procedures have been delayed or canceled specifically due to shortage.

Inventory reporting indicates that there are approximately 6 days of supplies within the hospital sector. Hospitals report relatively low instances of red cell and platelet shortages, and platelet inventories generally appear adequate.

There have been reports of student blood drives that have been impacted by H1N1 infections, and this certainly costs efficiency and some strain on local collections, but given that the local supply at least at this time remains strong, but it is being monitored very

carefully.

Within the government, there are interventions available to help preserve the blood supply. First and foremost is strong encouragement to the blood community to implement proactive planning.

In terms of blood donor appeals, there can also be HHS-sponsored national donation appeals. This has happened most recently, I think, at a very acute holiday shortage. HHS sponsored an appeal, and they are really quite effective.

There can be proactive consideration of mitigation for all possible levels of blood supply disruption. In other words, there is active planning in place that, if the situation should become severe from a blood donor availability standpoint, that there are plans in place to help mitigate this.

Then, finally, guidance regarding appropriate public health measures to maximize the safety of donors as well as blood and emergency response options under current regulations -- this is the guidance that was just issued the end of last week. I am going to close by summarizing that.

The link for the guidance is shown at the bottom of the slide here. The title is "Recommendations for the Assessment of Blood Donor Suitability, Blood Product

Safety, and Preservation of the Blood Supply in Response to Pandemic H1N1 2009 Virus." This is currently draft guidance for comment, and we expect that once comments are received, it will quickly issue as final.

The recommendations are for whole blood and blood components for transfusion, the first being FDA recommends training of adequate backup personnel, and suggesting more than one backup person, for all critical functions in a blood establishing using their establishment's existing procedures for training and training documentation.

The second point is a clarification of what is in the regulations stating that determination of donor suitability must be made on the day of collection. In some cases -- and one could imagine this, particularly in a time of blood center staff shortage -- that if a questionnaire is incomplete, this provides the ability to obtain complete information within 24 hours after the collection.

Briefly, available data do not support donor deferral for exposure to or contact with a person who has confirmed or probable H1N1 infection; however, donors with a confirmed or probable case of infection should be deferred similar to the CDC recommendation for at least 24 hours after they are free of fever without medication control.

Available data do not support deferral for donors

following vaccination or prophylactic use of antivirals. Post-donation information about a donor received within 48 hours after donation should be evaluated by the blood establishment's medical director per their existing procedures.

A change in the license procedures pertaining to use of a different outside test lab and implementation of self-administered donor history questionnaires. These are changed to CBE or changes being effected, license supplements instead of prior-approval supplements, which will help a blood center to immediately implement a change that they need to in order to help maintain their operations.

Biologic product deviation reports are not necessary for PDIs related to H1N1 virus events.

Recognizing that convalescent plasma and specific fractionated immunoglobulins may have a therapeutic role in the pandemic response, FDA encourages the development and evaluation of these therapies through clinical trials and suggests speaking with FDA before embarking on this.

Thank you very much. There are some references attached at the end of the slides and there are also references throughout most of the guidance documents. Thank you.

DR. SIEGAL: Thank you, Dr. Williams. Are there

any questions for Dr. Williams?

(No response)

If not, let's proceed to Topic I, since we are running a little bit behind. We will first hear an introduction by Dr. Sanjai Kumar of FDA on blood donor deferral for malaria risk associated with travel to Mexico. Dr. Kumar.

**Agenda Item: Topic I: Blood Donor Deferral for Malaria Risk Associated with Travel to Mexico**

DR. KUMAR: Good morning. I am going to introduce the malaria topic, blood donor deferral for malaria risk associated with travel to Mexico.

Here is the issue before the committee: FDA is seeking advice from the Blood Products Advisory Committee on whether it is acceptable to allow blood collections without any deferral from individuals who have traveled to certain Mexican states that have a low malaria transmission rate.

Some general principles first:

What are the major determinants of transfusion-transmitted malaria?

Malaria risk at population level, both internal and external sources. From internal what I mean is there is native transmission or natural transmission in the country.

Identification of high malaria-risk donor populations, whether it is locally acquired malaria, whether it is travelers who work where there are infections outside the country or immigrants, et cetera.

Identification of sources where risk is being acquired.

Any strategies to mitigate malaria risk.

So let's see how these principles apply to transfusion-transmitted malaria (TTM) in the United States.

Annual malaria cases reported in the USA. This sort of serves as an indicator of malaria transmission in the absence of transmission malaria cases in this country, malaria infection rates in this country. Also, it is very obvious that almost all malaria infections reported in the United States were acquired outside the country, although I cannot say that it never happens. Sporadic local transmissions have been reported but not to the extent that it becomes a problem for transfusion-transmitted malaria.

What are the geographical regions where U.S. malaria infections were acquired, if all cases have been acquired outside the country? The geographical malaria transmission rates, number of visitors to and from those areas, and number of imported malaria cases from that area, these are all important, and I will show you some data related to that.



Donor populations that present the highest risk of transmitting malaria by blood transfusions, and I think we have recognized those donor populations by now.

There is no FDA-licensed laboratory test to screen blood donors for malaria risk, and I think that is a major source of our concerns, why we are here today.

And what are the strategies that we are using to mitigate the risk of transfusion-transmitted malaria while causing minimum donor loss? That is the key here also. Also, the strategies have to depend on the absence of donor screening.

So there are four *Plasmodium* species. The biology and pathogenesis of malaria parasites depend on *Plasmodium* species and the intensity of transmission and where the infection is acquired. These are all very important.

Length of blood-stage cycle varies for each species; that is, the time after exposure, to inoculation of the liver, to the emergence of these liver forms that cause blood-stage infection. Some species can establish lifelong infections, and individuals from endemic areas may have chronic low-grade parasitemia. As you will see later, all of these aspects are extremely important in transfusion-transmitted malaria.

I am going to elaborate a bit more on this. The

prepatent period is defined as the time between the sporozoite infection to first appearance of blood-form parasites, generally, depending on the species, 9 to 30 days, but some species of *Plasmodium vivax* and *ovale* malarias have dormant liver-form parasites that may cause relapse infection that may last for months to a year and possibly more, so these cases are very difficult to identify in infected donors. *Plasmodium malariae* blood-form parasites can persist as chronic infections for up to 40 years and possibly more. It has been demonstrated very clearly up to 40 years in a case in the United States.

Individuals born in endemic countries or expatriates with prolonged residence in such areas can become asymptomatic carriers of malaria. As you will see later, these are the most important group of infected donors. Parasite burdens in asymptomatic carriers are not known, and the infectious dose of intraerythrocytic parasites is extremely low. It has been demonstrated in the 1940s that as few as 10 infected red cells can cause infection with *vivax* malaria. So not knowing what is the parasite burden in asymptomatic carriers and the infective dose being so low makes direct parasite detection for donor risk by screening test extremely difficult. Just imagine 10 parasites in a unit of blood, and the sensitivity of detecting even one parasite polymer doesn't make it good

enough for direct detection.

So what is the global malaria problem? Ah, in more current years, where malaria in the past used to be prevalent in many other parts of the world, in more current years it is restricted to mostly tropical and subtropical countries here in the dark brown, chocolate brown here. Still, this constitutes more than 100 countries, mostly the poorer and underdeveloped countries. Approximately 3.2 billion individuals are at risk of contracting malaria, around 500 million clinical cases each year and more than 1 million or so deaths and mostly in young children in Sub-Saharan Africa.

Now looking at the malaria in this country, natural mosquito-borne malaria infections are rare. Approximately 1,500 clinical cases each year are acquired outside the United States, and malaria can be transmitted by transfusion of blood from infected donors. That is why we are here today. These malaria clinical cases, CDC keeps a very good tab of malaria in this country. Those are reported primarily through the national malaria reporting system. You will hear a lot of detail about this from Dr. Paul Arguin from CDC later.

So these are malaria cases in this country. Again, this is an indicator of the malaria infection rate in this country, although it does not tell us about the

asymptomatic carriers, around 1,500 cases each year. All four species are represented here. The percentages here more or less are in accordance with distribution globally of these species, except these unknown here, non-determinant, 30 percent of cases, so that does skew the data a little.

How malaria infections reach the United States if it is not locally transmitted? Approximately 34 million U.S. residents arrive in countries where malaria is transmitted. That is a lot of countries, more than 100 countries. What is relevant here is just our southern neighbor here, Mexico. Approximately 18 million U.S. residents arrive in Mexico. So there is a lot of travel between the United States and Mexico that goes on.

Many malaria cases in this country are introduced by immigrants from endemic countries, and rates of malaria transmission greatly vary among different countries. So, in other words, the risk of acquiring malaria exposure depends directly on the area of travel or residence.

So all countries, there are more than 100 countries where it is transmitted, but all countries are not equal when it comes to risk of malaria there. You can look at the risk model here, and the highest risk is in Sub-Saharan Africa.

This is the imported malaria cases based on

looking at where the risk is mostly, where the infections are acquired. Out of 1,500, close to 1,000 or so cases, the ADR for acquisition was known. This is again CDC data that are published annually. This is data from 2007.

So two things are very obvious here. Sub-Saharan Africa, there are 64 percent of infections that are acquired in Sub-Saharan Africa. On the other extreme is our nearby Mexico, less than 1 percent of infections are acquired there.

So if we look again, more than half of the travel is to Mexico, but on the other hand, less than 1 percent as opposed to Africa, where 64 percent of infections are here, and less than 1 percent infection acquired in Mexico, which accounts for more than half of the travel of Americans each year.

So how do we mitigate the risk of transfusion-transmitted malaria in this country in the absence of donor screening? Mostly it is done by, not mostly, exclusively done by donor questionnaire. This is based on history of malaria, if someone has clinical malaria, or based on a history of travel or residence in malaria-endemic areas.

These are current FDA recommendations. If someone had clinical malaria, he would defer for 3 years. Prior residents of endemic countries are deferred for 3 years, but naïve residents from this country or other

countries who travel to malaria-endemic areas who had no prior exposure to malaria are deferred to one year. Here you see a list of malaria-endemic countries maintained by CDC, and here is the Web link for that.

So now directly looking at the transfusion-transmitted malaria cases in this country, this is a long view going back to 1963. Again, this is a doctor from CDC, Dr. Monica Parise, who is here among us, as she was the lead author on this paper. Total 97 cases now so far from 1963, all four species are represented here. But what stands out is the *Plasmodium* malaria is disproportionately represented here.

If you look at the global distribution of *Plasmodium malariae* in clinical cases it is approximately 5 percent or so, but here it is 26 percent of total infections, transfusion infections, were caused by *malariae* malaria. So this has become a prevalency-unique problem.

So what is the changing pattern there? The changing pattern now is that we are getting less transfusion-transmitted cases in more recent years. This is again 1963 to 1999, approximately 2.5 cases each year. If you include more recent data after this year here, it becomes two cases per year. If you look at it during the last 10 years only, we got four cases in 10 years, although Dr. Paul Arguin just tells us that there has been one more

case this month. So the transfusion-transmitted malaria has come down, there is no doubt about that, but these infections do continue to occur also.

Again, as I said in the beginning, who are those donor populations which cause transfusion-transmitted malaria? So we are looking at this. This is again a modification of a slide from Dr. Monica Parise's *New England Journal of Medicine* paper and some recent data introduced here.

If you look at the decade-wise breakdown, these are groups of donors that have caused transfusion-transmitted malaria, but the only thing I would like to emphasize here is during the last 10 years all four cases were caused by donors who were immigrants from Sub-Saharan Africa. So the donor population that causes transfusion-transmitted malaria has shifted from military personnel travelers to exclusively former residents of endemic areas.

What is the effect on blood availability? That is a very important aspect here. Approximately 150,000 blood donors are lost each year due to presumed malaria risk. I think there is enough scientific data that we can say these numbers with certainty: Approximately 1 percent of all donors are lost due to malaria-risk deferrals. Of these, disproportionately high numbers, around 40 percent, or 60,000, are lost because they have traveled to endemic

areas in Mexico.

Perhaps there are large numbers, but unknown numbers, of self-deferrals and also non-returning donors of those donors who were deferred because of malaria risk. So the total numbers may be significantly higher than these 150,000 donors, but in the absence of scientific surveys, we are not certain about those numbers at this time.

So FDA has been very active in this malaria-risk, donor-risk deferral issue. In the last 10 years there have been three BPACs and one public workshop sponsored by FDA, and I will go into great detail in each of these.

The 1999 BPAC which reviewed all of the modern technologies at once, technologies to detect malaria infections, so potentially there could be a donor-risk screening test for malaria. In particular the committee studied the feasibility of regulatory requirements for DNA tests, rapid antigen detection tests, ELISA and IFA to screen blood donors. But in the end, since this was an informal BPAC, no formal recommendations were made.

In 2001 FDA came to BPAC again, and this time the question was in regard to donor deferral for malaria risk for donors of plasma, of fresh-frozen plasma products only, because the current CFR requirement is that donors of fresh frozen and cryoprecipitate plasma products should be screened for malaria risk, and we continue to get various



requests from blood establishments, mostly post-donor information whether there should be donor risk screening for malaria risk, but the committee recommended that, in the absence of any new scientific evidence on the survival of malaria parasites in frozen plasma products, the current deferral policy should remain in place.

So then coming to this 2006 malaria workshop, many of you in this room today did attend that workshop, so that things of major consideration were the geographical area of travel or prior residence is the major determinant of malaria risk in prospective blood donors and that is the data I have been showing you so far also, but also a special emphasis was given to deferrals due to Mexico just because there is so much travel going on there, low malaria risk in Mexico, and large numbers of donors are lost due to travels to Mexico alone.

The question of laboratory testing was discussed at length for malaria parasites that we agree that would be the best strategy to screen blood donors with malaria risk and probably minimize donor loss as well. But then again, as I said, due to the low infectious growth of malaria parasites required to cause an infection and also the sampling issues involved, the direct parasite detection methods are not adequate enough. This is not a sensitivity issue right now, but this is a sampling issue now. But in

some countries they do test for antibody by ELISA to expedite reentry for those who are antibody-negative, mostly European countries and Australia and New Zealand.

But there was a panel recommendation at the end of the workshop to consider alternative strategies for donor deferral in areas of high travel but very low malaria risk.

Then we came back to BPAC again last year, and this time we did propose to screen blood donors, for those who had traveled to malaria-endemic areas in Mexico alone, for the presence of malarial antibodies as evidence of malaria exposure.

So our colleagues from the Office of Biostatistics presented an FDA risk model where we considered three scenarios: testing all blood donors, universal testing; reentry for all malaria-risk donors where the risk of exposure is acquired anywhere globally in the world; and then specifically reentry testing for only those travelers who visited malaria-endemic areas in Mexico. In these two scenarios, a 4-month deferral was recommended before testing would be allowed.

So the results showed of the risk model assessment that all testing scenarios would lead to donor gain, that most otherwise-deferred donors would be reentered without significantly increasing malaria risk.

But then in the end the committee felt that -- I think they asked us to come back again when we performed more risk assessment they needed that should account for malaria risk globally and then especially in Mexico, with and without antibody testing.

So this is our current proposal now, and this is why we are here today. The Mexican state of Quintana Roo -- and you will hear this data from me and then you will hear again and again this data -- so Quintana Roo has a very low malaria transmission rate, and visits to Quintana Roo, a popular tourist destination, have recently accounted for the largest number of malaria-risk-associated U.S. blood donor deferrals. Based on a risk assessment it has concluded, FDA seeks advice on whether the anticipated benefits outweigh the possible risks, if FDA allows blood donations from travelers to Quintana Roo without applying the recommended one-year deferral.

Then again, our colleagues at the Office of Biostatistics have developed a probabilistic benefit and risk assessment model to assess potential risks to blood safety and impact on donor availability, comparing the current malaria deferral policy with alternative policies that would allow either exemption from deferral for travel to all malaria-endemic areas of Mexico or exemption for travel to the state of Quintana Roo.

So the important thing to keep in mind here is risks and benefits. So the two go hand-in-hand here. We cannot assess one without the other.

The data inputs here for U.S. blood donor deferrals due to travel in individual endemic states in Mexico were based on surveys from a few participating blood centers in the Retrovirus Epidemiology Donor Study II (REDS II) and a study of Blood Systems Research Institute.

So let me acknowledge these people here. The REDS data was provided to us by Dr. Bryan Spencer and Bloods Systems Research Institute data was provided by Dr. Brian Custer. We wouldn't be here today discussing this issue if these two individuals had not very generously not only provided their unpublished data but in fact they initiated this data and analyses upon our request.

So let's look at the malaria situation in Mexico now. In the last 10 years, in 1998, there were around 15,000 cases of malaria reported in Mexico, predominantly *vivax* but some *falciparum* cases also. But then something happened the following year. There is a precipitous drop, more than a 50 percent drop in the following year. Then the rate is steady, somewhat stable.

Since 2006 these numbers have become stable again. There are around 2,400 to 2,200 cases, 2,300 cases a year. So this indicates quite a stable malaria

situation. Also, something else has happened here which is remarkable: Since 2006 no case of *falciparum* malaria has been reported in Mexico.

This is the data from the Health Ministry of Mexico.

This is a malaria map of Mexico showing both endemic and non-endemic states of Mexico. This is in the year 2008. So here are the boundary states here, continuing here with the Belize border, and the border of Belize and Guatemala here.

So now let's look at the situation of malaria in the usual Mexican states. This is the gradient map based on infection rate here, so these states with the highest malaria infections are reported here, and then the numbers come down here. So Chiapas and Oaxaca seem to be the top of the list of malaria here. But if you look at these numbers, some of these states have population of 3-to-5 million here. But if you look at the number of malaria cases which we call a high malaria rate in these states, 1,300, close to 1,500, 1,100 here, if you compared it to Sub-Saharan Africa, in some parts of Sub-Saharan Africa, every single individual gets malaria infection during the course of a year, so that in relation even these high-risk states or high-infection states have low malaria there. But then there are many states where the numbers are like

two cases in Veracruz, Jalisco, two cases, and here is Quintana Roo here, the numbers are stable.

So a few other things stand out here. It is low intensity. It is all very stable but also it is uneven. Even with this low-intensity transmission anywhere in Mexico, these numbers are not even throughout the country.

So then coming back to the data, these data are looking at the blood centers where we data was used. So in red here are the data from the REDS study that is provided by Bryan Spencer to us. These blood centers are located in these four northern states. Then BSRI data was provided here, because we were concerned that we were sampling only from one part of the country. We wanted to specifically know what is going on in these southern states that share the border with Mexico here. So this is from Texas, these blood centers located in Texas, in New Mexico, and in Arizona.

So deferral of U.S. blood donors in the REDS II study survey by malaria-endemic states they visited in Mexico, here are the numbers I have listed. Here are the names of the blood centers here, and also we have listed here only the states which were endemic states only. The predominant, 85 percent of deferrals in the REDS II study were caused by donors who had traveled to the endemic area in Quintana Roo alone. So 85 percent, that is a very, very

glaring number here.

This is the data from the BSRI survey. The REDS data was from 2006 and the BSRI data was from 2008. As I understand it, the methods of sampling and collection are very similar. You will hear a lot more in detail about this study by Bryan Spencer and Brian Custer.

Again, there are some differences here in these bordering states. There are a lot more states where the deferrals were reported. But then again, the trend remains the same. A little bit more than 37 percent of donors were deferred for traveling to Quintana Roo. We have to be cognizant of the fact that the travel mode and travel path(?) and the demographics and nature of the donors will be completely different from donors who were probably flying out from the northern states, and these donors from the bordering states are using a lot more vehicular traffic, I guess, and the places they will go were different.

But then we tried to simply meld this data from the REDS study and the BSRI here, and this is simply the average here. If you meld the two data, close to 70 percent of donors were deferred because they had traveled to Quintana Roo.

I am coming to the end of my introductory talk here. Here are the questions for the committee:

Does the Committee agree that, based on FDA's current risk-benefit assessment, it is acceptable to allow blood collection, without deferral, from U.S. residents who have visited Quintana Roo?

If the committee thinks this question is not sufficient, if not, then please comment on whatever other measures FDA might consider to reduce the donor loss from malaria deferral for travel to Mexico.

So these are the questions.

I just want to show you what follows after my talk. Dr. Paul Arguin will give you in-depth information about epidemiology of malaria in Mexico. That will be followed by Bryan Spencer, who is going to talk about risk of malaria infection among U.S. travelers to Mexico, and then next to that is Brian Custer, who is going to present the BSRI data, travel locations and malaria risk in United States donors in states bordering Mexico.

So I think we will have sufficient representation from blood establishments who have provided these data, and then my colleague, Dr. Mark Walderhaug, is going to show us the FDA risk analysis to show risk analysis of potential exposure to malaria in U.S. travelers to Mexico. Then I will come back before you one more time and give you the summary of the entire issue and present the FDA perspective.



I would just like to quickly acknowledge here the people who helped with putting this together, my colleagues at the Office of Blood: Dr. Hira Nakhasi, Dr. Paul Mied, Dr. David Asher, and Dr. Jay Epstein; my colleagues at the Office of Biostatistics and Epidemiology, Dr. Mark Walderhaug, Dr. Hong Yang, Dr. Richard Forshee, and Dr. Steven Anderson; from CDC, Dr. Paul Arguin has been always very interactive and helpful; and again, as I said, Bryan Spencer and Brian Custer, we would not be here without their generosity in sharing their data.

I will stop here and take any questions.

DR. SIEGAL: Thank you, Dr. Kumar. Let's hold questions for now until all the other talks have been gone through.

We are going to next here from Dr. Paul Arguin on the epidemiology of malaria in Mexico. Dr. Arguin.

DR. ARGUIN: Good morning.

We will be hearing about not just Mexico but a little bit about the surveillance for malaria in the United States as well.

I gave a similar talk to this group a little over a year ago, and so I thought I would start with the conclusions of my talk last time. So how many U.S. residents go to Mexico? Millions and millions, but only a very small percentage go to areas where malaria is

transmitted.

One-quarter of these travelers are VFR travelers. This is a travel-medicine concept, VFR standing for visitors to friends and relatives, usually first- and second-generation immigrants returning to their countries of origin for the purpose of visiting family and friends. They have been shown repeatedly to be at higher risk for certain infectious diseases such as typhoid, hepatitis A, but also malaria.

How many U.S. travelers get malaria in Mexico? At the time about five per year was the average, and over half of these being VFR travelers.

Where in Mexico exactly do they get malaria? Not exactly known. I will go into a lot more detail about the U.S. surveillance system. We collect information by the level of country, not subcountry-level information.

How much malaria is there in Mexico? Zero cases of *falciparum* and a little over 2,000 cases of *vivax*, with the incidence decreasing overall.

Where in Mexico is malaria occurring? Mostly in the south, with a need to maintain vigilance for reestablishment.

So just to start off, malaria worldwide, 300-to-500 million cases per year with an estimated over 1 million deaths. The map that you see here shows areas of the world

in green where no malaria transmission is known to occur. The areas in yellow show parts where there's transmission occurring in at least some parts of that region. In the areas in red, there is pretty widespread transmission occurring.

Just as a quick aside, this map was taken from the new CDC malaria map application which is available on the CDC Web site, designed with blood banks in mind to try to define parts of the world where malaria is occurring for the purpose of doing donor deferrals. Just to show you, there is a new search interface that allows you to get detailed information on specific destinations around the world. So if you haven't had a chance to take a look at that, I would encourage you to do so.

In the United States, endemic mosquito-borne transmission was interrupted in the 1940s, but we still get approximately 1,400 cases per year. Almost all of these cases are imported, and we do have, as has been mentioned earlier, occasional locally acquired cases. That does include the transfusion-transmitted cases. Our average currently right now is about one every other year, but that would also include congenital cases and mosquito-borne transmission. Our last outbreak was in 2003, so I would say we are overdue.

The National Malaria Surveillance System. It's

the oldest surveillance system at CDC, maintained since indigenous transmission was interrupted. It is a passive case-detection system, and I will go into a lot more detail about what this means. We collect our cases from state and local health departments for the most part, but we do also get some information directly from healthcare providers when they call the CDC malaria hotline for advice on diagnosis and treatment, and then we can collect the case information at the same time.

It is our goal to identify all cases of malaria that are diagnosed and treated in the United States, with particular interest for the locally acquired cases, so that we can rapidly implement any control measures if needed.

We monitor the epidemiology of imported malaria and feed this information directly back into our guidelines for prevention amongst travelers as well as our treatment guidelines.

This is the basis of our passive case-detection system. It is a paper-based reporting system. We ask state and local health departments to fill out this form that includes information such as demographics of the case, any preventive measures that were attempted, treatment issues, as well as characterizing the traveler and where they may have acquired it.

Just to show graphically, these are the

components of the system. You have the travelers themselves who need to do some things in order for the system to capture them, the healthcare system, state and local health departments, and then ultimately CDC. I am going to spend a little time on this.

First of all, we would like to have an accurate numerator in terms of U.S. travelers who actually acquire malaria while abroad. In order for us to capture this case, they need to have returned to the U.S. Cases that are diagnosed and treated overseas are not counted in the U.S. system, they would be counted in the system for the country where it's diagnosed and treated.

These travelers need to have sought medical attention in order for these cases to be detected and counted. In some instances, such as, let's say, a *Plasmodium* malaria case, symptoms can resolve without medical attention, to recur again later. In some instance people acquire some malaria medications and empirically self-treat. Those cases would also not make it into the system. Likewise, if there are fatal cases without autopsy, those cases would be unknown to us.

At the level of the healthcare facility, a doctor first needs to consider malaria on their differential diagnosis and order the appropriate diagnostic tests. There are, of course, false-negative tests that can occur.

Laboratories that lose proficiency with smear microscopy may not adequately detect actual cases of malaria. There can be false-positive tests. The occasional platelet sitting on top of a red blood cell can look like malaria to some people. There is no requirement for confirmation. So if we receive a report and it seems like a plausible scenario, it will be accepted as a report, and these potential false-positive tests can skew the data that we receive.

In some instances there is no species determination that occurs. So, once again, that data would be lost to us. Incorrect species determination at the level of the healthcare system. Just like with self-treatment, there can be empiric treatment without getting an actual diagnosis. Those cases would be lost.

Then, also, a key part of trying to determine the global epidemiology of imported malaria amongst travelers is to get an accurate travel history. Sometimes no travel history is collected, inaccurate travel history is collected, or even if the healthcare provider is aware of where they traveled and uses that information accordingly for treatment, (he) didn't actually record it and make it into the system.

Moving on now from the healthcare facility to the health departments and CDC, someone needs to transcribe

this data and report it to the state health department. Throughout the entire country, this is sometimes delegated in different ways. Sometimes it occurs by the healthcare providers themselves or sometimes the laboratories are the ones who report this information. Depending on which personnel are doing this, there may be some inherent biases in the reporting that ends up going to the state health department.

Possibilities for transcription errors. There may be incomplete forms due to lack of data within the medical record when someone is trying to transcribe that data.

In some instance, especially in jurisdictions with either large volumes of malaria cases or health departments that are potentially understaffed or under-resourced, they may actively choose to only report a subset of the available data. We have a fairly detailed form that I showed you before trying to collect a fair amount of information. Some states or local health departments may choose just to fill out the bare bones and not provide us with all the information that we need.

In some cases it may be intentional. It is certainly possible that there can be deliberate exclusion of cases for political reasons or trying to hide additional cases.

Then, ultimately, someone needs to send it to CDC so that we are aware of it. That is the passive component of it.

I can tell you one of the tricky parts when going over this data, determining country of acquisition is not always completely straightforward. There are very many similar-sounding country names, and I think this becomes an issue of geography for a lot of people who are filling out case reporting forms. Countries like Ghana, Guinea, Guinea Bissau, Papua New Guinea, Guyana, French Guiana. After I made these slides I had another one that arrived on a form the other day, Guana. So which one is that?

Also, when there are complex itineraries, a person traveled to multiple countries within a logical time frame, their malaria could have been acquired in any one. It's not possible to really determine the country of origin or the country of acquisition for that case of malaria.

So surveillance systems in general -- and I am speaking of both the U.S. as well as the Mexican -- have these inherent inaccuracies and potential for misclassification of the data, which I think does limit its utility for using this data to do really precise calculations. However, in aggregate, it does give us a very good idea of the amount of malaria diagnosed and treated in the United States. And because it is a



longstanding and stable system, it can show accurate trends over time, and we are able to perform some subgroup analyses with this type of data.

So that being said, let's look at the data right now. On this chart in the blue bars you see the total numbers of cases of malaria. Use the axis on the left and the yellow line shows the number of deaths in the United States. Using the axis on the right, you can see that we have on average about 1,400 cases reported in the United States every year and an average of about five deaths.

Of particular interest to this group is our transfusion-transmitted malaria. This is showing the cases since 1990. In the first half of this time frame, our average was about 1.4 cases per year, and it has come down nicely, so we are averaging right now about 0.5 cases per year or one every other year. So far in 2009 it has been a heavy year with two cases so far.

Here is detailed information on our most recently completed year, 2008. We had 1,298 cases reported in the United States, including one case of congenital malaria, none transfusion-transmitted. At least 41 percent of these cases were hospitalized. At least 9 percent qualified as severe cases. It is important to remember that not all severe cases are *falciparum*. We did have 8 percent of our severe cases which were *vivax*. Two deaths in 2008, one

*falciparum*, one *vivax*.

By population sector, 39 percent in 2008 were U.S. civilian travelers, 14 percent foreign civilians. That of course means people who normally reside in malaria-endemic countries who just happened to be in the United States when they were diagnosed and treated. Unfortunately, you can see 46 percent -- the form was not completed and so we are unable to categorize them into which population sector they belong to.

Of the U.S. residents, almost two-thirds of them, the purpose of their travel to the malaria-endemic country was visiting friends and relatives, so this higher risk traveler population.

Region of acquisition, you can see 43 percent of our cases were acquired in countries in Africa. Thirty-nine percent geographic information was insufficient to determine which region they acquired it in.

Looking at this with a little more granularity, I have listed the top six countries of acquisition: Nigeria, India, Ghana, Ivory Coast, and Sierra Leone. Then for the purpose of this discussion I've tacked on Mexico as well, and you can see three cases were acquired in Mexico in 2008.

Limiting this list just to the U.S. travelers, so eliminating the foreign visitors, you can see it is a

similar list of countries at the top of the list and two cases acquired in travelers in 2008.

Looking at that last number over time since 1999, you can see it has been a relatively small number of cases acquired by U.S. travelers in Mexico. Over the past several years, it is an average of about four cases per year that are acquired by U.S. travelers in Mexico.

Every year when we publish our surveillance summary, we try to put these numbers of cases in U.S. travelers in a bit of perspective of the volume of travel into those countries. This is very small type. I don't expect you to be able to read the whole chart, but in general, countries with estimated higher risk for the average U.S. traveler are clustered towards the top, and there's a gradient going down towards the bottom. Every year, as we would expect, countries in West Africa and Oceania tend to cluster right up at the top. Coming down the gradient, you can see other countries in Africa, Haiti, India, Honduras, and then down towards the bottom it's countries in Southeast Asia and Mexico.

Keep in mind why some of these areas appear to be low risk. There could be a lower intensity of transmission in that country. It could be that U.S. travelers take more precautions for that destination. But then, also, it could be that malaria does not occur throughout the whole

country, and the numbers are being slightly skewed by that population which is not truly at risk; also that U.S. travelers may not be going to the parts of the country where malaria is occurring.

Looking now at some Mexican surveillance data, Sanjai Kumar showed some of this before, but you can see that going back from 1985 there were between -- I guess in the early 1980s -- between 100,000 to 140,000 cases per year in Mexico, and with a fairly aggressive malaria-control program, that number has come down dramatically.

Looking in a little bit more detail, you can see that over the past several years it has plateaued nicely at about a little over 2,000 cases per year. Do note, though, however, for 2009 that is data that is year-to-date so far. So we are not quite done with 2009 yet, and they are at 2,348 cases. So it may be that there is a slight uptick in the number of cases happening in Mexico right now.

Also note Sanjai had shown that in 2007 there were zero cases of *falciparum*. They have recently revised their numbers 2 years after the fact, adding two cases in 2007, but still zero cases of *falciparum* in 2008, zero cases in 2009 so far.

What I have done here on this chart, I have superimposed two different data sources onto the same chart. The line in blue is the number of U.S. malaria

cases that were acquired in Mexico since 1985. The line in green is the number of cases in Mexico since 2005. I find this superimposed chart very reassuring in that with all of the inherent problems that I was describing with collecting surveillance data, these numbers are nicely correlated.

So I am fairly confident that one of the strongest predictors of the number of cases that we can expect to see in U.S. travelers, it is predicted by the number of cases of malaria that are occurring in Mexico. The smaller amount of malaria that there is in Mexico, the less likely we are going to have cases in our travelers.

Here I am just going to breeze through this quickly showing the geographic distribution of malaria in Mexico over time. With this aggressive control program that has been occurring in Mexico, they have been able to decrease the number of states where malaria transmission is occurring. Currently there is a fairly restricted area within Mexico where transmission is occurring. There is this little box that we draw up in the northwest corner of Mexico as well as these areas to the south. You will notice I do have a little question mark over the state of Jalisco, and I will show some of this data in a little bit more detail now, and I will start with Jalisco.

For all of these charts that you're going to see for the states where transmission is still occurring in

Mexico -- it is going from 2000 to 2009 -- it had come down nicely to just about two cases per year in 2005, 2006, and 2007, and then they've experienced a bit of a blip. I am still cautiously optimistic that this is just a blip and it will come back down. But as I mentioned at the conclusion slide at the beginning of my talk, we do always need to keep an eye on this. In parts of Mexico where they have successfully eliminated malaria, there really has not been a reintroduction. So that is good. But in areas where they have not yet completely eliminated it, there always is a potential for a recurrence or resurgence.

A couple of other states to keep an eye on: Nayarit had come down to less than 50 cases per year and in the past two years has experienced once again a little bit of a resurgence.

Chiapas is the state with the largest number of cases in Mexico. It had gotten down to just under 1,000 cases in 2005, experienced a bit of a resurgence in 2006, 2007, and it is now again starting to come down a little bit. As you can see, in 2009 so far they have just about 1,000 cases.

Oaxaca is the state with the second-highest number of cases in Mexico. As you can see, it has been going back and forth in Chiapas. In 2009 so far they are approaching 900 cases so far.

This area here in Sonora, Chihuahua, and Durango, this is that square area drawn up in the northwest corner of Mexico. This area had also been having a decreased amount of malaria up until 2007 where they've started to experience a bit of a resurgence, almost 400 cases so far in 2009.

A bit of, I guess, good news to end this talk. In the state of Sinaloa, continuing to decrease. They're now below 100 cases, and hopefully that trend will continue.

Tabasco, down to just about 10 cases. Hopefully, this trend will continue as well.

And finally, the state that we're all particularly interested in. As you can see on the little inset map there, it's over on Yucatan Peninsula over on the Caribbean side. It includes the destinations of Cancun, Cosumel, Playa del Carmen, Isla Mujeres, Tulum, very popular travel destinations for U.S. travelers, very large volume of travel going to these areas. The number of reported cases has dropped and has continued to drop steadily. In 2009 so far they have reported a grand total of four cases. That is year to date. Then, as I mentioned before, there is sometimes some adjustment of these numbers of cases after the fact, but in general you can see the trend over time. It has been coming down to quite low

numbers and staying quite low over time.

My conclusions this time:

The volume of travel to Mexico is still very, very high. Most of the air travel that goes from the U.S. to Mexico is into Quintana Roo.

How many U.S. travelers get malaria in Mexico? Currently about four travelers per year total. The likelihood that these four people will donate blood in the 24 to 48 hours prior to the onset of their symptoms is extremely small.

We still don't know exactly where in Mexico all of these four cases got their malaria.

In terms of how much malaria is there in Mexico, zero *falciparum*, about 2,300 cases of *vivax*, and I would say overall the incidence has plateaued. There is almost none reported in Quintana Roo. However, the incidence is starting to rise in some states, and so still we do need to keep an eye on these other states and, hopefully, support Mexico in their eradication efforts as well.

With that, I will try to get us back on the time schedule. Any questions?

DR. SIEGAL: Thank you very much, Dr. Arguin. Let's defer questions for now, as I said, and go on.

Now we will hear from Bryan Spencer from the American Red Cross on the risk of malaria infection among



U.S. travelers to Mexico. Dr. Spencer.

MR. SPENCER: Good morning and thank you for the invitation to speak, and thank you to the FDA especially for bringing this topic back to the table and framing it in a fresh perspective.

I will present some data from the REDS II group.

We have seen this graph which shows a trend we like very much, a greater than 90 percent reduction in transfusion-transmitted malaria from the late 1960s, early 1970s, with soldiers returning from a theater of war in Southeast Asia bringing malaria back with them, to a trend of generally zero or one cases each year currently. The case in 2005, that's an error, but generally we see zero, one, and, we just recently learned, two cases in 2008.

At the blood center we classify donors in terms of their risk basically into three different categories: those who acknowledge a history of malaria infection, those who have lived in a malarial country for a sufficient period of time to trigger a deferral, and those who may have simply traveled to a malarial area within the country. This is the group that this study focuses on, just those with travel history. For all of these groups, country of birth is not a factor taken into account at the blood donor screening process. It is in some other areas but it is not here.

So the context of a nice decline in TTM is contrasted a definitely increasing burden of travel deferrals. This is Red Cross system-wide data over almost a 10-year period. I have extrapolated to get 2009 results, but this is good through a week ago. We see basically in terms of the percent of donor presentations leading to a deferral, it has gone up by 50 percent over this 10-year period. So we see a very nice decline in the TTM, but we see it offset by a burden of travel deferrals.

As we already heard about some, this table goes through 2007. I did not have access to the unpublished data more recently, so in any case we see that those groups responsible for the large share of TTM in the most recent three decades are former residents of malarial areas, and they have three salient characteristics about them:

One, they've had sufficient lifelong exposure to develop a significant level of clinical but not sterilizing immunity, so they are walking around, presenting to donate, feeling healthy, but with parasites coursing through their blood.

Two, most of these, 60 to 70 percent, should have been deferred at the time that they presented. So for most of these cases of transfusion transmission, there was a failure at the health history screening process.

Then, third, we heard from Dr. Kumar that 25

percent of all TTM is attributable to *Plasmodium malariae*, which can be a particularly indolent infection. But another way to look at that is not just 25 percent of all TTM but two-thirds of all TTM where the donor was properly qualified to donate. So that is a biological constraint that's hard to overcome. But in any case, the one group that stands out as particularly low-risk, especially given the relative proportions of each group in the donor pool, is U.S. civilian travelers.

Sanjai presented data from four of the REDS II blood centers, and that is because, at the time that they needed to begin running their models, we only had partial data from four of the six centers. But REDS II is a consortium of six blood centers that all together collect about 8.5 percent of the U.S. blood supply, so it is based on that proportion that we extrapolate to the United States overall.

We are geographically dispersed, east and west coasts, middle of the country, and then the two regions that were not shown in the map are the southern region, which collects Georgia and a little bit from Florida and South Carolina, and then blood centers of the Pacific. So the map is a bit broader than that which was shown. We also have demographically diverse donor bases.

The data that was presented last year at this

meeting, what we wanted to do was to see how large was the group of donors deferred annually for routine malaria travel, find out where they had been, estimate traveler risk in U.S. civilian travelers to different parts of the globe, and then, using traveler risk as a proxy for donor risk, estimate the risk that presenting donors deferred from malaria travel might be parasitemic when they walk through the door; then also to evaluate change in risk estimates by altering the deferral guidelines.

So these were our results. We already heard some about this. About 150,000 donors deferred annually and 60,000 or more deferred for travel to Mexico -- ten times as large an impact in terms of blood availability as for travel to Africa. It looks like the risk for malaria is about three orders of magnitude higher for travelers to Africa than malaria-endemic parts of Mexico.

I am not going to present this detail in the third point, but it is in the paper which is available in this month's issue of *Transfusion*. But our estimates were that the deferral policy itself might interdict an average of two parasitemic units a year.

So one of the questions we wanted to answer is, okay, we've got declining TTM, a rising burden in terms of blood deferrals. What's the cost benefit? It looks like the policy really might intercept two parasitemic units per

year. That risk attaches almost entirely to donors having traveled to Africa, Asia, and Central America based on either very high risk in the case of Africa or intermediate risk in large numbers of travelers.

Finally, we estimated that eliminating the deferral requirements to malaria-endemic parts of Mexico might gain tens of thousands of units per year at an exquisitely small incremental risk.

I am not going to discuss in great detail the breakout of data here, but this is just for those who want to see the detail. Again, this reflects the percent of deferrals across each of the six blood centers having traveled to the respective regions. These 2,100 donors that we looked at was a 16 percent sample of the REDS center deferrals overall. To extrapolate to the United States, we again used that 8.5 percent of the U.S. blood supply to make projections to get us to about 61,000 donors deferred for travel to Mexico.

Sanjai noted that about 34 million U.S. residents travel per year to malaria-endemic countries in the world, and we wanted to make sure that our risk estimates reflected as accurate a projection, an estimation of risk, as possible. So we tried to adjust for the population at risk going to any given to any country. So that 34 million gets whittled away to about 8.5 million travelers.

The travelers to Mexico, of the 20 million or so going per year, we whittled that down to about 4 million. It may be true that not all of these have incurred risk, but this was the proportion that we think traveled to an area that would have triggered a malaria deferral. So independent of whether the risk is there or not, it looks like this many travelers went to areas that, had they come to donate, they would have been sent packing.

Over here we see the relative risk for malaria infection in travelers, Mexico lower than all other areas; Africa, about three orders of magnitude higher; and three countries in the Western Pacific higher yet, Papua New Guinea, Solomon Islands, and Vanuatu.

Malaria transmission can change quite a bit from year to year based on climate, population movements, other factors. So to show that the data that we presented and used in our risk estimates were not exceptional -- that was 2005 data -- we see that there is quite a bit of stability over time both in the absolute and relative risks associated with U.S. civilian travel to different regions of the area.

Courtesy of Dr. Arguin at the CDC, we received some greater detail of the data presented in the annual surveillance summaries that gives interval between return to the United States and the onset of symptoms. So if we

want to know what risk a donor has of being parasitemic at the time they walk through the door 1 month, 3 months, 12 months following their return from travel to an endemic area, we want to know how things manifest in U.S. travelers overall.

We see that with *falciparum* malaria, within a 3-month period, almost 100 percent, 99 percent, of cases have manifested, they are clinical. Beyond that point, the risk is very small. The onset is slower in *Plasmodium malariae*, *vivax*, and *ovale*, but still it is very front-loaded. The risk after one year is very small. It's not zero. About 2.5 percent for these three species still occurs beyond 365 days. So it is not zero risk even under the current policy.

In terms of residual risk, we estimate from our cohort of 150,000 donors, if they had the same risk for travel infection as U.S. travelers overall, about 13 of them would have become infected with malaria. Of these 13, based on the time to presentation -- so this is the actual interval -- 11 of them would have self-deferred. So these are people who would have become symptomatic prior to coming in the door. So 11 self-deferred, a little bit more than two interdicted by the policy itself. We come up with a residual risk under the current policy of about one contaminated unit collected every 6 years.

Our intent was to make a model that was conservative, that we were sure did not underestimate the risk. Based on the numbers, one over the last three decades of routine travelers implicated in a case of TTM, we think that our estimate of one contaminated unit per 6 years from this travel group is indeed conservative. So that was the main point there: Changing from the current policy to no deferral at all again implies a change in risk of about one contaminated unit every 15 or 16 years.

Finally, under no deferral at all for Mexico, the level of estimated risk is quite similar, just barely higher than that estimated with travel to Africa, Asia, and Central America under the current policy.

So before we dig down into the nitty-gritty of Mexico, I just wanted to show a graph showing that not just across the globe but even within the Americas there is a wide distribution in the levels of risk. We see that the northern part of South America -- Suriname, Guyana, French Guiana, all countries that are part of the Amazon basin -- have risks that are many-fold higher than other endemic countries.

This is data reported to the Pan American Health Organization each year. It is adjusted for population at risk. So all of the millions of people living in large cities that have zero risk for infection



are excluded from this. So for population-adjusted risk, we see that there is quite a gradient across the Americas, and Mexico is way down here, not the lowest risk of all the areas. The Dominican Republic is another country that is lower risk and also has a significant contribution to those 150,000 deferred donors. The data that we have collected suggest that about 10 percent or 15,000 donors are being deferred for travel to the Dominican Republic.

As was already discussed, Mexico has done a very nice job in reducing both the numbers and the distribution, the geographic distribution, of malaria transmission in its country. Not that long ago, about half of its population of 100 million was considered to live in areas of risk for transmission, and now it is less than 3 percent.

The Annual Parasite Index, which is a metric used by those engaged in malaria surveillance, counts cases per 1,000 population at risk, and we see that it is about one per 1,000 in Mexico for the population that is at risk. Again, we see U.S. travelers to Mexico has been fairly steady at about 18-to-20 million per year.

Where in Mexico does malaria occur? We saw some earlier maps. This county-level map was produced by a health GIS software vendor in Mexico, so it is taking surveillance data at the county level and making a map that is basically a yes or no, not relative risk across these

regions but is there malaria transmitted in these areas at all or not.

I believe that this is 2004 and 2005 data, not more recent, but as we have seen, the risk generally has been of decline from that point forward, not increase. Again, this maps to the risk area outlined by Dr. Arguin, and then the states Oaxaca and Chiapas, of course, are responsible for the lion's share of cases reported.

So for the period at study -- again, we looked at deferrals in donors presenting in the year 2006 -- this is how the CDC Yellow Book reads, and this is what blood centers rely on in developing their guidelines for the health historians. So it is risk in rural areas, including resorts, of the following states. It names several states. It includes Oaxaca, Quintana Roo, and then also in the state of Jalisco in the northern area, and then this box which occupies several states.

It says no risk along the U.S.-Mexico border and no risk in major resorts along the Pacific and Gulf coasts. So that is already a little bit at odds with the language at the beginning, and that comes into play at the health history process. In the case of uncertainty, the donor gets deferred. So again pointing out no risk along the U.S.-Mexico border, and the county-level maps certainly bear that out.

The current REDS II study sought to duplicate basically within Mexico the same thing that we had done on the global scale. We wanted to see where in Mexico the donors reported having traveled and to classify that to the county level, if possible, to the state level otherwise, and then if the donor gave such a vague description, went to rural areas or horseback riding or something like that, then we are going to use the country-level risk in our estimates.

We wanted to determine the risk for malaria for residents of the county in which travel was reported. As Dr. Arguin noted, we don't know where in Mexico U.S. residents who return and present with malaria got infected. They learn about that only incidentally for a small number of them, and in any case, the number is so small that trying to use that number to estimate risk for donors deferred would have a large amount of uncertainty.

We recorded into a database the information that was transcribed on the blood donation record of where they had gone. If they said they had gone to more than one area within Mexico, we assigned the location to the higher risk area. If they only gave us a state name, we used the state risk, again as reported to the Pan American Health Organization. Then if we didn't have the location, we're using the overall risk for the country. That is again

about one case per 1,000 residents.

That one case per 1,000 residents is an annual figure, so we need to adjust for duration of exposure. We are looking at that in a couple of different ways: the median exposure, and we have time of exposure, duration of exposure, only for three of the six blood centers and in total for about one-third of the donors, and then using a conservative figure of 2 weeks' duration.

Of those 2,100 deferrals that we looked at, 902, so about 43 percent, were for travel to Mexico. We were able to ascertain the location within Mexico for about 85 percent of them. The number is really more like 93 percent of those for which we had any information at all. One of the blood centers was unable to locate some of the records, so overall we have information on 85 percent of the deferrals, but 93 percent of those for whom we have any information we could classify it to a specific county or at least state.

So again, this is six centers' data, not the four centers that Sanjai was presenting. So the information is a little bit different, but we see that Quintana Roo still stands out as accounting for the predominant share of all donor travel destinations, 75 percent, followed by Nayarit, 6 percent; Guerrero, almost 6 percent; and then the first state with any really significant risk, Oaxaca, less than 3

percent.

It is worth noting that the risk gradient across these areas varies by 100-fold where it is not zero, so the first high-risk place -- one per, say, 140 residents -- is Oaxaca, and Quintana Roo is much, much lower yet again, accounting for the large share of deferrals.

I will present the results graphically at first and then quantitatively at the end. I am showing this map from a couple of years prior to the year's surveillance data, because again malaria transmission can vary quite a bit from year to year, and also, these maps will generally show a decline in risk where there is any risk at all. So the legend that I have used is based on a log scale, so as we go from red to orange and down, it is representing a tenfold decrease in resident risk annualized, for a year's time.

For 2003 and 2004, we see there are parts of the state that do not report any cases of malaria at all. One area, and this is where Playa del Carmen is located, reports a risk of less than one case per 100,000 residents and then a somewhat higher risk here further south, and then higher yet further south from that.

Again looking at 2005, the year's surveillance data that we are using to estimate risk for our travelers having gone to Quintana Roo, we see that this county drops

out, no reported cases in 2005, and then the risk has declined in these two counties themselves. So where have the donors gone? Eighty-two percent of the donors have gone to these parts of the state that report zero cases in 2005.

Costa Maya is a large area down here where it is not very developed, it is not heavily populated. There is a large port that ships dock at and donors disembark and go shopping in a large area for a few hours and get back on their boats. So about 15 percent are deferred for travel there. Again, I think we saw this with Dr. Arguin, that from 2005 forward the level is relatively stable and mostly declining. So from this point forward, it looks like the risk is lower yet.

Guerrero again, which is the next most common state involved in donor deferral, we see that the distribution of malaria risk looks to be very uneven. It seems to be absent for much of the territory of the state. Just to remind you, the language in the Yellow Book at the time refers to risk in rural areas of the following states, one of which was Guerrero, including resorts in these states. Acapulco is here, light blue, less than one per 100,000 residents, and then three counties bordering Oaxaca appear to have a slightly higher risk.

Now, it begs the question whether a county

reporting one or two cases per year is really indicative of malaria transmission as opposed to imported malaria, but in any case, these are what the surveillance data show for the 2 year preceding the data we used to estimate risk.

In 2005 it looks like the risk has vanished from the counties bordering Oaxaca. It remains very low in Acapulco. Where did those 5.5 percent of donors go? Well, about one in five of them went to Acapulco and three-fourths -- that arrow should be pointing to here, the county that has Ixtapa and Zihuatanejo, a popular tourist area. In any case, no malaria cases reported for 2003, 2004, or 2005, yet accounting for most of our deferred donors going forward. No cases at all reported in Guerrero, and in fact the current Yellow Book does not list Guerrero as a risk area.

A third state that I will show graphically before moving to the quantitative look at things. Nayarit looks to be -- it's up closer to that northwestern corner -- looks to be higher risk in general than the two previous states we looked at. It represents 6 percent of deferrals. We do see one county added, this one here, but generally a shift in risk, generally downwards.

So where are the donors who have been deferred for travel to Nayarit? Where have they gone? Well, it looks like most of those have gone to Nueva Villata

bordering Jalisco.

From that point forward, 2005 to 2009, there does look to be a slight bump in risk. I don't have county-level surveillance data beyond 2005, so I cannot say that the risk where these 89 percent went has not increased, but I suspect that given the 3-year timeframe with no cases at all that that would be the most likely explanation, that is hasn't increased there.

For our quantitative estimates, we had to adjust again for time. We used median time of exposure, which was one week for all of the deferrals -- again, we had it available only for about one-third of them -- and then a conservative 2-week assumption. If you look at the distribution of duration for those for whom it is available, it is definitely bimodal. The mode is 7 days. Most people go for about a week. But there is a large share, about 20 percent of those for whom we have the data, that have less than an overnight's exposure in the area they traveled to.

This slide for Quintana Roo shows at the county level the resident risk, the share of our donors having gone to each of those areas, the projections to the United States in terms of overall deferrals, and then how many infections we would expect in this number of deferrals under a 7-day or 2-week exposure. So we see, of the eight



counties in Quintana Roo, only two report any cases of malaria in 2005, and the frequency of infection is one per 32,000 and one per 24,000 residents for a full year's time. So that is a very low risk. Everywhere else has zero reported cases.

Well, where have those 75 percent of donors going to Quintana Roo traveled? Most of them went to Playa del Carmen, Cancun, and Cosumel. So that's where that I think it was 82 percent went, the northern part of the state. Some smaller share went to Costa Maya. We think from that almost 7,000 donors who are deferred for travel to that area, you might see five cases in 1,000 years, so one case every 200 years, and much lower risk for elsewhere. At the state level we would see probably about one case per 100-to-150 years if we were to not defer any of these 46,000 donors.

This is broken down to county level but aggregated at the state level, calculated the same way, though, where it's weighted by area of travel and risk within that area of travel from Guerrero, from the 3,000-plus donors that we estimate were deferred for travel there. We see a very low level of risk. Likewise for Nayarit. Only for Oaxaca do you see anything that is going to suggest a risk of an infected donor every handful of years. Again, this assumes that the donor is presenting to

donate on the very day they return from donation (sic). So in actuality we see that more than half of donors come in to donate 3 months or more following their return, so that is one of the ways, in fact the primary way, that the original model, and this study as well, was made to be deliberately conservative, is to assume that the very day they come home, they've come in to donate.

So, to conclude, a very large majority of donors deferred for travel to Mexico were deferred for travel to Quintana Roo. Available evidence suggests that the risk for malaria within this state is exquisitely small, if not absent, in the areas most frequently visited.

Quantitatively, it looks like if we rescind the deferral for travel to Quintana Roo that we could recapture about 45,000 donors annually with incremental risk of a contaminated unit perhaps every 100 or so years.

Thank you. I will take questions.

DR. SIEGAL: Thank you very much, Dr. Spencer, for an elegant presentation. I think again we will defer questions until all the presentations have been made.

I would like to call a break at this time with no objections other than the deferral of Dr. Custer for a little while. Let's come back in 15 minutes. Thank you all.

(Brief recess.)

DR. SIEGAL: We will resume, please.

Our next speaker is Dr. Brian Custer from the Blood Systems Research Institute. He is going to discuss travel locations and malaria risk in U.S. donors from states bordering Mexico. Dr. Custer.

DR. CUSTER: To begin with, I would actually like to thank Dr. Kumar and the FDA for the opportunity to present this data.

When this question came up and over the course of the last year, there have been lots of questions about, in addition to that data you just saw presented by Bryan Spencer for the REDS II centers, well, what would it look like for donors who are actually in border states? We would probably think that they might travel to different locations within Mexico, but what does that data actually look like?

So the FDA wanted to see, within aspects of some of our system, what the locations of travel were. So what I have done actually is duplicated a similar analysis to what Bryan just presented but at three locations adjacent to Mexico.

Before getting into that, I want to step back and just sort of put in perspective the number of donors who report travel to Mexico at all. If you will recall, at the time that we implemented *T. cruzi* screening for blood

systems, we also adopted questions that were actually added to the donor health history questionnaire to elicit locations of travel, including Mexico, under the possibility that there might be some sort of selective strategy related to *T. cruzi* testing. That is not the issue here, but this data actually represents a year's worth of travel history questions that we asked all donors. So this would be sort of the entire population, and I will cover that in just a second. But there will be a subset of these people who then go on to be deferred for actually travel to malaria-endemic areas within the countries.

In our donor populations for these three blood centers that I'm going to talk about, which are Arizona, New Mexico, and the Rio Grande region of Texas, which I will define in just a few minutes, for a year-long period that almost overlaps the year-long period that I am going to talk about for malaria travel deferral data, which is 2008, but from December 1, 2007, through November 30, 2008, we asked the donors if they spent time that added up to 3 months or more in Mexico. About 4.75 percent actually said that they have traveled to Mexico, accumulating up to 3 months' worth of time. In terms of traveling since the last donation, about 12.5 to 13 percent of donors report having ever traveled to Mexico or traveled since the last donation.

If you put that in terms of donations, just as background once again, it is the same information, but now obviously because we have donors donating multiple times, the number who say that they have spent time that adds up to 3 months or more is 3 percent, and the donors that have traveled to Mexico since their last donation is about 8 percent.

So out of that population, then there is this population that goes on to be deferred, and that's the one that I am going to now talk about.

As background, actually I don't have the 2007 or 2008 Yellow Book, but I did want to sort of make a point that obviously the CDC revises the Yellow Book frequently, and there have been changes to the Yellow Book since the one that actually Bryan Spencer reported. So the Yellow Book for 2010 actually says: "Limited to areas infrequently visited by travelers including small foci along the Guatemala and Belize borders in the state of Quintana Roo, and along the Guatemala border in the states of Chiapas and Tabasco; rural areas in the states of Nayarit, Oaxaca, Sinaloa" -- and in that box that has already been shown -- "which lies in Sonora, Chihuahua, and Durango."

In addition, the Yellow Book now says, "No malaria along the United States-Mexico border and in the

major resorts along the Pacific and Gulf coasts."

So for this particular set of information, what we actually did was we focused on these three blood centers that are in states adjacent to Mexico. They are United Blood Services centers representing Arizona, New Mexico, and the Rio Grande region.

We took a sample of all of the deferrals for malaria-related travel, and these were the first deferrals for each month, the even months of the year, so a total of 6 months' sampled, intended to be approximately 180 deferrals at each center.

More information about these centers just to give a little more information. The Arizona center is here. That actually represents -- in Arizona we collect a total of 11 of 14 counties, we collect from residents in 11 of 14 counties. In New Mexico we collect actually from a total of 30 out of 32 counties. In the state of Texas, it is actually only five counties. Those five counties, though, represent this area, McAllen, and the areas around El Paso, Texas. So it is a fairly representative sample.

All of the residents of Arizona and New Mexico and definitely for the state of Texas, only a sample that is for truly adjacent areas to Mexico.

For that same period, the number of presenting donors at each of these centers is listed here, a total of

407,000 presenting donors in 2008. Out of that there were 317,000 allogeneic collections over that same time period. For Arizona there were 1,800 malaria-related travel deferrals, or approximately 1 percent of the allogeneic collections. There were people who were deferred and were not collected, and slightly smaller percentages but overall representing approximately 1 percent of the allogeneic collections would have been from people, or 1 percent would have been deferred. Over 2,800 are deferred.

What was actually captured in the sample? There were 1,800 malaria travel deferrals from the Arizona center. Out of that we actually sampled 177, which represents just about 10 percent of the people.

For New Mexico and the Rio Grande region, the number of malaria travel deferrals are smaller. Therefore, our actual sample is a much larger percentage overall. Out of 2,800 malaria-related travel deferrals, we have a sample of about 17 percent of all of those deferrals.

So slightly different than what was presented for the REDS II data. Actually in this particular sample 60 percent of all of the malaria-related travel deferrals are for travel to Mexico. The next-highest location in terms of specific country is Costa Rica. Then you can see the other countries.

But I think the important thing about this slide

is just to point out that 60 percent are traveling to Mexico and actually are deferred. So then the natural question is, where are they traveling within Mexico?

This is just an example showing travel out of Phoenix. The arrows are actually intended to represent the relative proportion to, but they are not identical or specific, but the point being that the majority of people who are traveling from Arizona are actually traveling to Cancun and Quintana Roo. There are also people traveling to Jalisco, to Guadalajara and Mazatlan and Sinaloa, with much smaller percentages doing direct trans-border travel.

Looking at the malaria travel-deferral destinations, the dark bar represents the travel to Quintana Roo, so out of this population of this sample, 37 percent of people traveled and were deferred for travel to Quintana Roo. The next most common location of travel and deferral was Sinaloa, with approximately 15 percent.

You can see for the individual centers that it does vary where people are traveling, but generally speaking, I think that the summary across the three centers is a pretty good average for these three centers.

The areas in gray actually are the six or seven states that I'm going to talk about in a little more detail; for example, the two most common states of travel being Quintana Roo and Sinaloa. By far the most common



location to travel in Quintana Roo is Cancun, followed by Cosumel and Playa del Carmen and also Tulum, which is a ruins area. For Sinaloa, the most common location of travel is Masatlan.

These, just like in the analysis that Bryan Spencer presented, what we took were the specific locations of travel. We used the same process of analysis that he used to classify them to the county of travel, and then using that estimated county of travel, the estimated risk in the residents of that county and a 2-week median time, we tried to estimate what we think the risk of malaria infection would be in donors traveling to those specific locations and then aggregated that and summarized that on a state-specific level.

That state-specific-level data is actually presented right here. So in this sample -- and this is not projected outside of these three centers, it is only specific to these three centers -- for those 2,800 deferrals, 624 of them would be for travel to Quintana Roo; 255 for travel to Sinaloa; and this is the hierarchy of the most common locations of travel and the estimated number of people that we would expect to travel to those locations.

Taking that information then and sort of looking at that resident-specific risk for a median of a 2-week period, we estimated the number of malaria infections we

would expect to see exclusively in this population, and that is actually what is represented in the third column. Then the fourth column is just simply expressing that in a one-per basis. So for Quintana Roo, in this particular donor population, we might expect to see a malaria infection in one out of 588,000 donors, assuming this 2-week exposure period.

Similarly for Sinaloa, it might one out of 142,000 or 143,000. For Jalisco it is also quite low, one out of 1.25 million. Similarly for Nayarit, it is also one out of 120,000. For these other locations -- Oaxaca, Sonora, and Chihuahua -- the risk is clearly higher. The reasons why the risk is higher is because, truthfully, we don't have good indications of the actual specific location of travel within the state of Oaxaca, so we had to use that state estimate of Oaxaco, and that perhaps overestimates the risk of malaria acquisition.

What does this data tell us? The data actually says that travel to Mexico as reported by residents in border states is common but it is also dispersed. They travel to many different locations.

Nearly 15 percent of our donors at these three centers report travel to Mexico. Approximately 1 percent of the donation visits to these centers lead to malaria travel deferral.

Travel to Mexico resulting in deferral is most common for the state of Quintana Roo followed by Sinaloa. That actually represents 50 percent of our malaria travel deferrals at these three centers.

But, using the analysis that has previously been described, the estimated risk for malaria in those travelers based on location of travel is exceedingly small for travel to Quintana Roo, Sinaloa, Jalisco, and Nayarit.

So I just would like to acknowledge Bryan Spencer, who really developed the analysis approach. I would also like to acknowledge the REDS II study, an NHLBI-funded study, which also provided the support to do the original analysis that Bryan has presented. In addition, Anne Gultinan, Shrein Bahrami, and Maria Agapova at BSRI for actually collating the malaria travel data, and Blood Systems staff.

Thank you.

DR. SIEGAL: Thank you, Dr. Custer.

We will now hear from Mark Walderhaug, Ph.D., of the FDA on their risk analysis for potential exposure to malaria in U.S. travelers to Mexico.

DR. WALDERHAUG: Thank you.

The presentation I am going to give today will be the work of Hong Yang and myself. I would like to first give you the overview, and that is primarily to say I know

there have been a lot of statistics and figures, and I hope to keep them to a minimum, and I hope to minimize the number of old data that I will be showing you.

But I want you to go back to the September BPAC meeting and fix in your mind the model that we presented at that particular time, because I am going to use that model, I'm going to start, as Dr. Arguin did, with taking you back to 2008 and basically build on that to present to you how we are looking at risk in Quintana Roo by itself.

So from that September 11 meeting, we presented a model that involved having numbers of travelers, immigrants. We looked at the malaria prevalence in regions around the world and the species of malaria in imported cases and the delay between infection and the appearance of malaria.

One of the other big factors in our model as an input was the questionnaire effectiveness. That has a lot of effect on the final results. In the output we get potentially infected donors and the number of potentially infected collections, which is 1.75 times the number of donors. I think there is a slight difference between the collections that we're talking about as opposed to the donors that the Red Cross and BSRI were talking about earlier. But they are very similar.

You have seen this data before. This is Bryan

Spencer's data with respect to number of deferrals from around the world. This data is very important for calculating the specific risk for travelers going to Mexico and then coming back to the United States and not being deferred for travel to a malaria-endemic area.

So with this data we were able to calculate the total annual risk of transfusion-transmitted malaria in the United States being around 1.5 potentially infected collections per year, with a 95 percent to 95 percent (sic) confidence interval around zero to seven collections.

So there is a lot of uncertainty, but there is a lot of blood collected as well, and this represented a very small, about almost 1 in 10 million per collections.

As has been mentioned before, we have a little bit of the older data with respect to the observed annual risk of TTM. Dr. Arguin was mentioning it is now around .5 cases. As you can see, there is a difference between our model prediction and our observed annual risk of TTM. That could be due to our assumptions, it could be due to the fact that not all blood collected goes into healthy donors (sic) that survive long enough to measure whether or not they have come down with malaria. There are other reasons, too, why our predictions are higher than what is observed. In any case, we think it is a reasonable, conservative starting point for our model.

Using the data from the REDS study, we calculate that the number of infected donors who would appear, if we allowed everyone who traveled to a malaria-endemic area to donate, to have roughly 0.5 donors on an annual basis, or one every 20 years. That comes out to be around 0.88 potentially infected collections, with a confidence interval between .065 and .01.

I apologize for all these wonderful numbers. They add to the confusion, but I hope by the end we will have relatively simple numbers for you to consider.

The problem becomes how do we apportion that risk for each of the malaria states individually within Mexico. This is my approach, which is a lot simpler than the approach that has been presented both by Bryan Spencer and Brian Custer. That is to say the risk is dependent on the number of travelers to the area. So more travelers to an area, higher risk, necessarily. Also, the risk is due to the endemic amount of malaria present. So more reported malaria, more risk.

If we were to just take a simple product of the number of travelers based on deferrals times the number of cases, that wouldn't make sense because of the fact that travelers are exposed to much less than the annual cases. But if we take this product and we normalize it for all the states and all the travelers, I think we come up with a

reasonable way of distributing that .05 risk among all the Mexican states for our calculations.

As I mentioned earlier, there are limitations in this approach. There is a wonderful mathematical model called the Ross-Macdonald model which looks at malaria biting rates and prevalence of malaria and the lifespan of the mosquito. We could have made a very complex model for you. But we would still ultimately come up with, I think, a relatively small risk. So we could make this more complex, and I am resisting that complexity, though.

As mentioned by the previous speakers also, malaria risk is localized within the Mexican states. This model kind of takes a general estimate of the risk.

Also, our deferral data, although it is better now that we have the BSRI data and the REDS II data, it is still not necessarily nationally representative, and we are also combining different years. So that is kind of a drawback as well. It is also based on our probabilistic model that we had before.

So keeping all of that in mind as limitations, here is that malaria risk that we've seen before. Again, the key point here is that some states have higher risks than others. Malaria risk in Quintana Roo is relatively low compared to others, so that's an important component. Here's that other critical component, which is the

travelers deferred.

Here is a summary of selected Mexican states. There are more deferrals than the number of states that I am showing right here. But you can see there are interesting differences with the REDS II data right up against the deferral for BSRI's data. Both of them have substantial visitors to Quintana Roo, one being 85, the other being closer to 40 percent.

Some states, like Sonora, there are no deferrals for them in the REDS II data but relatively higher deferrals in the BSRI data. Conversely, you can see higher deferrals for Guerrero in the REDS data, lesser in the BSRI data.

Here is that risk calculation that I was talking about. This funny symbol over here is actually supposed to be a summation sign. I am hoping that in Windows 7 this problem will be fixed. But in any case, again, I am taking a very rough measure of malaria risk and number of travelers which are the number of deferrals on an annual basis divided by all the other ones summarized. This is called normalizing the risk for Quintana Roo.

Based on the REDS study, you can see that is .028 collections. BSRI is much lower, .05. If we combine the data sets, that's around .016 collections on an annual basis, which is low risk.



Similarly with the benefit component it is a little bit simpler. We are just taking the rough estimates for the number of deferrals for each one of the states and the number of collections being what we would expect for those 62,000, 61,000, donors who are being deferred times 1.75. As you can see, if we multiply by the fraction of deferrals, we get 92,000 collections for Quintana Roo, 42,000, 76,000 if we combine the data sets together.

Here is a summary slide, but the next slide I think makes it even more clear. Our current policy has about 1.5 units we would expect of contaminated collections on an annual basis, which represents around a risk of .088 on an annual basis. If we take the fraction of the risks that we're assigning to Quintana Roo, it's around, added all together, .15 for the REDS data, .151 for the BSRI, and .152 about the average of the two for the both of them combined.

Looking in terms of the numbers of collections on an annual basis, the increase for REDS data would be around a .06 percent increase in the blood supply based on around 15.7 million units collected, a .3 increase for Quintana Roo and a .46 increase for the relative gain from combining the data studies together.

Again, parentheses show a 5% to 95% confidence interval.

I think this is the way I would like to leave you with respect to understanding the data. I have restated the risk both in terms of relative risk and absolute risk, and I think this is informative from the perspective that, on a relative risk, you can see it's about a 1.8 percent risk increase for the REDS II data, BSRI data is lower, but for 1.1 (percent) risk increase overall for the two data sets combined, with only a .4 percent increase in the blood supply.

But, as was presented earlier, it is also useful to look at this in terms of the annual absolute increase in risk. Using the REDS data, we are calculating around an extra case of TTM, transfusion-transmitted malaria, for allowing donors from Quintana Roo to come without deferral of about one case every 36 years. With the BSRI data it's much rarer, about one case in every 180 years, and for the data sets combined, about one case in 61 years. Of course, this assumes that the rates of travel and the malaria stay the same. As Paul Arguin has alluded to, we think those rates for malaria rates are going to go down over that period of time.

During those periods of time where we would expect one case occurring, if we multiply that times the number of units that we could have been collecting over that period of time, we can see the absolute benefit would

be closer to 3.3 million units of blood collections over those 36 years, which is a substantial amount of blood to be collected.

Again, what is interesting for the BSRI data, around 7.5 million, and for both of them, 4.8 million units, the surprising thing about this analysis is that the safer the blood is, the more blood you're going to be able to collect safely. So even though BSRI reports less of an increase in terms of donors gained back, they ultimately have a higher collection rate because of the many more years they collect without that additional increase in transfusion-transmitted collection.

These are the familiar names that you've seen before. I would like to thank them all, and I would like to thank you as well. So I think we're ready for the next speaker.

DR. SIEGAL: Thank you very much, Dr. Walderhaug. That was very nice.

Now Dr. Kumar will summarize the FDA perspective and then we'll take questions and have a discussion after the open public hearing.

DR. KUMAR: Well, it was gratifying to see all these detailed presentations that support the FDA's proposal here today.

What I am going to do is very briefly here, so we

can get on with the discussions and then with the committee deliberation, I am going to quickly sum up the FDA proposal one more time for the benefit of the committee, and also a summation of FDA's risk-benefit data and then present the questions one more time to the committee.

You heard this many times now. I don't need to say it again. One hundred fifty thousand donors are deferred because of malaria risk, 40 percent for traveling to Mexico alone. The malaria had been in decline in Mexico the last many years where there were 2,300 cases, and those numbers are still the same for the current year, for 2009, for the most recent data.

There is a great disparity in the number of malaria cases reported from different Mexican states, and that is why we can treat different states differently in terms of donor deferral.

Again, the contribution of different states is highly uneven, and according to their survey, 85 percent of donors are deferred because they have traveled to Quintana Roo, with very low malaria transmission there. BSRI data shows somewhat different numbers, 37 percent, but these numbers are not surprising considering the locations of these blood centers and the proximity of these southern centers in the BSRI data. We were not surprised at all actually.

As you just heard a minute ago from Dr. Mark Walderhaug, FDA's model predicts a point estimate of .088 malaria-infected blood unit collections resulting from visits to endemic areas in Mexico; that's the entirety of Mexico.

Then you look at the breakdown with the data from REDS and BSRI, the risk estimate is .028 and .005, which is very low. Then if you meld the two data, the risk comes to .016 infected blood unit collections if the donors are allowed to donate blood after traveling to Quintana Roo without the current one-year deferral applied to them.

So to sum up again what you just heard, if prospective blood donors who visited Quintana Roo are allowed to donate blood without any deferral, the calculated risk of collecting infected blood units is predicted to increase from the current 1.5 to 1.53 for the REDS survey and 1.5 to 1.51 for the BSRI survey.

The predicted overall increase in risk for both surveys combined is from 1.5 to 1.52 infected blood collections per year. This means one additional case of transfusion-transmitted malaria in 36 years for the REDS survey, just to put it in perspective, one additional case in 180 years for the BSRI survey, and one additional case in 61 years for both surveys combined. So that would be the overall increase in risk. You might get one additional

case of transfusion-transmitted malaria if blood donation is allowed from visitors to Quintana Roo.

In return for accepting this small increased risk, the number of blood collections each year would increase by approximately 92,000 for the REDS survey and 42,000 for the BSRI survey and 72,000 for both surveys combined. This collection does not, as you heard again, take into account the additional gain in donors who self-defer themselves after visiting Quintana Roo or for any state in Mexico for that reason, or the failure of some donors who temporarily defer under the current policy to return, because the non-returning donors who are deferred is a bigger issue.

There are two additional points I wanted to make. I think from our perspective these are extremely important. They are as important as the rest of the FDA proposal:

In the future, if FDA might consider extending the exemption for travel to other low-malaria-risk Mexican states, if data show convincingly that substantial donor losses result from travel to states that remain at very low malaria risk, so that is given that the malaria situation does not change in the other states that we might consider in the future.

Conversely, FDA would reverse exemption from deferral of donors for travel to malaria-endemic states of

Mexico, if FDA becomes aware of a change in malaria transmission in Mexico that might increase the malaria risk for U.S. travelers. I would like you to go home with the message that this message is very important for us, also.

So again, just putting the questions back again to the committee:

Does the committee agree that, based on FDA's current risk-benefit benefit assessment and from the other two risk assessments you heard from Bryan Spencer and Brian Custer as well, it is acceptable to allow blood collection without deferral from U.S. residents who have visited Quintana Roo?

If not, then we would ask the committee to please comment on what other measures FDA might consider to reduce the donor loss from malaria risk deferral for travel to Mexico.

I will stop here now and take any questions.

DR. SIEGAL: It is time for questions. The floor is open. Tom?

**Agenda Item: Committee Discussion with  
Presenters**

DR. FLEMING: Dr. Walderhaug, if I could have you put your penultimate slide up, the one just before the acknowledgments.

I very much like the way you are kind of

summarizing the essence of what were very informative presentations throughout the morning. What I like about what you were doing was ultimately looking at what is the absolute risk, what's the risk of numbers of infections that would occur per numbers of transfusions? Basically, this number that you have here of the 3.3 million is indicating that would be three cases per 10 million.

Now, if we go back a slide, the question is, how do we put that into context? If we go back one slide, what you have in the far left is the current policy of 1.5 cases. From other data we have seen, that is in 15.7 million donations. I think you had said -- and I come up with the same numbers -- that translates into one per 10 million. So that's where we are, just as an anchor. We are currently, under current policy, having one infection per 10 million.

Just to also give context, what is the infection rate for people who are traveling to endemic regions? We have heard two figures. It is 1,000 to 1,500 in the United States, divided by 34 million, and that translates to somewhere between 300 to 400 per 10 million.

So just to kind of anchor all of the data that we're going to see, our current policy is giving one per 10 million. If you're a traveler to an endemic region, you're about 300-fold or two-and-a-half logs higher.



Now, what are we for Quintana Roo? The numbers are right there, and that's where you get the 3.3. It's .028 divided by 92,000, and that gives the overall calculation of three per 10 million. So if we allowed Quintana Roo, that's three per 10 million when right now we're dealing at one per 10 million.

Something that is not given -- it's interesting -- is look at Quintana Roo taken away from Mexico. That's .06 divided by 17,000. So if you look at all of Mexico except Quintana Roo, that's 35 per 10 million.

So you have basically four figures. What we currently have, one; what Quintana Roo would be, three; what the rest of Mexico would be, 35; and what a traveler to Mexico would be, which is 300. So basically, currently we are 300-fold less than the risk of a traveler to Mexico or traveler to endemic regions. We are 300-fold less. We would be tenfold less if we allowed Mexico outside of Quintana Roo. We will be 100-fold less if we allow Quintana Roo.

So, essentially, it helped me to use exactly your data but think of it in those terms. So, essentially, it's exactly as you're saying. It would be basically one case per 3.3 million, and by my calculation that would be 30 years. You said 36 years. But it would be 3 years for the Mexico minus Quintana Roo. But it's here 3.3 million, so

that would be basically, at 100,000 per year, it would take 30 years for one case to occur, and if deaths occur, one per 300, it would take 10,000 years for one death to occur or 1 billion transfusions in Quintana Roo to have one death.

Am I, I think, on the same wavelength as your summary?

DR. WALDERHAUG: I think that's pretty much a fair summary. My only point is that you're looking just at the REDS data by itself. For combining them together, it's an even lower risk.

DR. FLEMING: That's correct. If you use the other data, there is a factor of 2 to 4 decrease from what I'm saying.

DR. NELSON: I think the mortality rate from a transfusion-transmitted malaria in a susceptible host who has leukemia is more than one in 300, I think. But I agree with you overall.

DR. SIEGAL: Maureen?

DR. FINNEGAN: I have a question for Dr. Arguin. That is, since 2000, how many of the cases of TTM have been from U.S. citizens who traveled to Mexico?

DR. ARGUIN: None.

DR. FINNEGAN: Thank you.

DR. SIEGAL: Anybody else?

DR. ALLEN: A comment, not a question.

We have in our discussions this morning focused on the risk of collecting an infectious unit and, second, on the potential gain in terms of numbers of units of red cells that might be collected if we weren't deferring these donors.

There is one other issue, and that is that screening people in the donor room for risk of malaria from travel is administratively very difficult and time-consuming, and it is fraught with a lot of errors. We can, by making this change, simplify that considerably.

Now, it is better since there are the electronic maps available. That has simplified the process a bit. But it's still very cumbersome, and there are lots of callbacks after a unit of blood has been collected. The donor calls back and says, "You know, I went back, you asked where I had traveled and I've looked at it, and I was in these places." It turns one of them is in an area that has to be deferred. That unit of blood then has to be discarded.

But, administratively, that is a very difficult process. You cannot just throw it away because it has already been collected, it is in the system, it becomes a reportable error to the FDA, and so on, and creates quite a complex administrative hassle, and it is a relatively

frequent one in the blood-collecting system.

So this change will simplify the whole process a great deal at a very, very minimal risk increase of collecting an infectious unit.

DR. HOLLINGER: Can someone tell me how much dengue there is in Quintana Roo? Or in Mexico in general?

MS. TOMASHEK: I am not prepared to give you those numbers, but they do have a considerable amount of dengue in all of Mexico. This year they are actually having quite a big outbreak. But I don't have those numbers for you.

In 2007, for example, when we had our large outbreak with over 10,000 cases reported to us, they also in that year had a large outbreak along with the rest of the Caribbean, Central and South America, and they had several thousand cases reported.

The problem with dengue reporting, of course, is many of our passive surveillance systems, many of those cases are never confirmed, laboratory confirmed, because it is so overwhelming. So at some point you have to say, well, we have to make a clinical diagnosis.

But I can get you those numbers if this group would like numbers from Mexico to compare.

DR. SIEGAL: Colonel Rentas.

DR. RENTAS: I think I know the answer to this

question but just want to be specific here. When you're talking about 3.3 million units, you're only talking about red cells, you're not talking about the potential that we will be losing FFB and even platelets out of those units as well, correct?

DR. WALDERHAUG: We're estimating collections because a unit gets divided into multiple units. We are just talking about that single unit being collected at a time.

DR. ADAMS: So all of the data has been presented as annualized data. There must be seasonal difference as well, which would change the risk for different times of the year. Are there also climatic changes that could affect transmission rates in these areas?

DR. WALDERHAUG: Yes, there is some variability. I don't know the exact range and number of cases in Quintana Roo, but whether or not it would make sense to change deferral policies depending on the time of the year the traveler presented, I don't have that incorporated in the model and I can't answer that question.

DR. ADAMS: As a follow-up to that, is there any monitoring in place in Quintana Roo to see if there are significant changes in prevalence?

DR. WALDERHAUG: I believe the Mexican Ministry of Health has monthly, now weekly, updates of reported

malaria cases, so we do have access to some idea of the number of cases that are occurring per year.

DR. ARGUIN: If I could add to that answer, currently of the four cases that are reported in Quintana Roo, certainly being that the Mexican Ministry of Health does provide that data on a weekly basis, you could show the seasonality of the reporting of those cases. But it's a relatively small number, so I am not sure that would be particularly meaningful.

Also, you alluded in part of your question to climatic changes. I am not sure that would actually have a significant difference on malaria in that the *Anopheles* mosquito is already present, just like it is present in the United States. It is not simply the presence of that mosquito or the likely changes -- any sort of climatic changes don't really affect malaria maintenance in an ecosystem once the mosquito is already present. If malaria were to, let's say, be eliminated from a state, the mosquito is still present.

DR. ADAMS: I'm thinking in terms of a hurricane. I live in Florida, so it is something we think about, maybe not around here. So if control is largely based upon active abatement measures and then that breaks down following some sort of climatic event --

DR. ARGUIN: Malaria seems to go down sometimes

after hurricanes. You do certainly get loss of infrastructure, people don't have screens on their windows, et cetera, things like that. But you do also lose mosquito-breeding habitat, you have saline environments into areas that were fresh-water environments, so you do get actually a decrease in malaria sometimes after an event such as that.

DR. KUMAR: Maybe I can add a little to that for you. The effect of seasonality in Mexico is not as clear and prominent as one sees, for example, in Sub-Saharan Africa. There is not that clear a dry season and wet season where there is no malaria and then very high malaria after the rains.

So the other thing is the question how this would impact on donor deferral and also malaria risk in travelers. The data, I'm sure Brian Custer and Bryan Spencer can tell a lot more about that. The way they collected the data sampling sort of took care of that and equalized the data, because they collected every-other-month data, correct? Maybe, Bryan, you can tell a bit more about that.

MR. SPENCER: I was going to comment on the seasonality, how in many of the areas that were shaded on the maps I showed, it represented single-digits, sometimes less than a handful of cases. So looking at data that is

posted online every week with about a 2-week delay over the course of a year, if it's that few cases, the seasonality again isn't going to be terribly informative.

But as far as the surveillance and control, I want to note that the control has consisted of integrated measures, including aggressive surveillance, residual household insecticide spraying, and aggressive use of antimalarial medications where cases are identified. So that is looking to cut off the chain of infection in humans so that they don't remain infectious to mosquitoes.

Mexico countrywide looks at about 1.4 million blood smears a year, and Quintana Roo looks at -- I've seen estimates between 30,000 and 50,000 blood smears per year.

So the infrastructure is there, and they are looking. I saw online a report from a local Quintana Roo paper that was posted to the Internet talking about an outbreak where there were 13 cases in 2008, nearly all of which was attributed, for whatever reason, presumably taking a travel history, to people traveling from Oaxaca, Chiapas, Guatemala, and Belize.

So I think that they are looking, and they look at about 500 slides for each one that they find positive countrywide. So I do think that the surveillance and infrastructure are there.

I don't know if I got to the point that Sanjai



was asking about, but hopefully that provided some useful information.

DR. SIEGAL: Dr. Kulkarni?

DR. KULKARNI: I was just curious to know -- I mean a lot of folks from Canada also travel to these areas. Do they also have a policy like this, or other countries whose citizens travel to this particular area in Mexico?

DR. BIANCO: I can clarify that. They have a policy that is very similar to ours. However, their deferral rate is much higher because it is colder and they run away from the cold much more often than we do.

I wanted to ask Dr. Walderhaug another question. In terms of these analyses, you have focused entirely on Quintana Roo. I wanted you to tell us more or less why you restricted the analysis to this one state, and second, what kind of data -- you said that more scientific data would help, or Dr. Kumar, would help maybe extend these policies. What kind of data would you want to see in order to extend the changes in deferral?

DR. WALDERHAUG: I just wanted to let Dr. Kumar give a more complete answer. We were focusing on Quintana Roo because of the fact that it was a very high benefit-risk calculation for us in the sense that many, many travelers were going to Quintana Roo and being deferred in spite of its low risk. So I think that was the thinking

behind our analysis there.

In terms of the Ross Macdonald model that I was alluding to previously, there are lots of data that could be applied to this particular question in terms of going to individual malaria-endemic areas and gaining all this specific information. I cannot think of all the parameters that are in that model, but there are lots of them.

On top of that, we would also need to start trying to understand, as Brian Custer and Bryan Spencer started to do, is to look on a regional basis where how finely, how granularly, we would want to break up the model in terms of where people were traveling and their estimates, for example, of a conservative 2-week exposure. We could refine that further and figure out whether or not they were -- most mosquito bites occur at dawn and dusk, and we could quantify how often travelers were out at dusk and where they were when they were at dusk.

All this information would give us, with attendant uncertainties, a better idea of what the mean risk was. But I don't think that calculation, in spite of all the effort, would get us too much further away from where we are making our calculations at the present time.

Dr. Kumar?

DR. KUMAR: Well, I guess I would like to address the question in general why Quintana Roo alone.

Dr. Walderhaug did address it partly that the data was so glaring that the majority, 75 or 80 percent or so deferrals were occurring due to visits to Quintana Roo, and the malaria risk was so low.

With regard to other states, we do ask our blood establishments to send us the data, if they have data available, how much deferral is occurring due to travels to other states, so we will look at the data and also maybe blood centers at this point will become more aware, they will parse out the data and look at more details when they're collecting data on the travel from Mexico, which parts of Mexico they are going to, so in the future there will be more comprehensive data from blood centers that represent across the country. Then we will see, because we need to stay somewhere where we are comfortable looking at the risks and benefits. If we do accept some increased risk, we want to make sure that there is an equal amount of benefits too, or benefits do surpass the risks.

DR. BIANCO: But just one more thing. I think what Dr. Allen mentioned about the post-donation calls because of travel, this is 50 percent of all the post-donation information calls to FDA that come to -- I don't remember now the figure -- 20,000, 30,000 a year are related to travel deferrals. That's another component that should be added to the benefit increase to that, because

that tortures everybody, from the blood center, the hospital that receives the call, the patient that receives the unit, and for a benefit that is almost unmeasurable.

DR. SIEGAL: Dr. McComas.

DR. McCOMAS: So in relation to the possible suspension of a revision to this policy, I am just curious a little bit more about what would account for such a suspension, if there are sudden changes in malaria transmission patterns or a significant increase in the number of malaria cases in all of Mexico or in Quintana Roo or in states bordering Quintana Roo.

So I guess in looking at the data we've got 3 years back, and although Quintana Roo seems to be thoroughly stable, there's a lot of jumps in a lot of other places, and some of these would certainly count as significant. So I guess just a little bit more in terms of what the FDA is thinking what is going to count.

Then, second, in states bordering, I am also curious to what extent is the malaria rate in Belize being taken into consideration, given that it borders Quintana Roo?

DR. KUMAR: If we have a long view of malaria history, it's a very unpredictable disease, and we have to be cognizant that there could be -- people who are aware of the history of malaria in the fifties with the wider

display of WHO's involvement with DDT, malaria was wiped out from South Asia. I guess, if memory serves me well, from around 17 million cases in India alone every year, they have come down to a few hundred thousand.

Then things changed and they stopped the DDT intervention, then malaria came back raging within a few years. The same thing now in some parts of Tanzania, where infection rates used to be 40 percent, with the intervention from the Gates Foundation and other agencies, the rates have come down to 4 percent. But we don't know, if those interventions are taken away, how things may change -- ecologic, climatic changes, what may happen. So we want to keep a very close eye on it. So somewhat it will be subject to those factors, but then when it happens, we all will know it and we will see it clearly.

So it is very difficult to predict what those situations will be, but malaria has presented itself globally worldwide and it becomes very obvious that we need to listen to those changes. I think I would leave it at that.

In regard to Belize, I think that's a different question. I think that is perhaps a topic for another time, but right now we will try to monitor the situation within Mexico itself.

DR. SIEGAL: I have a question myself for

Dr. Arguin or anybody else who would like to answer it. As someone who lived through the early AIDS epidemic and the denialism that went through that and all the economic forces that would like to prevent knowledge of spread of diseases, especially in highly traveled areas, how reliable do you believe the primary data are in terms of really what's there? I mean are there enough checks and balances in your data-gathering to convince you that the primary data are good?

DR. ARGUIN: Yes. The one graph that I showed where it shows the two different data sources superimposed on each other does provide me with a fair amount of confidence that over an extended period of time they do tend to track each other quite well.

I have had some discussions with people in the Ministry of Health in Mexico, and based on those discussions and sort of knowledge of the level of the control efforts that they're doing -- Bryan Spencer was mentioning some of the control efforts they're doing in Mexico -- they go actually beyond a lot of other countries. In addition to, as you were saying, treating the cases very aggressively, also treating in sort of a ring fashion around, similar to the ring vaccination of smallpox. You get a case, then you also treat the family members, not just with agents against the asexual blood forms that are

the forms of malaria that cause the symptoms but also giving a round of primaquine to take care of the gametocytes, so transmission prevention as well. I have a fair amount of confidence in what they're doing in Mexico, that it's a very effective program.

With regard to the data in aggregate in Mexico, I also have a fair amount of confidence that what they're reporting is true. I think as you break it down smaller and smaller, you do get a little bit more uncertainty. I would say even if, let's say, in Quintana Roo they are off by a factor of 300 percent, that would mean they would have 12 cases instead of four. I am still okay that that's a very, very, very low number.

DR. SIEGAL: Thank you. Mr. Templin?

MR. TEMPLIN: I just have a quick question and a comment. Is there any test globally for malaria? You say there is no U.S.-licensed test. Is there any test globally?

DR. KUMAR: There is no U.S.-licensed donor screening test. In Europe there are antibody tests. Those are licensed. For direct parasite detection, CDRH has approved -- it's not a rapid detection test. So that's for diagnostic purposes but not for donor risk screening.

That doesn't mean that diagnostic tests are not used. For example, in 2007 or 2008 WHO used 25 million

rapid detection tests in Africa alone. So there is heavy reliance on a diagnostic test for malaria cure, but none of these are considered so far suitable enough or good enough for --

PARTICIPANT: Does species matter?

DR. KUMAR: Well, the species does matter, but the tests are mostly for *falciparum* malaria. There are some tests for *vivax* malaria. But no effort has been made to have a specific test for *malariae* and *ovale*. But a lot of times probably that is why we cannot with true certainty tell the prevalence of these two other malarias, *malariae* and *ovale*, because a lot of times their diagnosis is missed.

MR. TEMPLIN: Then I just had a quick comment. It seems to me that there's 150,000, approximately, donors that are deferred. If the blood-banking industry would do a better job to promote blood donorship as a sort of form of civic duty, they would make up the shortfall from those donors by new donors that would come on to be able to donate.

DR. SIEGAL: Dr. Branch.

DR. BRANCH: I think that the cost-benefit ratio is certainly convincing that the risk of having a malaria-caused infection by transfusion is very low. But I think this issue of granularity in the data and how careful



reporting is going to occur, and also the perhaps slowness, even in the best situation, slowness to detect an epidemic in a more rural area could help us to even maximize that ratio even more.

For instance, individuals who travel for more than 30 days to this area would be much more likely to go out to the fringe areas and to do that horseback riding that was unascertainable. I think that if you look at people who go to these areas and they report, "Oh, I went for 7 days," would perhaps have a truly minuscule risk, and the data reporting would be quite effective and accurate and fast in those areas.

The only question that I have, is it possible to ask a potential donor how long they traveled, and, if they traveled for more than 30 days, to have a little bit of a reservation under that circumstance.

MR. SPENCER: I would like to comment on that. In the REDS data that we showed for Quintana Roo and for most of the states presented, what really drives the risk estimate is much less the duration of exposure, whether it's the median time of one week or the conservative estimate of 2 weeks but, rather, the underlying level of risk.

One of my slides showed that in this ranking of states responsible for the deferrals, starting with

Quintana Roo, 75 percent, and then Guerrero, Nayarit, another 6 percent or so each, there's a 100-fold difference in risk adjusted for population for those states. Some of those states report zero cases. In those reporting cases, there's a 100-fold risk from Oaxaca to the lowest risk areas, Quintana Roo and whatnot.

So I do think that is important at one level, but at another level it is really the underlying level of risk that is driving the estimates, which as we see, even with modeling, are exquisitely small.

MR. KUMAR: So just to expand a little bit on that, Dr. Branch, your question is a very important one. So we are to see what are the in-built safety measures that are there that we rely on.

So the first thing is we rely on the data from the Health Ministry in Mexico. We are aware, as you said, there could be some delays in new malaria episodes or breakouts in new areas. But then again, the second line of defense we have is very important with CDC here, who keeps a very good tab on the malaria cases reported. So if we see a sudden increase not only in malaria in Mexico as well as bordering states where we are talking about here, but also the number of infections in those who are coming to this country from Mexico, if there is a dramatic increase there or a case of transfusion-transmitted malaria is

caused by travel to Mexico.

So I think all those things are there which we can keep an eye on, and I think the situation in Mexico monitoring is much better in Mexico than some other far-off country which would be a lot more difficult for us to monitor.

So having good safeguards and monitoring is going to be very important, and that's why we want to go stepwise, so we can monitor it for the time being.

DR. SIEGAL: Tom and then Celso.

DR. FLEMING: Dr. Walderhaug, could you put your previous slide back up again? I would like to just come back to the really important question about why was Quintana Roo the focus. I do think, just coming back to what we're seeing here, that there's a logic to it being the focus because, of all the cases that you're getting, only a third of them are occurring in Quintana Roo, even though 85 percent -- 92,000 of 109,000 -- 85 percent of all the donations come from Quintana Roo.

So, essentially, what this analysis is allowing us to do is to increase by half a percent the total donors from 15.7 million to 15.8 million, with a very small increment; i.e., with an increment of increased risk that is not very different from what it already is.

Dr. Allen made the point that this is also, from

a logistical perspective, important when you look at all the complexities that go through the screening.

It raises a question, and that is while the Quintana Roo versus non-Quintana Roo in Mexico shows a big gradient, there's a tenfold higher risk, so instead of being three per 10 million, it's 35 per 10 million. That is still only just under one per million case of malaria, even if we were allowing all of Mexico, and it raises a question in my mind, what is our standard? Obviously, our standard is extraordinarily rigorous to keep a blood supply safe, and allowing Mexico outside of Quintana Roo would only be adding another .1 percent to the supply, so it is not a huge added question.

But even though Mexico outside of Quintana Roo is tenfold the risk, it is increasing the risk from one-third per million to three per million. It is still basically one per million.

I guess the question for the committee, for the FDA, is, is that essentially our bar? The safety has to be essentially allowing something as serious as malaria one per million? Is that where we draw the line? If actually we are not that rigorous, do we make it even easier by saying, should the question be, do you allow all of Mexico? What's the line?

DR. SIEGAL: Celso?

DR. BIANCO: Thanks for asking these questions. We would like to know the answer. It is being very difficult, and that's something we've been talking about for the last 25 years.

I just want to remind the committee that the blood-banking community is very fast in reacting to a posting by CDC that there is a new area in which there was some malaria activity. Sometimes it's just a couple of cases. That was the case with Great Exuma and other incidents like that. There is immediately communication from the ABB, from the ABC, within ARC, to all the centers, and immediately those criteria are changed and those sites that are said to be a new potential source of malaria for travels are included in the deferral list.

DR. ADAMS: I have one question that came up briefly. It has to do with the risk for the transmitted cases. Is there any evidence that there is failure to respond to drug treatment that is contributing to this? And what is the role of the relapse? So is there a failure to radically cure cases with Primaquine as well as failure to treat the blood stage?

DR. ARGUIN: No, that has not been a factor.

DR. ADAMS: So in the cases of transfusion-transmitted malaria, they all respond to treatment when treated?

DR. ARGUIN: You're referring to the recipients, the people --

DR. ADAMS: Yes.

DR. ARGUIN: Yes. Once the case is detected and determined to be malaria, yes, they have been able to be successfully treated.

DR. ADAMS: And so there's no evidence of *vivax* chloroquine resistance in Mexico?

DR. ARGUIN: There is no evidence of chloroquine-resistant *vivax* in Mexico, that is correct. And we have not had a transfusion-transmitted case of *vivax* from Mexico. But, for example, I will say the case from Florida, for example, earlier in 2009, it was a case of *falciparum*, and that could then be treated with conventional treatments for *falciparum*.

DR. KUMAR: There are some recent studies, research studies -- I don't know if they are published yet or not -- by Dr. Tom McCutcheon(?) and Dr. Sue Winward(?) from NIH. They have found some evidence of chloroquine-resistant *vivax* in Mexico. How prevalent it is, I don't know.

The question of radical cure, obviously the four cases, at least the one I am fully aware of in the last 10 years who have cross(?) transmitted malaria, I mean, obviously they were asymptomatic carriers, so there was no

radical cure given to them when they came to this country, but there is no evidence that it was difficult to treat the recipients.

But, yes, if a radical cure is given to everyone upon return from endemic areas, that would solve the problem, but it is very difficult to say that that is going to happen.

DR. ARGUIN: Just to clarify that a bit, there are sporadic reports of drug-resistant malaria of all kinds all around the world. Where it becomes of concern, though, is when it becomes, if that becomes a predominant isolate that is sustained in that community. Currently chloroquine-resistant malaria is still a pretty rare phenomenon. There are only very small parts of the world where chloroquine-resistant *vivax* is an issue. Chloroquine-resistant *falciparum* is a different story, of course.

DR. SIEGAL: Maureen, you had a question?

DR. FINNEGAN: Dr. Kumar, I am going to put you on the spot. We're talking about a fairly flexible disease, and we're talking about tourism, which is a very flexible industry. So in 3 years we could be here sitting talking about Oaxaca as the next Quintana Roo.

Rather than having to do that, would the FDA consider using a combination of the CDC's Yellow Book, as I

think most people figure they actually know what they're doing when they write the Yellow Book, and the Ministry of Health from Mexico, and do a yearly -- these are the areas where deferral is required, and otherwise the rest of Mexico is not? I mean, those state and county pictures that were shown for 2007, I believe, were pretty impressive even for the high-risk states that there are a lot of counties that in fact do not have any malaria.

DR. KUMAR: So you are proposing to go by countywide rather than statewide?

DR. FINNEGAN: Whatever you're comfortable with, but rather than your having to bring this to committee every 3 years as the bug and the industry change, have a yearly philosophy where you say for 2010 the Yellow Book says X, Y, and Z, whether it's state or county, would be deferred, otherwise not.

DR. KUMAR: Thank you for bringing that point, actually. That's what we have in mind. The way we would proceed in the future is suppose the malaria situation does not change, and hopefully if it goes down, that's the approach we will take. But the reason we came to the committee this time is on the philosophical basis to knowingly accept an increased risk, albeit a very small risk, that's the question we are asking the committee. Hopefully, minor adjustments in the future we should be



able to deal with in consultation with CDC.

DR. SIEGAL: Dr. Glynn?

DR. GLYNN: I actually have a follow-up question to what Tom I think asked, and others. We are thinking right now, I mean we have a short-term kind of question in front of us which I personally think is rather easy to answer.

But the question is more long-term. What kind of increased risks are you looking for to say that there would need to make a change. Let's say that the committee and the FDA recommends that there is a change today. You're saying if there is a dramatic increase. Have you defined what that increase would be? And on the other side of the medal, which other states maybe would be willing to consider acceptance of donors traveling to those states, depending on the magnitude of the decreasing risk? What kind of decreasing risk would you like to see?

It is not clear to me that that has been defined. Is that something the FDA is going to do afterwards?

DR. KUMAR: Knowing the nature of malaria as a disease, it's very difficult to put a number or set a bar there. We would prefer those numbers to become zero. Then we don't have to do anything, no deferral will apply then. But it is very difficult to set the bar right now. If we say a 50 percent increase in a state, in some states it

will be two cases, 50 percent means one more case. We cannot say that we would reverse the policy then. But if those numbers become from two to ten or 20, then it becomes a log-four increase. A log-four increase in some states may become a very dangerous number, actually.

So just because knowing the number of risk is so small to begin with there, we have to consider it on a case-by-case basis. That's the best I guess I could say right now.

The way malaria can change itself, the way malaria can evolve, it is very difficult to comprehend in every single way right now, and that is why it is very difficult to give a final answer. But obviously it is not going to be very arbitrary, we're not going -- we just get ready and something happens and instead of 12 cases in Quintana Roo it becomes 17 next year, we are not going to change the policy. But we have to see if any dangerous trends, if *falciparum* malaria comes back in the area, if multi-drug-resistant *falciparum* is there, then we will consider the case certainly. If there is a change in mosquito populations there, if DDT-resistant mosquitoes become more prevalent, so we have to consider every single function(?) that is there.

DR. GLYNN: Right, so it sounds like you do have a formal plan. You just need to write it down, write the

various elements you're going to be looking at?

DR. KUMAR: Yes, okay, we will do that. I think that's a good idea.

DR. SIEGAL: Let's go to the open public hearing and then come back to further discussion.

**Agenda Item: Open Public Hearing**

DR. SIEGAL: I will have to read this document:

"Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency in the open public hearing session of the advisory committee meeting, FDA believes that is important to understand the context of an individual's presentation.

"For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include the company's or group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

"Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have such financial relationships.

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

I believe we have only one open public hearing speaker, and that is someone who is familiar to all of us, Dr. Louis Katz. Louie?

DR. KATZ: I am going to presume that the members of the committee know who AABB is and skip the boilerplate. In the interest of not repeating a bunch of data that you've hear now repeatedly, I am going to cut out large parts of AABB's statement.

A working group of the AABB Transfusion Transmitted Diseases Committee was formed to review the current status of risk for malaria in blood donors in the United States and to propose a strategy to balance the risk of malaria from transfusion reasonably with the loss of safe donors from a constrained donor base.

Proposals to amend the malaria deferrals, maintain acceptable blood safety, and allow continued use of donors at minimal risk of occult malaria can focus on several distinct aspects of malaria epidemiology. Rationalizing deferrals for travel to reflect current risks of infection, as FDA's proposal for Quintana Roo does, is the most straightforward and, frankly, welcomed of these approaches.

Modification of the current FDA malaria deferral policy to allow donations from donors who visit Quintana Roo is an important step in the right direction. We support the FDA's position on this issue and strongly believe that this change will increase blood availability without a material decrease in blood safety.

This proposed policy change is consistent with the position of the AABB Malaria Working Group from September of 2009 that was transmitted to the agency. Our principal recommendation based on malaria surveillance and modeling is that travel to most of Mexico and residence in Mexico for less than 5 years consecutively should not be cause for any deferral absent a clinical history of malaria.

CDC can provide guidance on the need to preserve deferrals for travel and/or residence in Mexican states where malaria control is less successful -- for example, Chiapas and Oaxaca -- and whether there are other countries with endemic malaria where the risk is low enough for a similar approach.

We encourage the agency to continue their evaluation of other areas in Mexico where we believe the data suggests it would also be acceptable to allow blood collection from U.S. visitors without deferral.

The AABB greatly appreciates the flexibility

demonstrated by the agency in the proposal under discussion today.

I am not allowed to ad lib. I am speaking for AABB. So now I am not speaking for AABB and speaking for myself. At one point several years ago I said in an open public forum, "Just give me back Mexico." I seriously never believed it would happen, and I wanted to express my personal thanks to the agency for bringing a very interesting and, I think, partial proposal to the floor.

Thank you.

DR. SIEGAL: Is there anyone else who wishes to speak in the open public hearing briefly?

(No response)

If not, let's proceed to the open committee discussion with questions for the committee and then a committee discussion.

**Agenda Item: Questions for the Committee**

DR. SIEGAL: Oh, I am sorry. Dr. Edwards. Well, it's time for you to talk anyway.

DR. EDWARDS: Thank you, Mr. Chair. I appreciate that.

I just had one question, and that was are we now talking then about the FDA changing the current policy from 1.5 to accept 1.53? And if that is part of the discussion, my question is, it seems to me that there were some

statistics that we showed TTM had decreased over the last 3 years. Was this policy established at 1.5 back over those last 3 years and that might be part of the reason why there is that decline? Or what are we saying here?

DR. WALDERHAUG: The 1.5 is a modeled risk as opposed to the reported risk. Dr. Arguin mentioned that we get a case about every other year, and as you can see, with 1.5 that would be more frequent.

So our policy is, my understanding, not set on a 1.5 risk. That's the risk that we're modeling what we're dealing with. The model deals with the fact that there are other things impacting the risk other than actual cases, that sometimes units of blood don't get administered that may have it.

I think it is also possible that the malaria parasite is cold-sensitive, so older blood might actually be safer than younger blood, for example.

So the 1.5 is what we think the risk is, but our point, I suppose, is that if we allow Quintana Roo to donate, that it is basically a 1.1 percent increase if we combine the data sets. That is a relative increase, and again, a relative increase is based on our modeled risk as opposed to the reported risk, and it is important to keep that in mind.

The second point is that that 1.1 risk really

represents only one case in about 60 years, and during that period of time there is a substantial benefit in terms of increased collections.

Does that answer the question?

DR. EDWARDS: Yes, and just for further clarity, in another 3 years as we look at the rest of Mexico, then will we be looking at a 1.51 rather than 1.50 because we have included Quintana Roo?

DR. WALDERHAUG: It's hard to say. This is our best interpretation of what the future is going to be like, but we don't know what the future is going to be like. So it's a usual number for relative comparisons, but I don't know if it's a fair reflection of what's going to happen necessarily.

DR. SIEGAL: Tom?

DR. FLEMING: The 1.53 is now off a denominator of 15.8 million, whereas the 1.5 is off a denominator of 15.7. So while 1.53 is a 2 percent increase over 1.5, you're having more donations; hence it is really only a 1.3 percent relative increase, which is what Dr. Walderhaug was correctly pointing out.

I asked a question I still don't know the answer to, and probably it is not easily answerable, and that is where is the bar for what we consider an adequate level of safety? Clearly, it has got to an incredibly high



priority, as everyone here is clearly committed to, to keeping the blood supply safe. Essentially, where we are now, not including Mexico, is a rate of malaria of about .1 per million, so one-tenth of a case per million. Quintana Roo will be somewhere between .1 to .3, so it is clearly below that one per million. The rest of Mexico lurks just slightly above one per million.

So if this committee were to act and say Quintana Roo can be added, actually increasing by 1 percent the relative increase in the global rate, then effectively the way we're acting on this then is if the rate is clearly below one per million, it is acceptable. If it's at or somewhat above one per million case of malaria per million donations, we're not there yet in terms of allowing it. That's essentially the way that we're proceeding if we say yes to Quintana Roo but not yes to all of Mexico.

DR. SIEGAL: Yes, Jim?

DR. ALLEN: I don't want to prolong the discussion and get into other areas, but if we're looking at this balancing of risks, based on what I've read in terms of the background materials that were provided and based on the presentations and discussion this morning, I would argue that a step that would increase the risk would be to permanently defer anyone who has a history of malaria --

PARTICIPANT: You mean decrease.

DR. ALLEN: Sorry, yes, decrease the risk by permanently deferring anyone who has ever had a history of clinical malaria, and perhaps also considering deferring permanently people who come from, born in, or lived extensively in malarious areas such Sub-Saharan Africa. So there are other steps that could be taken without the extensive analyses.

I personally am very comfortable with voting on the question that is being presented, which is very restricted. I would probably be willing to go today, based on what I've heard, to allow anyone who has had short-term travel to Mexico to donate without any restrictions.

DR. SIEGAL: Anybody else? Yes?

DR. ZIMRIN: I think that question of what risk are we willing to accept is a difficult one. The question that has been proposed today is much easier, because instead of just risk, we are talking about a risk-benefit ratio, which I think makes it a much simpler question.

But I agree it's tempting to think that the risk is still quite low, and I appreciate the FDA's willingness to continue to monitor the situation and adjust their policy as more information is obtained and more stable trends become obvious.

DR. SIEGAL: Tom?

DR. FLEMING: I definitely agree. When I refer to the risk level, I'm thinking of it as risk-benefit. It's for the benefit achieved by 1 million transfusions, what risk in malaria are we willing to accept? Essentially, if we vote yes for Quintana Roo but not broader than that, essentially we are drawing the line at as long as we have a risk clearly less than one case of malaria per the benefit a million transfusions, we accept it; when it is at or above that, we're not ready yet. That is essentially the way we're functionally acting if we say yes to Quintana Roo but not the rest of Mexico.

DR. SIEGAL: Dr. Epstein, do you have any things to add to this discussion?

DR. EPSTEIN: Not really. I think all the key points have emerged in the discussion, and really the salient point is that we're not putting forward an absolute level of risk acceptance. We're looking in relative terms and we're trying to find a zone of comfort. That is why we are looking for a recommendation of the committee.

FDA is saying, well, that's within our zone of comfort. This is a treatable disease, after all. It's transmitted at a low rate, and are we prepared to accept a very slightly higher rate, again given that it's low in absolute terms?

But I don't think we're in a position to tackle

absolute risk acceptance, even though this may be the forme fruste of such a discussion.

DR. SIEGAL: All right. Yes?

DR. PARISE: I just had one comment. I would caution against this absolute number just for two other reasons. One, the quality of data that you're going to get, say if you start talking about other countries, is going to be very variable. I think that I would argue to let FDA and CDC make that judgment. We have good data from Mexico. There are other countries that we aren't close to that.

DR. SIEGAL: Thank you. Any more discussion before we go to the question?

(No response)

Then let's proceed to the question.

DR. FREAS: While he is getting ready to read the question for the record, let me go over how we're going to vote.

At the current time there are 18 voting members sitting at the table. In front of each voting member there should be a little, small card with many buttons on it. If you would like to vote yes, you will be pushing 1A. If you would like to vote no, you will be pushing 2B. If you would like to abstain, you will push 3C.

DR. SIEGAL: We will read it.

DR. FREAS: We'll read the question before the vote.

MR. KUMAR: The question is: Does the committee agree that, based on FDA's current risk-benefit assessment, it is acceptable to allow blood collection without deferral from U.S. residents who have visited Quintana Roo?

DR. FREAS: Go ahead and vote. Please let me know when all votes are tallied.

(Committee members voted.)

DR. FREAS: We have 17 yes votes, one no vote, and nobody abstained. Could we have the names, please? I'll just read the name of the no vote.

I have lost confidence in modern technology ever since they took away my rotary telephone.

(Laughter)

DR. SIEGAL: We could ask for the volunteer to step forward. So Mr. Templin was the one no vote.

DR. FREAS: For the record, there were 17 yes votes, one no vote. Mr. Templin was the no vote and everybody else voted yes. That ends the voting. Thank you.

DR. SIEGAL: Thank you.

DR. KUMAR: Thank you to the committee.

DR. SIEGAL: We do not have to proceed to the second question.

Is there any other commentary on this discussion?

DR. NELSON: Yes. I would like to get back to an issue that Jim raised, and that is I think that the cost-benefit would be even much greater in terms if there was a permanent deferral for people who had had a diagnosed case of malaria, which would be a very small number of donors, I think. But showing the different distribution of *malariae* infections that have a long incubation period and can relapse, and *vivax*, et cetera, I think that -- and the fact that many European countries, including France that has a much higher risk of transfusion-transmitted malaria, is now a policy. The U.S. policy is deferral for only 3 years, and I think that it would -- if you want to increase the at least public perception of donor safety, transfusion safety, moving to permanent deferral of those who had a diagnosed case of malaria might be a way to go.

DR. SIEGAL: Other comments?

DR. HOLLINGER: Kenrad, also, I think on that same thing, the risk appears to be also higher in those who go visit friends and relatives than those that have tourism, which is another kind of question that could be asked in terms of deferral too, although not maybe for a permanent one. But I agree with your other comment.

DR. NELSON: Right. I've seen many cases of malaria, not transfusion-transmitted but people who came

back from visiting their relatives in Africa or India. So this is clearly a major cause of the 1,500 cases of malaria that are reported in the U.S. every year.

DR. SIEGAL: Other comments from the committee or elsewhere?

MR. SPENCER: I didn't have time to get this into my slides before I forwarded them to FDA, but a salient point which I should have mentioned during my talk, regardless of not having a slide, is that for the REDS data we did collect country of birth, and we have that for the overall set of 2,000 deferrals. We haven't looked at it just for those 900 deferred for travel to Mexico. But of those 2,100 deferred donors, there are 11 who say they were born in Mexico. So even assuming all of those 11 were deferred for travel to Mexico, then we have at most a 1 percent VFR population in these deferrals, whereas Dr. Arguin noted that more than half of the malaria diagnosed in returning travelers from Mexico are VFR travelers. So 1 percent or so of the deferrals are part of that relatively higher risk population.

DR. SIEGAL: Any further commentary?

Have a nice lunch. We'll be back at 1:30.

(Whereupon, at 12:20, the meeting recessed for lunch)

A F T E R N O O N   S E S S I O N   (1:30 p.m.)

DR. SIEGAL: Good afternoon. I hope everyone had a nice lunch. Let's embark on Topic II, study designs (Phases 3 and 4) for product development of human platelets using the Cerus INTERCEPT Blood System for Pathogen Inactivation.

Before we do that, I think Bill has something to say.

DR. FREAS: The conflict of interest statement that was read into the record this morning remains in effect for this afternoon, with the following addition:

Colonel Rentas has requested that, as a representative of the Department of Defense to the BPAC, it is appropriate that he recuses himself from the discussions involving those in topic II of today's BPAC session. So he will not be participating in the afternoon session today because of a conflict of interest with his employment.

Next, you will notice the table has changed slightly. I would like to welcome to the table Dr. Jonathan Sevransky, Assistant Professor of Medicine, Division of Pulmonary and Critical Care, Department of Medicine, Johns Hopkins University.

There is an empty chair, third from the end, which will soon be filled by Dr. Jason Christie, Assistant Professor of Medicine, Pulmonary, Allergy, and Critical



Care Division, University of Pennsylvania.

Everything else from the morning remains in effect. Back over to you.

DR. SIEGAL: Thank you, Mr. Freas.

**Agenda Item: Topic II: Study Designs (Phases 3 and 4) for Product Development of Human Platelets Using the Cerus INTERCEPT Blood System for Pathogen Inactivation**

DR. SIEGAL: For the introduction, we will go to Jaro Vostal of FDA.

DR. VOSTAL: Good afternoon. This afternoon we are going to discuss the evaluation of pathogen-reduced platelets. This product is made by Cerus Corporation.

My introduction is going to cover the FDA perspective on pathogen-reduction concepts in general, and then I will talk about some of the specific clinical trials that were done with the Cerus pathogen-reduced platelets.

To start off with, this is the state of the art for pathogen-reduction platelet products. Currently the way this method is done is that there is an addition of a pathogen-reduction chemical to a product that is thought to be contaminated or possibly contaminated with pathogens. This chemical interacts with nucleic acids, and upon activation of this chemical with UV light, it can crosslink nucleic acids and prevent proliferation of various pathogens.

So after this treatment, the product is thought to be much reduced in terms of pathogen contamination, but in addition to reducing the pathogen load, it is also possible to get collateral damage to the transfusion products. This is one aspect of the pathogen reduction that is not frequently discussed.

Because of potential problems or potential damage to the transfusion products, there are some general concerns about the chemicals and the UV-lights-based pathogen-reduction methods. The pathogen-reduction process creates a novel mixture of chemicals and biologic products that is infused intravenously to a wide range of patients of different ages and different states of health.

There are now known effects of pathogen reduction, and these are that pathogen-reduction chemicals are not specific for nucleic acids and can bind to proteins, lipids, and cell organelles. Also, UV light energy can damage cells. So we know that some of this collateral damage that takes place could have negative effects on the performance of these transfusion products.

The concerns that we have are that the treated cells may lose efficacy, and for platelets it would be an increased bleeding in thrombocytopenic patients. The treated cells may have altered in vivo kinetics and distribution, and this could mean that different doses and

transfusion frequencies may need to be modified. Finally, transfused patients may also have unexpected adverse events.

Now, when we are evaluating pathogen-reduced products, at the end we will look at the benefits versus the risks of using these products. The potential benefits of these products are the reduction of the current transfusion-transmitted disease risks. You can see that actually the current risks are quite low, especially for viral-based agents. You can have frequencies of one per 2 million, and this can decrease down to one per 300,000 for HPV. The highest risk for transfusion-transmitted disease now is bacterial sepsis. This comes in at about one per 80,000 transfusions. So that is the current risk.

There is also a potential for benefit of pathogen-reduced products in terms of dealing with emerging pathogens. However, it is very difficult to quantitate the benefit you get from these types of products if you don't know which pathogen you're dealing with at a particular time.

These are the potential benefits, and they will try to offset any comparable risk that would be from the toxicity or adverse events associated with these transfusion products.

So that is our general concept in terms of

evaluating pathogen-reduced products. Now I am going to start talking specifically about the Cerus S59 pathogen-reduced platelet transfusion products. This product, S59, is the chemical that gets added to the transfusion product, and it is then activated by UV light.

The evaluation process started over 10 years ago, and it started with Phase 1 preclinical trials. They identified some moderate lesions in platelet in vitro studies. But it is difficult to predict from in vitro studies how these products are going to perform in the clinic, so the product moved into Phase 2 clinical studies.

Phase 2 studies involve radiolabeling studies in human volunteers to define the platelet kinetics; that is, the recovery and survival of the pathogen-reduced products in circulation. This type of study, however, does not assess the ability of the treated platelets to participate in hemostasis.

In order to be able to get at that aspect of the evaluation, we have to move to Phase 3 clinical studies, which do assess the ability of these cells to participate in hemostasis, and they also identify any types of adverse events and toxicity. The study that was done with the Cerus S59 platelets in the U.S. was called a SPRINT trial, and it was a randomized, blinded, controlled study.

Besides this Phase 3 study done in the U.S. there

are also other clinical studies that have been done with these products, and they are available for our evaluation. I am going to talk about several of these. The ones that were randomized and controlled were both done in Europe. The first one was called a euroSprite trial, the second one was called the HOVON 82 study done in the Netherlands, and we are going to hear more about the study later on today.

Finally, there are also observational studies that don't have that concurrent control. These are coming from the current clinical use of these products in France and Belgium, and the efficacy and safety of those products are captured through hemovigilance studies.

To get a little bit more detail in terms of the results of the Phase 2 clinical trials, this was a study that utilized healthy volunteers. These volunteers came in and donated a platelet product by apheresis. The product was then treated with the pathogen-reduction process, was put on the shelf for up to 5 days, and a small portion of that product was then sampled at that point, radiolabeled with a tracer, and reinfused into these human volunteers. Those volunteers then donated serial blood samples to be able to determine the survival of those products in circulation.

If you look at the control platelets, the recovery of those platelets at time zero was estimated to

be 50 percent. In comparison to the treated products, the recovery here was 43 percent. So a relatively modest decrease of about 15 percent.

If you look at the survival for the control platelets, it was about 6 days. This was reduced to 4.8 days, about a decrease of 20 percent. So taken individually, these differences are relatively minor.

However, if you look at the area under the curve of the product, and that will be having recovery on the Y-axis and survival on the X-axis, and this area under the curve represents the amount of time those platelets spend in circulation, with these minor reductions in recovery and survival, there is about a 30 percent reduction in terms of the area under the curve.

After the Phase 2 studies, the product moved into the Phase 3 clinical trial. This was a blinded, prospective, randomized study with apheresis platelets. These were conventional platelets stored in plasma versus the S59 Cerus platelets. It was a large study, had 645 patients, and 76 percent of these patients were stem cell transplant recipients.

The primary endpoint of this study was proportion of patients with Grade 2 bleeding as assessed by a standardized scale. There were secondary endpoints which had additional hemostasis parameters and also monitoring of

adverse events.

This table shows the results, or a brief summary of the results of the SPRINT study. The primary endpoint was proportion of patients with Grade 2 bleeding. The study met the primary endpoint because it was non-inferiority study, and this P-value represents that the treated platelets were not inferior to the conventional platelets.

However, there were a number of secondary kinetic and hemostatic parameters that did not support the primary endpoint. For example, if you looked at the days of Grade 2 bleeding in these patients and the mean number of days of Grade 2 bleeding, the patients in the treatment arm had 3.2 days of bleeding versus 2.5 days in the conventional platelet arm, and that was statistically significant.

If you looked at the number of platelet transfusions in the treatment arm, it was about 30 percent greater than in the conventional arm, and this actually corresponds very nicely to the number we saw of the area under the curve in the radiolabeling studies.

There was a significant increase in number of platelets used, and that is because the patients in the treatment arm required more platelet units, which was 8.4, versus 6.2 in the conventional arm, and more frequent transfusions of 1.9 days versus 2.4 days.

The decreased response of the products transfused to these patients was reflected in their corrected count increments. If you compare the corrected count increments at one hour, it was 11,000 for the treatment arm, 16,000 for the conventional arm. If you look at the 24-hour CCI, it was about 7,000 for the treatment arm, about 10,000 for the control arm. These differences are all statistically significant.

Finally, if you compare the number of patients who were determined to have platelet refractoriness, which is actually two consecutive transfusions with a CCI response of less than 5,000, it was 21 percent in the treatment arm versus 7 percent in the control arm.

As a result, the primary endpoint suggested that these platelets are equivalent, but the secondary endpoints were actually giving us mixed signals in terms of being able to demonstrate that these platelet products are equivalent in terms of hemostatic efficacy and in the kinetic parameters.

This study also measured hemorrhagic events and captured hemorrhagic events in a different way. It captured them through the adverse event monitoring. In this study the adverse event monitoring was done by the NITTC scale for measuring severity of adverse events. The bleeding events were graded through zero to Grade 4. If



you look at individual grades, these are compared in terms of their difference statistically.

An initial valuation indicated that there was no statistical difference between these grades when they were taken individually. However, if you break them down into minor bleeding events, which would be no bleeding or Grade 1 bleeding, and clinically significant bleeding events, which would be Grade 2 through Grade 4 bleeding, there is a statistical difference in the number of patients who had this Grade 2-to-4 bleeding, and it is 113 versus 138, and this was a statistically significant difference going against the treated platelets.

So again, we've got another mixed signal in terms of being able to support the primary endpoint for that clinical study.

To summarize the hemostatic effectiveness of the S59 platelets in the SPRINT clinical trial, the study met the primary endpoint, which was proportion of patients with Grade 2 bleeding, but the study failed other indicators of platelet efficacy, and these were increased number of days of Grade 2 bleeding, increased number of patients with Grade 2-to-4 bleeding.

In terms of kinetic parameters, there was increased platelet utilization, 30 percent over the control arm; decreased time between transfusions; decreased post-

transfusion platelet count response; and an increased number of platelet refractory patients.

Besides looking at the hemostatic effectiveness, the study also monitored the adverse events. These were reported by blinded observers of the patients involved in the study. The adverse events were coded according to the Medical Dictionary for Regulatory Affairs. They were compared between the treatment and the control arm.

There were close to 900 terms that were compared between the two groups, and out of these 900, 11 turned out to be statistically different between the two groups. In all 11 cases, the statistical difference went against the treatment arm. You can see some of these. These adverse events include the ones that were statistically different, and you can see that there are also bleeding-related adverse events such as petechiae, fecal occult blood positive, and mucosal hemorrhage.

Out of these 11, there were four that were graded as Grades 3 and 4 or clinically significant adverse events. These were hypocalcemia, syncope, pneumonitis, and acute respiratory distress syndrome, also known as ARDS.

Out of these four, ARDS was the one we were most concerned about because a diagnosis such as ARDS carries a relatively high mortality. So the frequency of ARDS in this study was reexamined again by the sponsor. The

initial prospective blinded evaluation of the patients during the clinical trial identified five cases of ARDS in the treatment arm and zero cases in the control arm.

A retrospective review of selected medical charts by a blinded expert panel reidentified, separated the events into acute lung injury or ARDS. This reanalysis identified 19 cases of ALI in the treatment arm and 16 cases in the control arm. Out of these 19, 12 were identified as ARDS, versus five were identified as ARDS in the control arm. So the statistical difference between the ARDS cases went away after reanalysis, but you can see that there is still a two-and-a-half times increased frequency of ARDS associated with the treatment arm.

These are the FDA conclusions from evaluation of the SPRINT clinical trial. These are that the efficacy of S59 platelets in controlling bleeding is not confirmed compared to conventional apheresis platelets, and that secondary bleeding endpoints and transfusion responses suggest reduction of efficacy of the S59 platelets.

The adverse event profile is not favorable towards S59 platelets, and we have concerns over clinical Grade 3 and 4 adverse events and particularly over ARDS.

There are additional studies that utilize S59 platelets to examine the efficacy and safety of these products. One of these studies was done in early 2000, and

it was called the euroSprite study and was done in Europe. This was a blinded, prospective, and randomized study. It utilized plasma stored buffy coat platelets versus S59-treated buffy coat platelets and was a relatively small study with a total of 103 patients. Thirty-five percent of these patients were stem cell transplant recipients.

The primary endpoint of this study was that corrected count increment, or CCI. The secondary endpoint was hemostasis in adverse events.

The results looking in terms of CCI, the one-hour results were 13,000 in the test arm of the study versus 15,000 in the control. This was not statistically different. However, at the 24-hour CCI, it did have a statistical difference that it was about 7,000 in the test arm and about 11,000 in the control arm. So again we are getting mixed signals in terms of efficacy from this study. The CCI at one hour is equivalent and at 24 hours is not equivalent.

In addition to monitoring CCI responses, the study also looked at hemostasis adverse events. Overall there was no statistical difference in total hemostasis adverse events, but 90 percent of these adverse events monitored went against the test product.

Currently there is use of S59-treated platelets in Europe. This has been going on for several years now.

The safety and efficacy of these products is being monitoring through the European hemovigilance system. So that is actually a data set that is available for us to examine in terms of trying to resolve some of the issues that were identified in the SPRINT Phase 3 U.S. study.

In the hemovigilance studies, at least these reports reported patients -- there are about 600 patients in this report and 1,400 patients in this report compared to 300 in the U.S. SPRINT study.

The patient population is quite different because 70 percent of the patients in the SPRINT study were stem cell transplant recipients, as opposed to 7.2 versus 8.6 percent in the hemovigilance studies.

If you look at the reaction rate monitoring, or at least reaction rate reporting, over 99 percent of the patients in the SPRINT study had a reaction reported. When you compare that to reaction reports from the hemovigilance study use, it is only 6.5 percent here and 3.2 percent here, so a significant difference in terms of reporting reactions.

Reports of platelet-related reactions, it was 26 percent of patients in the SPRINT study had platelet-related reactions versus 5 percent in the hemovigilance studies and 3 percent in this hemovigilance study.

Finally, if you look at the percent of patients

with serious reactions, it was 27 percent in the SPRINT study versus .5 percent and .3 percent in the hemovigilance studies.

So there are differences in terms of being able to report adverse events associated with transfusion of these products. It is not clear whether this is due to the level of monitoring between the two studies or whether it's the difference between the patients that are enrolled in these studies.

Finally, the most recent study that utilized S59-treated platelets was the HOVON 82 study, which was conducted in the Netherlands in 2007. This was a prospective and randomized study that utilized buffy coat platelets stored up to 7 days. However, the data that we're going to hear about today is platelets stored only up to 5 days.

The study involved three arms. The first arm, the control arm, was plasma-stored platelets. The next arm was additive solution-stored platelets. Finally, it was additive solution-stored platelets with S59 pathogen-reduction treatment.

This study identified significant differences between control- and S59-treated platelets in terms of CCI counts and bleeding scores, and the difference was significant enough for the study to be halted by the Safety

Monitoring Board of the study.

We will hear a full report on this study coming up later in the discussion.

This is the overall FDA evaluation of the S59-treated platelets: S59 pathogen-reduction process damages platelets; the damage results in reduced circulation of treated platelets which leads to lower corrected count increments and more frequent platelet transfusions.

Hemostasis appears to be impaired after S59 treatment of the platelets in comparison to conventional platelets due either to low platelet counts or loss of platelet efficacy or a combination of both.

The S59-damaged platelets appear to be associated with acute respiratory distress syndrome, hypocalcemia, syncope, and pneumonitis not otherwise specified.

The final conclusion is that an additional Phase 3 clinical is needed to resolve the hemostasis efficacy and adverse event profile of the S59-treated platelets.

That concludes my introduction. I would just like to focus your attention to the questions that we're going to be asking the committee. The initial question is the overall product development plan includes pre- and postmarket studies to resolve the safety and efficacy concerns raised by the outcomes of the SPRINT study.

For the premarket evaluation, the Phase 3 study

is designed to provide sufficient information to evaluate safety and efficacy. This is a new Phase 3 study design. The question is, is acute lung injury (ALI), inclusive of ARDS, an appropriate safety endpoint?

If yes, is the proposed magnitude of the differences between the treatment and control arms acceptable; namely, a difference less than 5 percent and less than a doubling of the ALI rate? The next question is: Is mean days of Grade 2 bleeding an appropriate efficacy endpoint?

The second questions we will be asking to the committee are: Does the committee agree that, A, the conduct of a postmarket study to exclude a 1 percent increase in ALI compared to the control group will provide meaningful additional safety data? And does the committee agree that, B, a staged rollout is a prudent and necessary approach to the initial commercial launch of the product?

So those are the questions we will be discussing later on.

This is the agenda for the rest of the discussion, so I just concluded the introduction. The next topic will be a talk about the mechanisms of platelet-mediated acute lung injury. This will be followed by the description, a full description of the study that was done in the Netherlands. Then the sponsor, Cerus, will have



their presentations. Finally, FDA will discuss the new Phase 3 clinical trial protocol in terms of the study design and the statistical plan design.

Thank you very much.

DR. SIEGAL: Thank you, Dr. Vostal. Are there questions for Dr. Vostal from the committee at this point? If not, then let's proceed to the presentations.

The next presenter will be Klaus Ley from the La Jolla Institute for Allergy and Immunology, speaking on the role of platelets in acute lung injury. Dr. Ley.

DR. LEY: Good afternoon. My name is Klaus Ley. I am a professor and head of the Division of Inflammation Biology at the La Jolla Institute for Allergy and Immunology. I study the role of platelet neutrophil aggregates in acute lung injury.

Acute lung injury is defined as an acute-onset bilateral infiltration on chest radiographs with no clinical evidence of left atrial hypertension. ALI is often defined as a ratio of  $\text{PaO}_2/\text{FiO}_2$  less than 300, whereas ARDS is more severe, and then this ratio goes under 200.

The incidence is about 78.9 per 100,000 person-years, and the mortality is still 38.5 percent, which translates into about 190,000 cases per year in the United States, of which 75,000 die.

The acute lung injury is caused by damage to the alveolar-capillary barrier. It is associated with the neutrophil recruitment, which is partially dependent on adhesion molecules such as ICAM-1 in endothelial cells and LFA-1 on the neutrophils.

Different inflammatory mediators that are involved include tumor necrosis factor alpha, interleukin-8, platelet activating factor, and thromboxane. There are also abnormalities in the coagulation system.

This is taken from a review in the *New England Journal of Medicine* by Ware and Matthay. It outlines some of the important players in acute lung injury. On the right-hand side here, breakdown of surfactant, apoptosis and necrosis of wall cells, especially type 1 cells, and formation of hyaline membranes and then accumulation of protein-rich fluid or lung edema.

We studied in mice a model of acute lung injury. This is an acid-induced model which has some similarity to the clinical situation of aspiration of gastric contents. In this model hydrochloric acid at a pH of 1.5, which is similar to what you find in the stomach, is instilled into the trachea, and then the mice are ventilated with mechanical ventilation under controlled conditions. Then blood samples and lungs are harvested so that parameters of lung function can be measured.

When you look at these lungs systologically, they don't look all that bad. There is not a whole lot of neutrophil infiltration. It doesn't look as bad as, for example, in LPS inhalation. However, there is significant edema and the model is so severe that after 3 hours all mice that received this treatment are dead -- this is just a Kaplan-Meier survival curve -- whereas all the control mice that received saline are alive.

So the first inkling of what was going on there came from a depletion study with busulfan, which is a bone marrow suppressant. Eleven days after treatment, you can get a reduction in platelet counts. Under these conditions, the oxygenation was improved. As you can see here, this is the vehicle control and this is the platelet depleted. Also, the number of neutrophils in the BAL and the bronchoalveolar lavage fluid was reduced in the platelet-depleted group.

Depletion was repeated with an antibody, so antibody depletion had the same effect as this bone marrow suppressant.

This also translated into a benefit in terms of lung edema as measured by total protein in the bronchoalveolar lavage fluid. You can see here that both methods of platelet depletion moved this toward normal, although it did not quite reach normal. These are the

untreated mice.

When we focused on the neutrophils, we found that many of these neutrophils, after hydrochloric acid-induced acute lung injury, were actually decorated with platelets. This is fairly easy to measure. You can simply do flow cytometry. Neutrophils do not express CD41, which is part of the platelet integrant, but you see a lot of CD41-positive platelets that are neutrophils, identified as GR-1 positive, 7/4 positive cells in green, whereas very few in the control. The filled red curve is the isotype control.

When you look by electron microscopy, you find neutrophils that are decorated with platelets also in the lungs. You can show that the number of neutrophils that are decorated with platelets goes down dramatically when platelets are depleted.

There are many factors that mediate platelet aggregation or platelet interaction with neutrophils. This is a slide that is taken from a textbook chapter than I wrote on the subject of platelet-neutrophil and platelet-monocyte interaction. I don't have time to go through all of these mechanisms, but the first-order mechanism and the most important one of these is the interaction of platelet P-selectin, which is an adhesion molecule that comes up on activated platelets, with considerably expressed ligand for P-selectin called P-selectin glycoprotein ligand-1, or

PSGL-1, expressed on neutrophils.

Again, the first indication that this was important came from the use of a P-selectin antibody. When we used a P-selectin antibody in this hydrochloric acid-induced model, we saw that the number of CD41-positive or platelet-decorated neutrophils went down dramatically after this treatment with a P-selectin antibody but not with an isotype-control antibody. Of course, this antibody interacts with the lectin domain of P-selectin and blocks the interaction with the ligand PSGL-1.

Now, does this do any good clinically? It increases the PaO<sub>2</sub> over FiO<sub>2</sub>, so improves oxygenation. It reduces the number of neutrophils in the bronchoalveolar lavage fluid, and it also reduces the lung edema as measured by the total protein content in the BAL.

P-selectin is expressed on both endothelial cells and platelets, so in order to figure out whether the platelet P-selectin specifically was important, we constructed bone marrow chimeras in which P-selectin knockout bone marrow was put into lethally irradiated wild-type mice to generate mice that had only endothelial P-selectin or, alternatively, wild-type bone marrow was put into lethally irradiated P-selectin knockout mice, so these mice have only platelet P-selectin, or knockout bone marrow was transplanted into knockout mice so that these mice had

no P-selectin at all.

I show these with these little symbols, so the gray mouse with the green dots only has endothelial P-selectin, and the green mouse with the gray dots only has platelet P-selectin.

When you look at this, the disease really tracks with the platelet P-selectin, because when you look at the oxygenation, you see that the mice that do have platelet P-selectin are worse off, significantly worse off, than the mice that don't have platelet P-selectin.

It is maybe even more impressive in the lung edema as measured by the BAL total protein, so the total protein content in the bronchoalveolar lavage fluid is high when platelets express P-selectin, and it doesn't really matter whether endothelial cells also express P-selectin or not, but it does not track with endothelial P-selectin.

Indeed, platelet P-selectin also determines neutrophil accumulation in vivo. This is measured by a flow cytometry method that I don't have time to go into in details, but you can use injection of monoclonal antibody into the blood of the mice to determine which of the neutrophils are intravascular versus extravascular. You find again that platelet P-selectin determines accumulation of these cells, although in this case the endothelial P-selectin also participates. So when endothelial P-

selectin is also present, you get more intravascular neutrophils than when it is not, whereas in the BAL the number of neutrophils tracks with the P-selectin expression on platelets, not with the P-selectin expression on endothelial cells.

How does this work? For this we resorted to some in vitro studies in which cultured lung endothelial cells were incubated with neutrophils or platelets or both, and we measured the neutrophil adhesion. So platelets by themselves don't do much for neutrophil adhesion. But when either the neutrophils or the platelets or both are activated, you get a very large increase in neutrophil adhesion.

This is partially reduced by a blocker of TP which is the receptor for the thromboxane A<sub>2</sub>. This is true whether the platelets were incubated with activated neutrophils or the activated platelets with neutrophils. I think this would be the relevant bar here. This is thromboxane A<sub>2</sub> dependent.

So if this is true, then probably these platelet-neutrophil interactions induce some adhesion molecules. A good candidate on the endothelial cells would be ICAM-1, so we measured the messenger RNA for ICAM-1. That is expressed here as fold induction over control. When at least one cell is stimulated, so either the neutrophil or

the platelet is stimulated, and when you add activated platelets with neutrophils -- this is the highest part here -- then you get about a 3-to-4-fold elevation in expression of ICAM-1.

Again, if this is through thromboxane A<sub>2</sub>, it should be possible to measure this. Now, thromboxane A<sub>2</sub> is not stable, but it forms a stable product, thromboxane B<sub>2</sub>, which you can measure by ELISA. You can see that whenever platelets are activated or neutrophils are activated or both, you get a quite significant amount of thromboxane B<sub>2</sub> in the cell culture media as compared to controls.

Maybe the more impressive is the visual, so we can use a thromboxane-A<sub>2</sub> analogue, U46619, which after 15 minutes at moderate concentrations already causes these rings of F-actin in human pulmonary endothelial cells, and after 30 minutes we get a similar picture. So these cells contract, which is probably the pathophysiological substrate of the lung edema, because when the endothelial cells contract, you get holes between them, and that's where the fluid and the protein leaks out.

This is a quantification of these same data. You can see, when either the platelets are activated, second-to-last bar, or both the neutrophils and the platelets are activated, you get a large amount of fluorescence, which is the measure for the polymerized actin, and it shows this



endothelial cell contraction.

So if this is true in vitro and it is relevant, then we should also be able to measure this in vivo. So we measured thromboxane B2, either in mice that were not platelet-depleted or in mice that were platelet-depleted, and we found that the amount of thromboxane B2 indeed is reduced when the mice are platelet-depleted.

When we interfered with thromboxane-A2 signaling by either blocking the thromboxane-A2 receptor or nonspecifically block Cox enzymes, we saw a decrease in the neutrophil number in the BAL and a very significant decrease in the BAL total protein which reflects lung edema.

Maybe most importantly, when we treated mice with either an antibody to P-selectin, up here, they survived for 5 hours, whereas, as I had told you, all the untreated mice did not survive the challenge with hydrochloric acid.

Mice that were treated with the TP inhibitor SQ29548 -- so this is the blocker of thromboxane-A2 signaling -- had an intermediate phenotype. So some of them, most of them survived, but a few of them died.

In conclusion, then, in the lung we of course have direct neutrophil interactions with endothelial cells, but also we have platelets interacting with endothelial cells that then express P-selectin and present that to

attract neutrophils through PSGL-1, and this is probably participating in getting neutrophils out. I've shown you data that when you don't have this, you get few neutrophils out.

But probably the more important effect is the neutrophil-platelet aggregation. Let's focus in on this for a summary. When platelets interact with neutrophils, we get this production of thromboxane-A2 which then acts on TP receptors on the endothelial cells. This causes endothelial cell contraction and causes plasma proteins to leak out and cause lung edema, which can be catastrophic for these mice.

Thank you for your attention.

DR. SIEGAL: Thank you, Dr. Ley.

Are there questions for Dr. Ley? Mark?

DR. BALLOW: So there are differences in the patient population between the United States Phase 3 study and the European studies. Can you relate the differences to any of your scientific findings? For example, in the Phase 3, I think it was mostly stem cell transplant patients that I assume are neutropenic, at least initially. I don't know the timing. That wasn't discussed, the timing of the adverse events in those patients, whether it was early or late or whether it coincided with the return of the bone marrow in those patients or what their

circumstances were. But do you have any conjecture of why there is a difference in the two patient populations?

DR. LEY: Although I am a medical doctor, I am not a specialist in transfusion medicine or hematology. I know that these bone marrow transplant patients go through various where they are neutropenic and then they also have low platelet counts. But I cannot comment on this question.

DR. SIEGAL: One question that comes from Dr. Ballow's query is whether there is a synergistic defect in the host defense when you have both lacking platelets and granulocytes in terms of what's left of granulocyte migration out of blood vessels.

DR. LEY: Based on animal studies and first principles, that should be very likely.

DR. SIEGAL: Any other questions?

All right, thank you, Dr. Ley.

We will next hear from Jean-Louis Kerkhoffs from the Sanguin Blood Bank in the South West Region of Rotterdam, the Netherlands, speaking of the three-armed trial with regular, InterSol, and PRT platelets. Dr. Kerkhoffs.

DR. KERKHOFFS: Thank you very much.

I work as an epidemiologist in a hospital, and at Sanguin I do my thesis-writing work amongst things studying

platelet infusions, and I will discuss with you a few things. In front of the HOVON trial we did some in-vitro work, and most of my talk will deal with my results, first results, and it still has to be published, of the HOVON 82 trial.

In the pre-HOVON trial, it was required by regulatory offices that we show that platelets at the start were fulfilling the requirements in the Netherlands. So we did a set of requirements techniques to show the metabolic measures, we performed hypotonic shock response, and we looked at platelet activation.

All the products we tested, you see the three arms, plasma, PAS3, and PRPAS3, were fulfilling the requirements for transfusion up till the age(?), although I have stated that the age of PRPAS3 platelets was on the edge.

Swirl was present in all the products during storage, and the Bac T Alert was negative.

As to metabolic measures, we studied the glucose concentration. It is obvious that the glucose concentration is lower in the additive solution products by one-third, and it reduces during storage. In contrast with that, the lactate increases during storage were not very different between the arms.

Heat(?) shock response is lower for both additive

solution products, as well without as with pathogen reduction. Activation marker P-selectin is increased in both additive solution 3 without and with pathogen reduction, but it seems to increase more in the pathogen-reduced platelets.

So as the requirements for transfusion were met, we started off with a trial. We deal with difficult platelets in the Netherlands, so we had three arms. Plasma was our control arm, PAS3 was one of the study arms, and PRPAS3 pathogen reduction using the INTERCEPT blood system was the third arm.

It was a non-blinded study. It was not possible for us to blind the study. We used as a primary endpoint CCI-1, and we were comparing the PAS3 with the plasma and comparing the PRPAS3 with plasma. The margin of non-inferiority was 20 percent.

Secondary endpoints we had were 24-hour CCI bleeding events, use of platelet cultures and red blood cells, transfusion interval and adverse transfusion reactions.

Analytic methods we used were intention to treat, per protocol. We did random effects multivariate regression models, both the CCI and the counts. The bleeding and adverse reactions were tabulated with Kruskal Wallis and a Chi-square test for the statistics.

This is the accrual of patients. We started off March 2007 and we stopped May 2009. There was an interim analysis performed between the period August 2008 and the end of 2008, suggesting inferiority with respect to the CCI of the platelet-reduced platelets as well as more bleeding complications, so the DSMB advised us to stop the third arm.

This is a total overview of the trial. All the patients are on this slide. In the middle you see the evaluable(?) patients. We had 99 patients in the plasma arm, 94 patients in the PAS3 arm, and 85 patients in the PRPAS3 arm. The number of transfusion events is shown in the yellow boxes.

The reason that some patients were dropped off was they didn't receive any transfusion during the study or they had HLA antibodies and were not permitted to continue.

This is table 1. There were really no statistically significant differences between the study arms. As you can see on the slide, approximately one-third of the patients -- sorry, 40 percent of the patients -- underwent a transplantation.

This is a kind of table 1 for the platelet products, and it was really a problem for us because sometimes study subjects(?) were not available for transfusion, and when clinicians wanted to transfuse them,

they took off-protocol transfusions and it was significantly more in both study arms. So that is the reason, the main reason, for performing intention-to-treat as well as a per-protocol analysis.

The indication, there was no difference between the groups and there was no significant difference in the premedication. The most significant problem was that the dosage of the platelets used in the PAS3, also the pathogen-reduced platelets, were significantly less than used in the control arm. That's a known problem.

The storage time did not show any statistically significant difference.

Here you see the distribution of the off-protocol transfusions and also the number of transfusions per patient. You can see the white is the plasma arm, gray is PAS3, red is PRPAS3, and you see that the number of off-protocol products was higher in the PRPAS3 arm. The other graph shows you the number of transfusions per patient. You see here that the patients receiving PRPAS3 received more platelet products as compared to the PAS3 and the plasma arms.

Now to the primary endpoint of our study. This is to first show you that the table above is the intention to treat and the table below is per protocol. This is the one-hour CCI. It is showing a very significant difference

between PRPAS3 and plasma, with a mean difference of almost 30 percent, and also per-protocol the difference is reaching 36 percent.

We did a multivariate analysis to see whether other factors were involved, and apart from the INTERCEPT, also storage time and having an enlarged spleen or fever were negatively influencing the increments.

For 24 hours I show you the next slide. This is the same analysis, again intention to treat and per protocol, and again there was a very significant lower CCI for INTERCEPT platelets, about one-third also, and 42 percent when we analyze it per protocol, with the same multivariate factors influencing the increment.

This is the storage time of the platelets. This is the CCI-1. You see the black line is the plasma, the blue line is the PAS3 line, and the red line is PRPAS3. At each storage time level, the CCI-1 of INTERCEPT is lower than of plasma platelets.

The same is true for the 24-hour CCI, although the difference is smaller.

This is the multivariate regression analysis. You see this is a linear regression performed. Of course, there was a dosage difference between the products. We performed a multivariate linear regression analysis taking account for difference in area, difference in pre-count,



difference in storage time possible, and then we see on the X-axis the platelet content. This is the one-hour post count. You see that there is a difference between INTERCEPT and plasma at all dose levels.

The same is true for the 24-hour CI. At every dose level the increment is less with PRPAS3.

Then the number of secondary endpoints. We have to stress that we are still working out all kinds of statistical correlates, especially for the bleeding problems we saw.

There were significantly more platelet transfusions needed for the patients in the INTERCEPT arm. That was not true for the red blood cells. There was a significant shortening of transfusion interval, and what worried us the most, there were significantly more patients bleeding in the INTERCEPT arm.

There were no differences with regard to infections of adverse transfusion reactions or any other serious adverse events.

At the moment I am now looking at every bleeding detail because I want to learn about relating the dosage and the storage time with the bleeding complication. It could be that patients bleed when they receive more platelets concentrated with a lower dosage or more platelets with storage above 5 days. That could be an

explanation for this problem.

My conclusions, and these are virtually the same as I draw recently on the AABB, these data at least. There is an inferior transfusion response. It is independent of dose and independent of storage time. We found more patients bleeding in the PRPAS3 arm. I don't know at this time point whether this is a quantitative or qualitative effect of pathogen reduction, but I am trying to work it out in a multivariate model.

When you would like to correct the increments, you should add two or three more buffy coats in the PRPAS3 treated products as compared to plasma.

The transfusion response of non-pathogen-reduced PAS3 products was not significantly inferior as compared to storage in plasma.

I think that was my last slide.

A lot of academic hospitals participated in the trial, all over the Netherlands, and it was quite successful for us to include so many hospitals and so many patients.

Thank you.

DR. SIEGAL: Thank you, Dr. Kerkhoffs. Are there questions for Dr. Kerkhoffs? Maureen?

DR. FINNEGAN: Would you state that your study showed that there was no significant infection rate between

the groups?

DR. KERKHOFFS: No, there was not. And a lot of those patients have infections. Of course, all neutropenic patients needed(?) chemotherapy, so it is a very difficult thing.

DR. SIEGAL: Kenrad?

DR. NELSON: I just wondered, in these studies, the platelets are often from multiple donors, and maybe hundreds or even more, but there are also single-donor platelets. I wonder, are there any differences in any of these endpoints by whether or not it's a pool of many donors or just a single donor or a few donors? Does it relate to the source of the platelets at all?

DR. KERKHOFFS: When you compare pheresis platelets from one donor with the buffy-coat platelets from five donors, there is not a large difference between those two. So there are differences from all aspects, but it's not really related to increment or bleeding complication. They are virtually the same efficacy.

DR. CHRISTIE: Do you have any more details on the other adverse events, like you had a slide with 11 other adverse events in the plasma group and six or so in the PRPAS3? Specifically, were the respiratory events calculated?

DR. KERKHOFFS: There were only three adverse

events, each in one group, possibly related to the platelet transfusion. One of the three was a pulmonary problem TRALI, but was not in the INTERCEPT group.

DR. SIEGAL: Anyone else? Perhaps I missed it, but did you tell us why the data safety and monitoring board stopped the study?

DR. KERKHOFFS: There were two reasons. The first reason was that they saw and noticed significantly more bleeding for patients in the INTERCEPT arm, although it had not reached the difference stated in the protocol. But at the same time, the primary endpoint was reached by far. There was no expected changes in regard to the CCI-1. That was the reason that was stated. You don't learn more from this trial by recruiting more patients in the INTERCEPT arm, but you have the risk of more or more severe bleeding complications when you proceed with the INTERCEPT arm. So that's the reason that they advised me to stop.

DR. SIEGAL: Thank you.

Anyone else? All right, if there are no more questions, let's proceed to the Cerus presentations. We'll start with Carol Moore, the vice president for regulatory affairs, quality, and clinical.

MS. MOORE: Good afternoon. I am Carol Moore with Cerus.

First and foremost, I want to thank both the

panel and advisors and FDA for the time today that you've spent in preparation for this meeting reviewing our materials.

I would like to provide an overview of the presentation, and I would like to start with the speakers.

Our first speaker today after myself will be Dr. Georges Andreu, who will provide a brief overview of the use of INTERCEPT in France.

Dr. Larry Corash will provide a review of the previous Phase 3 trial -- we've talked a little bit about that, the SPRINT trial -- and an overview of the critical aspects of the proposed second trial with specific focus on the primary efficacy and safety endpoints.

Dr. Gordon Rubenfeld is an expert in acute lung injury, and we've asked him today to come and provide a medical background on the diagnosis and assessment of ALI, especially as it would be used in our primary safety endpoint of this proposed Phase 3 trial.

Dr. Claire Sherman will provide a brief overview of the statistical design, and I will provide some final summary and closing remarks.

We are here today to discuss the proposed second Phase 3 trial for the platelets treated with the INTERCEPT technology. We will be discussing both the Phase 3 trial design in a fair amount of detail as well as a summary of

our commitment to the Phase 4 postmarketing follow-up.

The proposed Phase 3 study has been discussed extensively with FDA, and this represents what we believe to be a fairly good consensus with regard to the path forward on the data necessary to bring this technology forward for licensure.

I would like to talk for a minute on the product overview. A detailed description of this product overview was provided in your pre-read, so I only want to highlight a couple of key points.

This is a technology with a broad-spectrum application. Cerus has data on inactivation of over 20 bacteria, 19 viruses, and five protozoa. In many cases the log reduction was limited by the log titer of the starting inoculum, not the technology itself.

From this morning's presentation, I would like to just comment that this technology does inactivate malaria, dengue, and H5N1 as a model for H1N1.

For additional important secondary aspects of the technology are the inactivation of CMV, inactivation of T-cells, replacement of bacterial detection, and, as shown in both our European trials and our SPRINT data, reduction in acute transfusion reactions.

This is a map that primarily focuses on our European presence, but I do want to highlight that this

technology has been in place in over 20 countries in 60 centers. In many of those geographies, it has replaced bacterial detection, gamma radiation, and CMV serology, which has been a very significant opportunity for increased efficiency in these centers.

The technology has been CE Marked in Europe, Class III drug and device combination. This has allowed market throughout Europe, and some other international markets have accepted the CE Mark as well.

In addition to the centralized CE Mark procedure, we have had additional reviews by the French agency, AFSSAPS, the German PEI, and the SwissMedics as a review for the final marketing authorization as a blood product.

I would like to now introduce Dr. Georges Andreu. Dr. Andreu is actually on the telephone today because he is calling from Paris, France. It was not easy for him to travel here today, so I hope you will accept him being on the phone.

Dr. Andreu is Counsellor of the General Director, National Institute of Blood Transfusion, and a member of a special group within the French health authority, the AFSSAPS that I just mentioned, that reviewed this technology in France, which is in charge of blood component marketing authorization.

So, Dr. Andreu, I will advance your slides and

bring up your first slide, if you can provide your remarks.

DR. ANDREU: Thank you very much. Can you hear me?

MS. MOORE: Yes, we can hear you well. Thank you.

DR. ANDREU: Okay. Good afternoon, Mr. Chairman, members of the panel. I am (inaudible) working at the National Institute of Blood Transfusion in Paris, and I thank you for accepting that I give this presentation directly from Paris.

As a medical and scientific director of the French National Blood Service between 2004 and 2006, I have been (inaudible) introduction of (inaudible) in France in 2005. Since that time, we had several (inaudible).

But I would like to focus on the full-scale use in a single blood center, namely Strasbourg, that was performed in 2006 (inaudible), and, of course, I can answer to any question of this panel about the implementation in LeReunion or all the other initiatives there.

Much information may be obtained by (inaudible) for blood component preparation (inaudible) -- can you hear me?

MS. MOORE: We're getting some feedback (inaudible).

DR. ANDREU: In a word, I can say that we had no



major adaptations to organize the processing organization and to adapt it to INTERCEPT preparation, and we had no production failure, no problems (inaudible) control of --

MS. MOORE: Dr. Andreu, can I stop you for a second? If you're speaking on a speakerphone, could you pick up the handset? That might help us.

DR. ANDREU: Yes. Is that better?

MS. MOORE: We'll see. Go ahead and continue with your remarks.

DR. ANDREU: I would like to focus my talk on the total platelet consumption, next to the efficiency in patients that are usually not selected for (inaudible) clinical trials and I will give you examples for patients with thrombopathies. Finally, I will focus on the adverse reactions.

As you may aware, we have in France an (inaudible) hemovigilance network under the responsibility of AFSSAPS, and we can now compare the adverse reactions observed in (inaudible) with those described at the national laboratory (inaudible).

But first I would like to present the work done in (inaudible) which is a comparative study with an (inaudible) control. The first (inaudible) study is the period 1 marked in blue (inaudible) figure where all (inaudible). Then there were intermittent periods where

(inaudible) solution began to be used, leading to the second period mentioned in red, where all the platelets used were (inaudible), and finally the third period where all platelets were treated with InterSol and INTERCEPT.

You see in this table (inaudible) period 3 where all patients were INTERCEPT treated and the period 1 where all patients were (inaudible), and you can see that the number of patients in these two periods are very equivalent. The median age, the sex ratio, and the main diseases that the patients had are very similar, and so there is no difference between these two populations, and they are comparative.

In the lower part of the table you can see that the number of (inaudible) very good in these two periods. I can mention that about two-thirds of the products are buffy-coat (inaudible) concentrate, one-third or slightly more are (inaudible).

You can see that there is an increase of about 25 percent between period 3 as compared to period 1. This, of course, is also observed when we consider the mean number of platelet concentrates that are (inaudible) increased (inaudible).

On the following line, you can observe that the total amount of platelets used per patient expressed in  $10^{11}$  are very similar in the two groups, and there is no

difference in the quantity (inaudible) and the number of red cell concentrate used per patient.

When we consider not total for the patient population but most typically hematology patients which corresponds to almost 700 people in the two groups, you can observe exactly the same phenomenon, with an increase of 26 percent of the (inaudible) while the total platelets (inaudible) are very, very similar in the two groups, and again, the number of red cell concentrate is very similar (inaudible) of INTERCEPT.

So this is quite a paradox, a paradoxical situation, because we know from clinical studies that CCI with INTERCEPT platelets are known to be reduced as compared to control platelets prepared traditionally in plasma.

So how can we explain this phenomenon? We have at least three possible answers, and I think the combination of these is probably the right explanation.

First, when in Strasbourg they decided to implement the INTERCEPT, at the same time they decided to harmonize and to standardize more their platelet production in terms of platelet quantity. So in addition to the loss of platelets related to the INTERCEPT process, which is about 7 percent, they proposed to modify their preparation at collection for apheresis platelet concentrate in the lab

for vertical preparation to be close to  $4^{11}$  platelets per product.

So that led to, as you can see in this table, a reduction of between 22 and 28 percent of the platelet content between period 3 and period 1.

You are probably aware of the fact that the less you use platelets, the less quantity of platelets you use for a single transfusion and the less you consume globally in this total period of transfusion for a given patient, and this was clearly demonstrated recently by the (inaudible) study. So that [inaudible] possible [inaudible].

Also, we can pontificate that the CCI may be less impaired than expected when we use vertical platelet concentrates (inaudible), and also that is not mentioning the fact that apheresis platelets prepared (inaudible) may have better recovery than (inaudible). I think more important is the fact that (inaudible) presentation of INTERCEPT (inaudible) using more gamma irradiation related to the fact that the prevention of QVHD(?) could be provided by the INTERCEPT prospect.

Now the second topic, and I would like to mention to you that three patients with Glanzmann type I with gypsy mutation that were known at our blood center and that had been treated already with a high-dose regimen in the case

of a surgery situation were treated with INTERCEPT platelets in surgery situations like ovarian cyst surgery and a cesarean during periods of about 10 days, and another child with the same disease was treated continuously for 6 days after two teeth extractions, and they all were well-controlled during that time and completely recovered.

Finally, another example of a young child that is now transfused from two years and a half in Strasbourg with a thrombocytopenia with neuritis, a very rare disease, and he received about one INTERCEPT-treated concentrate per week, and we observed no adverse reaction, and he is well-controlled in terms of hemorrhage up to now.

Now, the third topic is the immediate adverse reactions. In France, arbitrarily, we define them as all adverse reactions observed by 7 days post-transfusion. You can see on this slide where the results are expressed in the rate of adverse reaction per 1,000 platelet concentrate.

Between the first period and the third one, there is a dramatic reduction in the rates of adverse reactions. This was already observed with platelet-additive solution as we knew for years now that platelet-additive solution per se can reduce dramatically adverse reactions. But this is still enhanced by the use of INTERCEPT platelets.

The next slide is rather a more complicated slide

but, I think, easy to understand. It shows the rates of adverse reactions now written for a million platelet concentrate. That was to avoid any doubt or (inaudible) different always between the French and the Anglo-Saxons. So on the left part of the table are the apheresis platelet concentrates; on the right part are the buffy-coat platelet concentrates. In each part, for the left and the right, we compare the Strasbourg experience with INTERCEPT with the national results of hemovigilance in the same period. You can see the numbers, of course, are very different, about 16,000 in the apheresis platelet concentrate in Strasbourg as compared to almost 400,000 at a national level, and the same for buffy coats. The (inaudible) of Strasbourg is much higher, 26,000 as compared to slightly more than 100,000.

All these are expressed by, translated in adverse reactions per million-platelet concentrate. We can go and have a look at all the adverse reactions.

First, as we expect, we have no transfusion-transmitted bacterial infection, which is the first line, with the INTERCEPT product, whereas there are a few events at the national level. Actually, there had been 14 bacterial transmissions at the national level at this time, including three deaths in that period. But still the difference is not significant due to the very, very low

numbers, and we have to wait several years before reaching any significance.

For the (inaudible) the pulmonary complication by (inaudible) overload, we have no significant difference. The same applies with TRALI, and actually these data correspond to two cases of TRALI with the apheresis platelet concentrate in Strasbourg, and the two being with high (inaudible) and with antibody found in the products corresponding to the (inaudible), so they belong to a mechanism that is already known for any product, and we believe are independent of the fact that they have been treated by INTERCEPT.

We have also no difference in the induction of anti-red-blood-cell antibody after platelet transfusion either with the apheresis or the buffy-coat platelet concentrate.

But when we go to the febrile non-hemorrhagic transfusion reaction, we can see that for apheresis platelet concentrate they are about four times less frequent than in the national experience, which reaches a probability of 0.01 that the (inaudible) would lead to such a result.

For the allergic reactions, they are much more frequent. They are the most frequent reactions observed with platelet concentrate, and they are, again, far less

frequent with the INTERCEPT product as compared to the national experience with non-INTERCEPT platelets. This reaches a very high level of probability.

Of course, the total adverse reactions are statistically different.

So in conclusion, in our experience with the routine use of INTERCEPT platelets, with an experience of more than 2,000 patients compared with similar population transfused with platelets in plasma or an additive solution, we observed that there is an increased number of platelets transfused along with the reduced dose. We have a similar total amount of platelets transfused. No indirect sign of more hemorrhage, as shown by red blood cell concentrates consumption, and far less adverse reactions than with the use of conventional platelet concentrates, the difference being very significant with allergic and febrile non-hemolytic reactions.

So, in our experience, INTERCEPT platelet concentrate fits with our expectation for both the quality and for safety. Thank you.

MS. MOORE: I apologize for the technical difficulties in the beginning of that. I think it got a bit better, but --

DR. ANDREU: A bit better?

MS. MOORE: Yes, it is better now, but I wonder



if the panel has questions for Dr. Andreu while he is on the line.

DR. SIEGAL: Anyone?

DR. HOLLINGER: Could you go back -- I think I misinterpreted one of the things on the Alsace study, one slide back. I think I am missing something, but on the TRALI, it said 121 out of 16,000 what?

DR. ANDREU: Oh, no, no, no. Excuse me. It's 121 per million platelet concentrate. It's strictly a (inaudible) to organize the comparison. Everything, every value in the table are expressed as adverse (inaudible) written on the top, rates of adverse reactions per million.

But just for your information, I thought it was important you knew that that was based on actual values of 16,000 as compared to 400,000. So that explains why it doesn't reach, for TTBI, for instance, any significance. Am I clear?

DR. HOLLINGER: I think so. So it's 121 per million versus 31 per million with no treatment, no pathogen reduction. Is that correct?

DR. ANDREU: Yes, exactly, and that was absolutely not significant. The P was ridiculously low -- high, excuse me. The P-square was very low. Actually, if you want, you can calculate it. I gave you all the way to calculate it by yourself if you want.

Another question?

MS. MOORE: Any other questions?

DR. ADAMS: I wonder if you can describe how you define TRALI and whether or not you have any data on the number of times that people with TRALI required mechanical ventilation, since there's a lot of variation in how people define it, and how people are treated often will change.

DR. ANDREU: I think that since the consensus conference, we all define now TRALI according to the Toronto definition. We have a special group in AFSSAPS which is completely devoted to TRALI and that analyzes all declared notification of adverse reaction with TRALI.

I can say that until 2002 in France we completely ignored TRALI. But we learned how to recognize it since that time, and we have about between 30 and 40 cases a year we can observe. We are in a phase of better understanding about the clinical side, and we recognize better TRALI than we did in the past.

All the observations are, as I mentioned to you, analyzed by an expert panel related to ABFFAPS, belonging to the AFSSAPS.

So I really think that now we have distinguished very well in France TRALI from (inaudible), and as I mentioned to you for the two cases, because the 121 per million corresponds actually to two cases per 60,000(?),

and these two cases were extremely significant cases with presence of HLA antibodies recognizing the corresponding antigens in the recipients. So it is a very classical immune TRALI.

For buffy coat, the 38 per million represents actually one case, and that case was considered as below imputability days, so they may (inaudible) possible (inaudible) the relation with the blood component as new immune (inaudible) was found, first, and second, this patient had maybe other causes of ALI that could also be responsible.

So that's the three cases that were observed with the INTERCEPT platelets.

DR. NELSON: Could you repeat again the rate of bacterial infection in the national --

DR. ANDREU: Yes. It's with the INTERCEPT we observed no new bacterial infection. At the national level, there were at the same time 14 cases including three deaths.

DR. NELSON: So about one in --

DR. ANDREU: A very high (inaudible).

DR. NELSON: About one in 2,000 then, right?

DR. ANDREU: Yes, absolutely.

DR. FLEMING: So under the national, the 28 represents, by my count, 11 cases.

DR. ANDREU: Yes.

DR. NELSON: I thought he said 11. Yes, that's what I thought.

DR. FLEMING: So 11 would give you the 28. So that's 11 cases.

DR. ANDREU: Yes, and we have actually, if you want everything, we have 12 cases with apheresis platelet concentrate including two deaths and three cases with buffy-coat platelet concentrate including one death during that period.

DR. FLEMING: So it's 11 cases.

DR. NELSON: And the rate is one per 3,000?

DR. FLEMING: And the Strasbourg has one-twenty-fifth as many people. So if the rate is the same, you would expect eleven twenty-fifths of a case. You would expect about one-third of a case and there were zero.

DR. ANDREU: Yes.

DR. FLEMING: There is no data here, and this is lack of randomization besides, so you're --

DR. ANDREU: No, it's not for lack of -- we have, of course, no randomization, but we expect to have no bacterial infections (inaudible) by transfusion treating (inaudible) and actually was unknown. We expect the treatment is efficient against bacteria.

DR. NELSON: Wasn't the previous, one of

Dr. Jaro's previous slides was one in 8,600 was the risk of bacterial infection? So this presumably is quite a bit lower than that. Six thousand? The risk apparently is higher, right?

DR. ANDREU: With the conventional platelet, of course, it's (inaudible) observed much higher, and we have no cases with INTERCEPT. But I think we have really to wait at least two additional years --

DR. NELSON: I'm talking about the background rate, not the --

DR. ANDREU: Oh, no, we have that for years. In the 15 years of hemovigilance, we had 16 deaths and a total amount of about 95 -- that's just by memory, but I can find it very quickly -- cases of bacterial infection transmitted by transfusion. Although it was very much reduced by the use of 100 percent (inaudible) reduction and by several measures that are not all applied around the world as are applied in France, and we published that we reached about the same level of rate as our experience and the Finnegan(?) experience without bacterial detection. That was published in (inaudible) in 2008. The rate observed that I mentioned to you is really what we expected, what we expect now with our measures.

MS. MOORE: If I could just maybe stop this discussion at this point, because this is just being

provided for background. I think we just wanted you to know that this product is in use in France, and we provided these data just for your background.

The real data to be considered today are based on the trial that we conducted previously in the United States and the trial that we are proposing to conduct. So maybe we should transition into that, because I think we have a fair amount of data to prepare you for your questions today, and allow Dr. Corash to step up and speak to the U.S. Phase 3 trial that we conducted and the one that we're proposing. So if that is all right, I would like to transition into that.

DR. SIEGAL: No more questions from the committee. Then let's proceed.

DR. ANDREU: Thank you.

DR. CORASH: Thank you, Georges.

Mr. Chairman, members of the committee, I would like to focus the next section on how information obtained from prior clinical trials has been used to guide the design of the proposed studies; that is, the Phase 3 study that is under consideration and the proposed Phase 4 study.

As noted, we are using information gained from these prior studies, and we are focusing on efficacy (with) hemostatic endpoints, because platelet transfusions are indicated to prevent and treat bleeding. For safety,

because of the observation of ARDS, which is an infrequent but important adverse event, we seek confirmation in the next clinical trial for the incidence of this event.

The purpose then of the proposed Phase 3 trial is to assess the efficacy and safety of INTERCEPT platelet components. It is a randomized, controlled trial, double-blinded, intent to treat. The population of interest are hematology-oncology patients heavily population with stem cell transplants but also including patients with primary hematologic disorders. This is a population which is amenable to study for assessment of hemostasis, because despite profound thrombocytopenia, they are reasonably stable.

The study will use a non-inferiority design for both endpoints of efficacy and safety. Specifically, it will use prospective, defined protocol assessments to assess these endpoints.

The primary endpoint is days with Grade 2 bleeding. This is based upon an observed difference for this one hemostatic endpoint in the prior clinical trial.

Because understanding efficacy of platelet transfusion support to prevent or correct hemostasis requires a synthesis of clinical information, we look at multiple endpoints. These are secondary endpoints: the incidence of Grade 2 bleeding and Grades 3 and 4 bleeding;

time to onset of the first Grade 2 bleeding event, because the majority of platelet transfusions are given for prophylaxis to prevent bleeding; and we look at platelet and red cell use during the period of support.

For safety, the primary endpoint is the incidence of acute lung injury. Secondary endpoints will include high-grade respiratory adverse events; mortality, because acute lung injury is a highly morbid event; hypocalcemia, high grade; syncope, because these were identified as Grade 3/4 adverse events with differences in the prior trial; and to evaluate Grade 1 bleeding, because adverse events related to Grade 1 bleeding with differences were observed.

The basic design of the study then is a randomized trial with a single cycle of transfusion lasting up to 21 days with an additional period of 7 days' surveillance for adverse events after the final platelet transfusion. The study will enroll 1,024 patients of which a substantial proportion will be stem cell transplants.

Importantly, the study requires per-protocol daily assessments for hemostasis, as was done in the SPRINT trial, but in addition now daily assessments for pulmonary status such that we can evaluate these patients using the American-European consensus criteria for acute lung injury.

These study methods require the use of dedicated, trained research personnel rather than just ad hoc



reporting by clinical investigators. These daily hemostatic assessments will involve the use of assessment for eight organ systems, as we did in SPRINT, and will use daily pulmonary assessments by these trained personnel, and using oxygen saturation as a screening tool to make sure that we do not miss patients with pulmonary compromise.

We will have dedicated personnel for platelet production with active management of platelet doses. We will speak more about this in a moment.

Lastly, because there can be differences in the way people diagnose acute lung injury, we propose using an expert panel, blinded to treated assignment, so that there is one group of people providing adjudication for the diagnosis of acute lung injury.

As noted before, the transfusion period is up to 21 days of support, with hemostatic assessments for 3 days following the last transfusion, because transfused platelets circulate for approximately 3 days.

Acute lung injury assessments will be done for 48 hours after the final transfusion but for all days on study until the final transfusion and then for 48 hours after.

All adverse events will be evaluated in every 24-hour period after each platelet transfusion, but serious adverse events for 7 days after the last platelet transfusion.

For patients who are platelet-dependent and have active acute lung injury at day 21, they will continue on transfusion of the assigned product up to day 28. For all patients, then, mortality will be assessed 28 days after the first study transfusion, so that there is an equal observation period with respect to mortality.

For the Phase 4 study, we are proposing that this be multi-center, open-label, non-randomized -- thus an observational study -- during the period of staged rollout of the technology. The purpose will be to further refine the incidence of acute lung injury, which can only be done in a very large patient population.

The endpoint again will be acute lung injury as defined by the AECC criteria. The population of interest now will be hematology-oncology patients supported with mechanical ventilation. These are high-risk patients. Again, we will do prospective collection of pulmonary event data using defined assessments.

This will require dedicated hemovigilance personnel; a focus on these patients transfused with INTERCEPT and supported with mechanical ventilation. Because the FiO<sub>2</sub> will be known, arterial blood gases will be in the medical record. As noted, this is a seriously affected patient population.

Again, an expert panel will be used to diagnose

acute lung injury so that uniform criteria are applied. This will permit further definition of the incidence of ALI in a very large patient population. I would note that the incidence of acute lung injury in the control population today of hematology-oncology patients is very poorly defined.

How has information from the prior clinical trials been used to guide design of these proposed studies? This is a high-level overview of the clinical development program for the INTERCEPT product. I am going to focus on three trials: recovery and survival of treated platelets in a Phase 2 study; the euroSPRITE trial which looked at count increments with buffy-coat platelets; and lastly, the SPRINT trial, which was designed specifically to look at hemostasis and assessment of bleeding involving 645 patients.

As already noted, recovery of photochemically treated platelets is 8 percent lower in test compared to control, and the lifespan is 1.3 days less. We believe that recovery and lifespan of these platelets is sufficient, though, for therapeutic support, and we note that recovery and lifespan are not direct measures of hemostatic efficacy.

The European trial called euroSPRITE was a randomized, double-blinded, intent-to-treat trial. It

enrolled hematology-oncology patients supported with buffy-coat platelets for up to 8 weeks of transfusion support. The primary endpoint was the one-hour corrected count increment. The study was designed with power to detect a difference in CCI of 3,000.

As already presented, this trial demonstrated no statistical difference in the primary endpoint, the one-hour CCI. However, we did detect a difference in the 24-hour corrected count increment. It is important to note that the corrected count increment is not a direct measure of hemostasis, and the corrected count increment is a ratio measure with multiple variables that can impact the measurement of CCI. Those variables are the precount, the body surface area, which is a surrogate for blood volume, and the platelet dose.

Important data have been obtained not only from our own study but also from the TRAP trial as reported by Slichter and colleagues, with respect to the impact of the number of platelet transfusions on count increment and transfusion interval. What was learned from the TRAP trial and other clinical trials is that as you have multiplicity or repeated platelet transfusions, one-hour and 24-hour count increments fall rapidly and, with that, transfusion interval. So the number of platelet transfusions has an important impact on interpreting the effect and the

response of a count increment.

Recent studies conducted under the auspices of the NHLBI Transfusion Medicine/Hemostasis Network, which examined the impact of platelet dose on count increment transfusion interval and Grade 2 bleeding, also provide valuable information to help in designing future clinical trials.

The PLADO study, which was a platelet dosing study, enrolled large numbers of patients required to assess hemostasis and examined platelet doses of two, four, and eight times  $10^{11}$ . This is considered standard dose, this is low dose. As would be expected, with increasing dose, count increment rises and transfusion interval prolongs. As noted here, though, Grade 2 bleeding remains the same. The proportion of patients with Grade 2 bleeding remains the same for all three dose groups. Thus, Grade 2 bleeding is not highly correlated with count increment.

In context, in the SPRINT clinical trial with platelet doses of test and reference around the standard dose, similar count increments to that observed in the PLADO trial were also observed, with similar range of intervals. Again, the incidence of patients, the proportion of patients with Grade 2 bleeding, was very comparable to that observed in the PLADO trial.

In the euroSPRITE trial, which was powered to

look at count increment but not to look at bleeding, there was no difference observed between the groups when WHO hemostatic assessments were used to look at pre- and post-transfusion Grade 2 bleeding.

The Phase 3 SPRINT trial was specifically designed to evaluate hemostasis. It was a randomized, controlled, double-blinded, intent-to-treat trial, with non-inferiority, comparing INTERCEPT platelet components with conventional platelet components. The population was hematology-oncology patients heavily populated with stem cell transplant but also enrolling primary hematologic disorders.

This study randomized these patients to two cycles of transfusion support if needed. The primary cycle, though, was called Cycle 1. A small proportion of patients who needed continued platelet support during the 2 years the study was open went into a second cycle that was identical in that it lasted up to 28 days with an additional period of surveillance of 7 days.

Because only 15 percent of patients in both treatment groups went into Cycle 2, I am not going to discuss those data further, but they are similar to the data for Cycle 1.

The primary endpoint in SPRINT was the proportion of patients with Grade 2 bleeding. This was selected

because it is a sensitive endpoint, and it was selected based on prior clinical trials, primarily the threshold dose trial of Rebuta published in the *New England Journal* in 1997. Any one event of Grade 2 bleeding meant that the patient met that endpoint during the 28 days of platelet support, so we believe highly sensitive.

Secondary endpoints to further characterize hemostasis looked at the proportion of patients with higher grade bleeding, Grade 3 and Grade 4; the incidence of Grade 2 or higher bleeding after transfusion; days with Grade 2 bleeding; and pre- and post-transfusion bleeding by system/organ class.

In the conduct of this trial, we specifically used per-protocol daily assessments of bleeding as opposed to adverse event reporting under the CTC criteria. We did this to gain more sensitivity and uniformity of diagnosis.

The WHO bleeding grade scale has greater specificity for hemostasis than the common toxicity criteria scale. This was a bleeding grade scale that had been used in other clinical trials, previously the threshold platelet dose study by Plado and the stock(?) studies.

This involves active assessments for each 24-hour period on study, beginning 12 hours before the first platelet transfusion, with systematic evaluation of eight

organ systems for bleeding.

Surrogate endpoints were used as secondary endpoints in the SPRINT trial: count increment, clinical refractoriness, transfusion interval, and the numbers of platelet and red cell transfusions.

A summary of the SPRINT study, which you have already seen, showed that non-inferiority was demonstrated by the primary efficacy endpoint. One secondary hemostatic endpoint, mean days with Grade 2 bleeding, was statistically different when analyzed by analysis of variants.

Surrogate endpoints did demonstrate statistical differences, and four Grade 3-or-4-level adverse events preferred terms were identified as potential safety signals.

So it is these differences that have guided the design of the proposed clinical trial.

Taking a look at the primary endpoint, which was the proportion of patients with Grade 2 bleeding, we observed a difference of 1 percent between the treatment groups. This was far from the upper bound of the confidence interval for this difference; thus, a robust rejection of inferiority with a small P-value.

We observed a similar type of outcome when we looked at higher grade bleeding. Here Grade 3 and Grade 4



bleeding were evaluated together, because these are very low-frequency events. The incidence of Grade 3 or 4 bleeding was actually lower in the INTERCEPT group, 2 percent difference, again far from the upper bound of the confidence interval, with a robust rejection of inferiority.

Because platelet transfusions are administered to prevent bleeding, we felt it was important to look at the ability to prevent the first Grade 2 bleeding event. So we looked at time to onset of the first Grade 2 bleeding event, and we observed the median time was 8 days for both treatment groups, not statistically different.

We also looked at the distribution of maximum bleeding grades by the WHO daily bleeding assessment criteria for the two treatment groups using Fisher's exact test and observed no difference in the distributions between the groups for all grades of bleeding.

We also looked at the proportion of patients with a maximal bleeding grade of 2. It was not different between the treatment groups. We looked at the number of Grade 2 bleeding sites. Multiple bleeding sites are an indication of hemostatic failure, and we found no difference in the number of bleeding sites per patients when Grade 2 bleeding occurred.

Lastly, we looked at the proportion of

transfusions that were given to treat breakthrough bleeding; that is, failure of prophylaxis. Primary care physicians ordered all transfusions in this trial. They were blinded to treatment assignment. The bulk of the transfusions were prophylactic, ordered on the basis of the daily morning platelet count. But if breakthrough bleeding ensued, they could order platelet components as required.

We observed a statistically lower number of transfusions administered for breakthrough bleeding in the INTERCEPT group compared to the reference group.

Turning to days with Grade 2 bleeding, we did observe a difference in the mean when analyzed by analysis of variants. However, note that the distribution is highly skewed. The vast majority of patients have two or fewer days of Grade 2 bleeding. But the shape of the curve can be heavily influenced by a few outlier patients who may have large numbers of Grade 2 bleeding.

When we analyzed these distributions by the Wilcoxon rank sum test, we did not see a statistical difference, and the median days with Grade 2 bleeding were one in each treatment group.

As previously noted, secondary endpoints with statistically significant differences were detected for the transfusion interval, the numbers of transfusions, platelet dose, and the one- and 24-hour CCI, and also clinical

refractoriness. However, clinical refractoriness, when looked at for immunologic refractoriness and persistent refractoriness, was not different between the treatment groups. This information is described in the clinical trial report and the publication by McCullough.

So we believe that these endpoints are informative, but they are potentially impacted by platelet dose, and they are not directly correlated with hemostasis.

An important learning from the SPRINT clinical trial was that management of platelet doses was difficult. When we looked at the proportion of transfused platelet doses in the two treatment groups, we observed that in the INTERCEPT group 20 percent of the products contained fewer than three times  $10^{11}$  platelets, compared to only 12 percent of the products transfused in the control arm.

The reason for this was the following: First of all, in order to stay on protocol, any dose that was available was transfused in preference to going off protocol. Secondly, because the reference product could be shifted between study and non-study patients, much more reference product was available. But test products could only go into people in the test arm. Although large efforts were made to stay on protocol and provide as many doses as possible, in order to avoid excessive wastage, small doses were transfused to stay within the protocol

when nothing else was available.

When we look at the days of platelet support, we see that greater than 80 percent of the patients in both groups had 21 or fewer days of platelet support. Therefore, we believe that 21 days is a sufficient transfusion period based upon these data for the duration of maximum platelet support in the proposed clinical trial.

Turning now to safety assessments, based on an analysis of 26 system/organ classes with all grades of adverse events combined, we observed differences in two system/organ classes: skin and subcutaneous tissue disorders and infections and infestations.

In the skin and subcutaneous tissue class, these differences were driven by Grade 1 differences in dermatitis not otherwise specified, so nonspecific dermatitis and low-grade rashes. For Grade 1 bleeding, petechiae drove the differences in the skin class.

For the Grade 1 bleeding events, we are proposing now to use a more precise Grade 1 bleeding assessment -- that is, microscopic hematuria -- and I will not discuss that further at this point.

I want to turn to the pulmonary adverse events because these were higher-grade events, and these are the events of greatest concern.

When we looked at all Grade 3/4 adverse events by

system/organ class in the SPRINT clinical trial, built on a base of 898 preferred terms, there were four preferred terms that were different that favored control. Within the respirator class, there was not a difference for Grade 3/4 adverse events within the system/organ class. Importantly, I would note that mortality was not different between the treatment groups in the SPRINT trial.

The Grade 3/4 adverse events with preferred terms that were different were hypocalcemia, syncope, pneumonitis not other specified -- that is basically a term of last resort when the investigator could not find another suitable classification -- and ARDS, acute respiratory distress syndrome. I am going to focus my comments now on the respiratory events.

When we saw these data, it was clear that the incidence was ARDS was below the level expected for this patient population. Despite this difference in ARDS between the treatment groups, 5 and zero, mortality was similar between the groups for what is regarded as a highly morbid adverse event.

Turning for a moment to the diagnosis of acute lung injury, and this will be covered in greater detail by Dr. Rubenfeld shortly, ARDS is a subset of patients with acute lung injury. Acute lung injury is defined by hypoxemia with a P/F ratio below 300, acute onset,

bilateral infiltrates, and the absence of left heart failure, left atrial hypertension.

ARDS is a subset of patients defined by a P/F ratio of less than 200. At the time of the SPRINT trial, there was no MedDRA code for acute lung injury.

In order to understand how patients with ARDS or with other severe respiratory events were coded and why we did not see more ARDS, we conducted a retrospective review employing the use of an expert panel. We used an expert panel of pulmonary and hematology experts to select patients from the entire population with potentially clinically serious pulmonary adverse events. The experts selected these patients and then data was extracted from primary medical records by extract reviewers blinded to treatment assignments.

The expert panel then used these extracted data and the American-European ARDS consensus conference criteria to diagnose acute lung injury and ARDS. The panel selected 148 patients out of the total population, approximately one-quarter, who had potential clinically serious pulmonary adverse events. They confirmed that 16 percent, 100 patients, had what they felt were clinically serious pulmonary adverse events, and from this population they diagnosed 35 patients with acute lung injury, 6 percent, equally distributed between the treatment groups.

And from the group of 35 patients with acute lung injury, they were able to define 17 patients who met the criteria for ARDS.

We went further to examine the relationship between transfusion exposure and mortality in these different patient groups. In the group, the majority of patients who had no clinically serious pulmonary adverse events, there was no difference in transfusion exposure in terms of days of support or transfusions between the treatment groups, and, as one would expect, mortality was very low.

When we looked at the patients with clinically serious pulmonary adverse events, as defined and identified by the expert panel, there was more transfusion exposure, days of support and transfusions were not different between the groups, and mortality increased but was lower in the INTERCEPT group.

When we examined the patients with these events who did not have acute lung injury, they had similar days of transfusion exposure and transfusions between the groups, and mortality again was lower in the INTERCEPT group.

When we looked at those patients who met the criteria for acute lung injury, they had similar transfusion exposures as the patients who did not have

acute lung injury, but they had higher mortality. Again, mortality was lower in the INTERCEPT group, but these numbers are too small for statistical comparisons.

Lastly, when one looks at the group of patients with ARDS, P/F ratios less than 200, we again see similar transfusion exposures compared to the patients with ALI and no ALI. Interestingly enough, the patients with ARDS in the control group had fewer days of support because they died much more quickly; they had 100 percent mortality. So that was an observed difference, but the numbers are too small to draw conclusions.

So the use of the SPRINT outcomes guides the current study design. We will focus on hemostatic efficacy and focusing on the one endpoint with a difference demonstrated; that is, days with Grade 2 bleeding. And we will focus on safety endpoints with differences, primarily acute lung injury.

I would now like to turn the platform over to Dr. Gordon Rubenfeld. He is a professor of medicine at the University of Toronto and has published and done extensive research in the field of acute lung injury.

Following Dr. Rubenfeld, Dr. Claire Sherman will present the statistical analyses.

DR. RUBENFELD: Thanks very much.

My role here today is to provide a little



clinical background on acute lung injury. I appreciate that there is significant expertise on the panel, so I apologize if some of this is review.

The two main questions I'm going to cover today are: Are acute lung injury and ARDS different syndromes? And what is the best way to identify patients with acute lung injury?

I think it needs to be clear from the preceding that ARDS and, as I will explain, acute lung injury is a syndrome. By this I mean it's a constellation of clinical findings. We don't have a diagnostic test for it. There is no gold standard for defining who does and does not have acute lung injury.

In this classic presentation of the syndrome, Ashbaugh and Pettie described it quite well, and in fact, like all classic clinical presentations, it has all of the criteria in this original article that later became clear: acute hypoxemia, chest radiographic abnormalities, infection and trauma being the primary risk, and patients improve with application of positive and expiratory pressure.

The problem with research in this area is it quickly became populated and confusing by a number of terms: Da Nang lung, shock lung, traumatic wet lung, congestive atelectasis, post-traumatic respiratory distress

syndrome, idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, pump lung. Everybody was defining and talking about acute lung injury in their specific patient populations, and the literature became rapidly completely uninterpretable.

So in an effort to kind of harmonize the definitions and try to make things a little bit clearer, both for clinical trial enrollment and for epidemiologic studies, a consensus conference was convened to come up with these criteria. This is a sentence from the consensus conference that proposed acute lung injury:

"It was agreed, however, that the term 'acute lung injury' could be applied to a wide spectrum of this continuum of pathologic process so as to acknowledge and define it. . .thus all patients with ARDS (meet the criteria) for acute lung injury, but not all patients with acute lung injury (meet the criteria) for ARDS."

So the whole idea that the panel was struggling with was they recognized that this was a syndrome with a continuum. The idea was, the panelists felt that there were a large number of patients with the syndrome, with significant mortality and morbidity, that weren't being studied and certainly not studied reliably.

So what are the criteria? A number of previous speakers have alluded to these. It's a triad: acute

hypoxemia measured by the  $PiO_2$ -to- $FiO_2$  ratio, chest radiographic abnormalities, and the absence of clinical heart failure. The only thing that distinguishes acute lung injury from ARDS is the degree of hypoxemia.

Again, I think it is extremely important to realize, although you will see this term "ALI/ARDS," it doesn't mean anything because you can't compare ALI to ARDS. ARDS is a subset of ALI. They are in fact completely encased circles like this.

So it's important to realize that there have been a number of studies that try to tease out the differences between patient populations with different degrees of hypoxemia. This is a large cohort from Scandinavia that tried to study patients with acute respiratory failure that did not have acute lung injury. This group of patients that they called "ALI not ARDS," which are patients who present with a mild degree of hypoxemia, and then ARDS patients.

So in fact the way they have defined this, which again is confusing, it's not quite using the AECC criteria, this "ALI not ARDS" group of patients, you can compare them. In fact when they looked at mortality for these three groups of patients out to 90 days, they looked the same. So no different based on the presentation, degree of hypoxemia, and mortality over time.

This is a cohort of patients that we reported on, a population-based cohort of patients with acute lung injury. I am just going to kind of walk you through this because in fact these data look very similar to data that have been presented from France and from other large cohorts of patients with acute lung injury.

If you look at a group of patients who present with acute lung injury -- that is, P/F ratios less than 300 on presentation -- of those patients, 828 or, say, 70 or 80 percent of them, met the criteria on presentation for ARDS; that is, they had P/F ratios less than 200. The rest had P/F ratios between 200 and 300. You will note that I don't have a name here because there really is not an accepted name for this group of patients with mild hypoxemia. But I break them out because they are the group of interest here.

Now, of this group with mild hypoxemia, in this population about 20 percent or so progress to develop criteria for ARDS. In other cohorts of patients, this group is a bit larger. Then another group remains, even when followed over time, with mild hypoxemia.

So what are the mortalities in these groups? The mortality in the patients who present with severe hypoxemia, the ARDS patients, is about 41 percent. In the patients who progress to have severe hypoxemia, it is about 41 percent. This was the idea that the folks who came up

with acute lung injury sort of figured, that this would be catching people earlier.

Not surprisingly, the people who don't get worse do a bit better. I think that's sort of common sense. But they don't do great. So even the patients who present with mild hypoxemia -- and again, this is not acute lung injury; there is no name for this group of patients -- but these people who present with hypoxemia and don't get worse still have a mortality of 29 percent. So it's pretty hard for me to say that this group of patients has a catastrophic event and this group of patients with 29 percent mortality, or roughly triple the mortality of an acute myocardial infarction, don't have something important going on. So even in the setting of patients who present with mild disease who don't get worse, their mortality is still considerable.

Well, what is the best way to identify patients with acute lung injury? I can tell you certainly the ways not to identify patients with acute lung injury, and that's to rely on doctors. There are now a number of studies that have looked at clinical recognition of this syndrome and documentation of this syndrome, and doctors do a terrible job. We just don't recognize it, and if we do, we certainly don't write it in the chart.

The range in the literature is somewhere between

20 and 48 percent of cases get documented in the chart with a diagnosis of acute lung injury. This is in clinical practice. We tend to identify patients who are sicker, if we identify them at all.

This is unreported data from our cohort that was reported in the *New England Journal of Medicine*. It doesn't present too well, but in King County doctors are no better than they are anywhere else. Only 41 percent of patients in this cohort were recognized and documented as having acute lung injury. Again, we tend to recognize the patients who are the most sick in this group of patients and those who end up being on the ventilator longer. I guess this gives us enough time to kind of figure out what's going on.

I just want to point out two things in this table, one kind of humbling: that doctors in academic hospitals were no better than doctors in community hospitals at recording this diagnosis; and the other is that the mortality in the recognized patients, at least in this cohort, although their lung disease was worse, their overall mortality was not that worse.

So if we can't rely on doctors, what should we rely on? The problem here actually has as much to do with physician behavior as it does with the actual definition. So although the definition is agreed on -- we all sort of

agree on that triad -- when it gets operationalized, it doesn't work very well. By that I mean that even experts tend to disagree on what we mean by bilateral infiltrates consistent with pulmonary edema. Unfortunately, this P/F ratio that is the marker and measure of hypoxemia is quite treatment-dependent, so how you ventilate patients in your ICU versus mine may change whether you find more ALI or more ARDS, depending on how you use PEEP.

Frequently we see patients with congestive heart failure who also have acute lung injury. So it's not the case that it definitely excludes the diagnosis.

Then lots of these other things just simply have not been studied.

Relative to this group, although there is a consensus conference panel definition of TRALI, our actual ability to reliably distinguish patients with TRALI from other patients, to my knowledge, has not really been studied. So the definition has some reliability issues.

How can we improve reliability? With a protocol.

These are data from the validation phase of the screening protocol that we used in our community-based cohort. When we were developing this, we figured, well, there is no gold standard, but we're going to compare this to clinical trial screening. At the time we were screening and enrolling patients in ARDS network trials, and this was

an ICU nurse who worked with the intensive-care study clinician to identify patients. Their job was to identify not just patients they were enrolling in the trial but everybody with acute lung injury at our hospital. So that was our gold standard.

Here was our protocol-based screening. We were not very happy on the initial pass-through for our protocol, because we saw that there were significant errors. We were apparently over-calling patients with acute lung injury, and our protocol was apparently missing patients with acute lung injury. So this was a concern.

What we did was we actually took all of the cases where there was disagreement, and we blinded the review panel to whether the patient was deemed a case or not, and by whom, and reviewed them with a radiologist, an intensivist. We found that a lot of these were just failure to use and reliably deploy a chest radiographic definition, and some of them had to do with the simple fact that although the research nurse was supposed to be identifying all patients with acute lung injury, even when we were carefully looking for everybody, we were still missing people on the weekends for this cohort.

So using a protocol after adjudication actually identified patients quite well compared to our adjudicated gold standard and was actually significantly better at



identifying patients than our standard clinical trial enrollment.

The point here is that a rigorous protocol is needed to reliably identify patients with acute lung injury. You cannot rely on even routine clinical trial enrollment data, and you certainly cannot rely on physician identification of the syndrome.

It takes a bit of an effort to put together a protocol. There's a lot of training that goes into training the research staff and screening staff. We used a lot of Web-based materials for this and paper materials. Others have used some of these since then.

In conclusion, ALI is a syndrome defined by clinical criteria that doesn't have a specific diagnostic test. ARDS is a subset of ALI with more severe hypoxemia but similar mortality and similarly heterogeneous pathophysiology.

ALI was designed to be more sensitive. The whole idea behind expanding the definition was to have a more sensitive measure to pick up patients early in the course of their critical illness for clinical trial enrollment and to use as a morbidity measurement.

Morbidity measurements should be sensitive compared to clinical trial enrollment criteria, which, depending on what you're testing in your clinical trial,

may want to be quite specific and targeted.

Finally, without protocolization, the syndrome definition for acute lung injury has demonstrated poor reliability.

Thanks.

DR. SHERMAN: Good afternoon.

I will briefly review the statistical aspects of the proposed Phase 3 protocol that is currently being assessed.

The development of this protocol stems from the statistical imbalances that Dr. Corash presented from the SPRINT trial. With regard to hemostasis, the only imbalance observed was mean days with Grade 2 bleeding.

The safety endpoint of primary importance from SPRINT is proportion of patients diagnosed with acute lung injury. Due to the seriousness of this medical condition, as we will find out later, the sample size for this trial is driven by the safety endpoint.

With regard to the primary efficacy endpoint, as Dr. Corash pointed out, from 12 hours prior to the first study transfusion to 3 days after the last study transfusion, each patient is hemostatically evaluated daily by trained medical personnel to determine whether the patient exhibits Grade 2 bleeding. The sum of these days whereby Grade 2 bleeding is detected represents the primary

endpoint of interest.

Count data are typically skewed right and do not lend themselves to common statistical methods of analysis that assume normality.

The negative binomial models successfully fit days with Grade 2 bleeding data from SPRINT, unlike the Poisson models attempted, which were shown in the pre-read. The negative binomial model assumes that certain patients have greater risk of Grade 2 bleeding than others, which is in sharp contrast to the Poisson model, which assumes Grade 2 bleeding is a random event and that all patients have an equal chance of having one, two, or more days of Grade 2 bleeding.

The choice of a non-inferiority margin is a dilemma in clinical trial design. It is further complicated in transfusion medicine because of lack of placebo-controlled trials. The only data available that provide guidance with regard to a non-inferiority margin is the SPRINT trial. From this trial, the upper bound of the 95 percent confidence interval of the log ratio of mean days with Grade 2 bleeding indicates a margin of greater than 50 percent would be required to reject inferiority.

Given the manner in which hemostatic assessments are made, less than one day difference in mean days with Grade 2 bleeding is not considered clinically meaningful in

this patient population. So by taking the lower confidence bound of the parameter representing mean days with Grade 2 bleeding for the reference arm, a margin of approximately 40 percent is obtained.

Now I will shift my focus to the primary safety endpoints, since this is what is going to require the most work in this study.

The primary safety endpoint is the proportion of patients diagnosed with acute lung injury. The sample size estimates to ensure adequate power to address the safety endpoint require a precise estimate of acute lung injury in patients receiving standard platelets.

As Drs. Rubenfeld and Corash have discussed, acute lung injury is a challenging diagnosis for clinicians. Without prior diagnostic consistency of acute lung injury, the acute lung injury rate in patients receiving standard platelets will remain relatively unknown.

The SPRINT trial reassessment provides guidance in this regard which leads to the primary safety hypotheses being considered. The rationale for employing co-primary hypotheses is to minimize the risk of rejecting inferiority when inferiority truly exists. For the rate difference, which is shown on the left, inferiority is rejected when the difference in acute lung injury rates between test and

reference are less than 5 percent. For the rate ratio, inferiority is rejected when there is less than a doubling of the test acute lung injury rate in relation to reference.

When using only the rate difference hypothesis, it becomes easier to demonstrate inferiority as the reference acute lung injury rate approaches zero. Thus, if we use both hypotheses that must be rejected, then we have greater assurance of non-inferiority at the specified type 1 error level, which would be .025.

As already mentioned, the acute lung injury rate in hematology-oncology patients receiving standard platelets is not well characterized due to difficulties in clinical recognition. We may derive an estimate from the SPRINT trial, but its relevance is tied to an assumption of constancy. However, the standard of care for hematology-oncology patients has changed over the years since SPRINT, which may affect this rate.

This is the basis for proposing an adaptive clinical trial design. To ensure sufficient patients are enrolled to adequately power the analysis of the primary safety endpoint, sample-size re-estimation will be employed. What this means simply is that if our initial estimate of acute lung injury in the reference arm is not what is being observed in the trial, which would ultimately

result in an underpowered study, the trial size may be increased so that the statistical assessment of acute lung injury is adequately powered.

Logistically, this means estimating the acute lung injury rate in the reference arm in the latter part of the study. If the rate of acute lung injury in the reference arm does not result in an increase in sample size, the trial will continue with the prescribed initial estimate of 1,024 patients. If the estimate of acute lung injury in the reference arm results in an increase in the sample size, then additional patients will be added to the study accordingly and the trial will end once enrollment meets the re-estimated sample size.

Based upon the co-primary hypotheses, we need to estimate the sample size required to reject inferiority at a minimum of 80 percent power. When the reference acute lung injury rate is less than 7.5 percent, the sample size is driven by the rate ratio, which is that curve that climbs really fast. Sample-size estimates increase precipitously when the reference acute lung injury rates are less than 3 percent. If the reference acute lung injury rates are greater than 7.5 percent, the sample-size estimates are derived from the rate-difference hypothesis. As you can see, with the rate-difference hypothesis, the sample sizes climb in a linear fashion.

Now, if we want to assume that constancy, and we're going to collect patients similar as those in the SPRINT trial, and we're using the same AECC criteria, we can build a confidence interval around our pooled estimate that we had used at the beginning of the study of 6 percent and derive a 95 percent exact confidence interval which is between 4.2 and 8 percent.

If we look at this confidence interval and we have these assumptions of constancy in a similar population, it is unlikely that study size will exceed 1,438 patients. Conversely, if the acute lung injury rate is greater than 6 percent and no greater than 9 percent, we will not see an increase from the original estimated sample size.

It is our expectation that the initial sample size that we've estimated at the beginning of the study will be adequate and sufficient to assess the safety endpoint of interest. The sample-size re-estimation plan provides assurance that the study will be adequately powered to look at that efficacy endpoint.

Thank you.

MS. MOORE: I would like to bring our presentation to a close with some remarks about the trial design.

I am sure you can appreciate from what you've

heard today that this is going to be a challenging trial. I think we want to reassure you, though, that Cerus remains committed to the Phase 3 and Phase 4 designs we've discussed.

But we do want to point out a few things that are on our minds as we think about this trial. This is one of the largest transfusion studies ever conducted and will require the coordination of both the blood bank as well as the hematologist/oncologist physicians to enroll the platelet-dependent patients in the trial.

We've had a lot of discussions around the rate of ALI, but while we expect the ALI rate to be between 6 and 9 percent in the transplant population, we've also learned that this rate is not well understood in the medical community. So it is something that we are going to continue to look at through the trial.

Regarding the Phase 4 design, we want to restate our commitment to implement a Phase 4 design or trial after licensure of the technology to the centers who enroll in the study as well as may implement the technology.

But we are concerned about prospectively designing the requirement to exclude a 1 percent excess of ALI in the treated versus control arms, given that the actual rate of ALI is not well understood. So again, that is a question to the panel, and we would like to express



our concern that perhaps the best time to establish the actual requirements for the trial will be once the data from this trial are available. Probably we will stand before this committee at the time of licensure and we can discuss the actual requirements for the Phase 4 design.

Finally, with regard to the use of platelets, we have heard from a number of centers that are interested in participating in this trial that efficient use of platelets will be essential. We have heard that centers are concerned about their platelet inventory and the ability to designate platelets for this study. So we are going to have to begin to determine how to move platelets from one center to another to supply the study.

We wanted you to be aware that we did have, and it has been discussed, some platelet discard during the SPRINT study because of the fact that you have to have platelets available under the randomization codes to be able to treat the patients, but the platelets that are treated may expire before they are used, so there may be some discard that we will experience.

I think one thing that we have pointed out is that elimination of the bacterial testing for the INTERCEPT arm will help provide platelets one day sooner and perhaps give us some relief in the platelet supply.

Finally, again, we have stated this, and I think

Cerus and FDA believe this is the study that is required to bring this product forward for licensure, and we expect this Phase 3 study to take around 2 years from the time of the first patient enrollment.

Thank you.

**Agenda Item: Committee Discussion with  
Presenters**

DR. SIEGAL: Are there any questions from the group at this point before we take a break? Yes?

DR. ADAMS: If I could just ask one question about the data from the SPRINT trial, which is hard to tell. For the five patients that developed ARDS, did they all require mechanical ventilation or life support? And do you have any sense of how many of those patients died?

DR. CORASH: Yes. The five patients in the reference group who required mechanical support, all required mechanical support -- can we have the backup slide of the time to mechanical ventilation from first platelet transfusion? They all died. There was a 100 percent mortality for those reference patients.

What was very interesting was then when we examined time from the first platelet transfusion to the implementation of mechanical ventilation, it was actually longer -- that is, there were more ventilator-free days -- that's the slide, thank you very much. Let's look at two

slides. So for the ALI/ARDS group -- well, ALI/ARDS; I've just committed a mortal sin -- for the patients with acute lung injury, if we look at time from the first study transfusion to the implementation of mechanical ventilation, interestingly enough, there was a longer time for the test group, so the implementation of mechanical ventilation compared to the reference group.

If we now go to the next slide, which looks at those patients classified with ARDS, we see the same pattern. Your question, the five patients with ARDS, all mechanically ventilated, 100 percent mortality. That may be one reason why the time to mechanical ventilation is shorter, because they're dying.

DR. FLEMING: Can we keep that slide up?

There are a lot of analyses here that are really very misleading, because you're conditioning on having an event and then you're looking at the time-to-event distribution when you have more people having the event in the intervention group.

I wish we had a lot of time for discussion here. All throughout this analysis and through these presentations, these kinds of biases are induced: slides 48, 49, 62 here. So, for example, you talk about mortality and the fraction of people who have died. Can you show us that slide? By -- I'm trying to remember what slide number

that is.

DR. CORASH: By transfusion exposure?

DR. FLEMING: Well, actually by the fraction of these patients who had ARD events, ARD estimates.

DR. CORASH: Can you go -- oh, I have it here. I'm sorry.

DR. FLEMING: And the same kind of bias was apparent in just that previous slide. I think it was 62.

DR. CORASH: This slide?

DR. FLEMING: Right. So this is an example, and this theme shows up throughout. So basically, in the INTERCEPT group you have a lower mortality. Seventy-five percent of these 12 patients died, whereas 100 percent of these five patients died. Well, that's five deaths here and nine deaths here. So you're almost doubling the death rate.

But when you condition on having ARDS, it looks like the mortality is less. But you're not talking about comparable types of people. You have 2.5-fold as many people who have had ARDS occur in the intervention group.

You see the kind same kind of thing in your earlier analysis, where you condition on having an event and then you look at the distribution by grade to show they're the same.

If you look at the transfusion data -- I think

that's slide 49 -- if we can go to 49? Maybe it's 48 because your numbers change.

So, basically, this is conditioning given that you have an event. The distribution is the same. But you could have 1.5-fold as many people having events here. So the answer is not, conditioning on having an event, is the distribution the same?

Go to the next slide.

So here you're looking at proportion of transfusions with breakthrough bleeding, 6.5 percent against 9.9 percent,  $P$  of 001. So this is saying if you have a transfusion, is it for breakthrough bleeding? But aren't there one-third more transfusions in the INTERCEPT arm? Isn't the average 8.4 against 6.2?

DR. CORASH: There were more transfusions in the INTERCEPT arm.

DR. FLEMING: Right. So, basically, you have to multiply all of these by four-thirds. Throughout your presentation, you're conditioning on an event and then looking at the difference in distribution. You're missing the treatment effect.

When you go back to the global analyses, you clearly are inducing an increase in the mean number of events. In fact, you also say throughout your presentation that Grade 2 is more sensitive. Well, the percent of

people that have a Grade 2 is more sensitive in the sense that you have more events, but it's not necessarily more sensitive to treatment effect on what matters.

So what the FDA is pointing out is the average number of days when you have a Grade 2 event is one-third higher; the average number of transfusions is one-third higher. The number of patients that have ARDS is 2.5-fold higher. If you condition on having any of those events, then you're going to see other differences by treatment arm. But you're conditioning out the consistent indication of an excess of events.

When you refer to the Grade 2 as being more sensitive, it can readily be insensitive to all the things that I just mentioned. It can be insensitive to the seriousness or frequency in which those events are occurring.

DR. EDWARDS: I wanted to ask about the comparative effectiveness research and how that plays into what you're doing in terms of research, and that is, as we're going to look at applying this to a diverse population, how are you involving that diverse population in the research?

DR. CORASH: The patients that are enrolled in this study are patients that are coming to treatment in centers that transplant patients. It is heavily populated

with transplant patients. We rely upon the distribution of population diversity that's in that population. There's no specific selection of any specific classification of patients, other than they come for transplantation.

DR. EDWARDS: But does that play at all into your research and how you go about doing that, recognizing that you want to be able to apply this to that population?

DR. CORASH: The patient mix is reflective of the patients that are in what are largely academic medical centers. They tend to be urban medical centers that service those populations.

DR. SIEGAL: Roshni?

DR. KULKARNI: In terms of your lung events, I was wondering, these are very heavily pretreated patients, I presume, since they come for transplant. Was there any difference in the patient population in terms of radiation to the chest or getting drugs like neomycin prior to -- for their initial reason for cancer or whatever underlying condition they had?

DR. CORASH: Yes. First of all, this patient population is a very heterogeneous patient population. We're not looking at initial treatment of acute leukemia of any one specific type. We're looking at patients who have come to transplant after having multiple other therapies.

More patients in the test group had total-body

irradiation than in the control group. We couldn't stratify for that. That was what came in the door, so to speak.

The study, although large by transfusion standards, was not large enough to stratify for that difference. We are looking at some potential means to stratify in the forthcoming study to try to avoid those problems.

The other thing that's important is the mix of auto versus allo. These are very different patient populations.

DR. HOLLINGER: Dr. Corash, just a couple of things. In the earlier slide you talked about the PLADO trial, I think, and Grade 2 bleeding, with low and medium and high levels. But the PLADO was with conventional platelets. Do you have similar data on the pathogen-reduced platelets in terms of bleeding, Grade 2 bleeding and so on, for those kinds of levels?

DR. CORASH: No, we have not been able to do -- you would have to do a very large trial at each dose in order to study that. PLADO is the first adequately powered study of its type, and it was, as you noted, done with conventional platelet components.

So we have looked at the relationship between bleeding per transfusion or per total dose of platelets



transfused and not seen a relationship of Grade 2 bleeding compared to conventional platelets. But you would need a study of a large size like PLADO with very defined platelet dosing in order to do that specific comparison.

DR. HOLLINGER: The other thing is on the corrected count increment at one hour and 24 hours, I noticed in the study that there was quite a bit of variability at which those were done. I think for the one hour it was like from less than one hour up to 4 hours, and for the 24-hour, from 18 to 24 hours. Was that analyzed to look and see where that played a role in the data that you obtained?

DR. CORASH: When one looks at a mean value for -- these are mean values for CCI on a per-patient basis. Because of patient-related factors, when you look at a large number of transfusions over time, you have a lot of variability. So that is very typical of the type of variance that you see when you look at mean CCI responses in these types of patient populations.

DR. HOLLINGER: It is still a pretty good, wide spread there for the one and the 24-hour anyway.

The other thing, you have the expert committee formed to look at this, and as we've seen, they found about three times, or actually, yes, a significantly larger number of, yes, 17 versus 5 in there.

So in the design of the trial that you're having, what are you going to do, what are the differences that they found, these three people found, or the expert panel that was formed, versus what was found in the different centers? How are you going to try to make this better in terms of picking this up?

DR. CORASH: Let me just point out, can we have the slide that looks at the diagnoses that were made by the primary clinicians? The primary clinical investigators didn't miss patients with serious pulmonary adverse events. They coded them differently. So they didn't code them with acute lung injury because that code wasn't available in MedDRA, first of all.

They identified five patients, unfortunately all in one group, with the diagnosis of ARDS because that code did exist, but they used a variety of other codes to identify these patients. For example, the two most common codes were pulmonary hemorrhage and pneumonia, viral pneumonia or pneumonias of various types. These were coded as serious -- in other words Grade 3 and Grade 4 -- adverse events. It wasn't that the patients were missed.

What we are going to do in the proposed trial is have trained personnel using data-extraction methods and looking at the patients every day and providing specified criteria to an adjudication panel, as Dr. Rubenfeld

indicated, using defined criteria, which were not used in this trial, for making the diagnosis of acute lung injury, including the subset of ARDS.

DR. HOLLINGER: Well, I certainly commend you for putting together something that is going to have a randomized trial where you can compare these two groups, because as we know, the European experience has mostly almost all been based on active hemovigilance, and clearly that is not as good as having a randomized trial where you have observers that are trained to look for these issues.

DR. CORASH: I would point out that the European experience is -- the methodology and the intent is very different than the intent in this clinical trial. So the active hemovigilance program that we implemented in Europe and what is done even by the French National Transfusion Service, which has its own active hemovigilance program -- and by active that means that each transfusion is reported regardless of outcome. But in our European active hemovigilance program, the patients are evaluated for adverse events only for 24 hours after each transfusion event. If they are not transfused, on a day when there's not a transfusion, they're not being assessed for acute lung injury. And they're being assessed for the emergence of a new acute lung injury, if you will, in that 24-hour period after transfusion. They are using AECC criteria

because we provided those criteria to them to use. What we are not seeing is treating-emergent acute lung injury in that broad population.

Now, that's a very different population than we are examining in this trial. It has only a small subset of people, approximately 5 to 6 percent, who are, first of all hematology-oncology patients, and then within that 5 percent, a small proportion are getting transplantation.

I'm sorry, it's about 30 percent are hematology-oncology. About 5 percent are getting transplants. It's a mix of auto transplant and allo transplant. So that, I think, explains some of the differences in the incidence of acute-lung-injury-related events that are being reported.

DR. SIEGAL: Dr. Ballow.

DR. BALLOW: I have to applaud Cerus and the FDA for getting together to design this very comprehensive Phase 3 trial. But I still come back to the interest in the difference in the populations, in the European population and your proposed population, that maybe we can learn something about the pathobiology of acute lung injury.

I was wondering whether, aside from the clinical aspects of this trial, whether you have any thoughts of perhaps going a little bit deeper to try to understand what the mechanism, what the pathophysiology, pathobiology is of

these altered platelets, perhaps, and acute-lung-injury relationship.

DR. CORASH: We have actually been in discussions with the Heart, Lung, and Blood Institute to use this trial as a means to ask some of those questions, specifically working with investigators in the ARDSNet to look at the utility of some of the biologic markers for early detection of patients with acute lung injury.

There is a great paradox here. Platelets are critical for support of patients who have no platelets to prevent bleeding. And yet if it is possible that platelets somehow contribute to acute lung injury, we need to identify whether or not there might be better platelet components for these patients or better transfusion strategies for these patients or when platelet transfusion should maybe be modified in some way.

So I think that those are valuable questions to ask, and we have been consulting with Heart, Lung, and Blood around the potential to actually ask some of those research questions in the context of this trial.

DR. BALLOW: I think it is critically important, because as you go into, if you get there, an extended Phase 4 study, that information may be very, very important.

DR. CHRISTIE: Dr. Rubenfeld gave us some information about how difficult it is to classify acute

lung injury. I was wondering if you had any plans to handle the potential for misclassification of your primary outcome, acute lung injury, in your power calculations. Because even with the protocolization that Gordon showed, there is still a reasonable amount of misclassification.

So with that uncertainty built into the system, considering that this is essentially a non-inferiority or equivalency study, one would think that that would bias towards showing non-inferiority if you have misclassification of your outcome.

For example, if you take a 10 percent outcome or a 15 percent outcome misclassification, you're going to put noise into the system such that it will be more difficult to detect a difference. Some of that may be what we saw in the retrospective analysis when you went to look at acute lung injury after.

So my question specifically was, absolutely, the most important thing is to try to reduce the misclassification up front using some of the principles that Dr. Rubenfeld put forth. However, I was wondering if, A, you had plans to look at the population of 'tweeners or chest x-ray missing people, as Gordon did. I think you had 38 out of this 317. Or, B, whether you were going to plan to power extra for that known misclassification rate of ALI diagnosis.

DR. CORASH: We're in the process now of defining a detailed, specific protocol. I think those are considerations that we're going to have to deal with. I don't think we've reached that point yet, but I think that the question is -- and I have been struggling with this as we look at how to do this -- what's the gold standard for making this diagnosis? I haven't found a source that can tell us that, other than use protocols, use blinded adjudicators, because this is poorly recognized by primary physicians.

DR. BALLOW: It's a syndrome, and it's prone to misclassification, as Gordon stated.

My question is more, since you're doing the general power right now -- and if you have an outcome incidence of 6 percent and you misclassify 10 to 15 percent of people, you're going to really crank up your required sample size. I will leave that to Drs. Troxel and Fleming to figure that out. But it's going to really affect the necessary sample size to look at this.

DR. SIEGAL: Roshni and then Tom.

DR. KULKARNI: My question is more as a pediatric hematologist. I looked the French data, and it showed I think a 2-year-old child given this product. I was wondering if you had any data on the long-term effects. As I was reading your briefing manuals, it looks like the

final product still contains some of the InterSol, and I know it cross-links with the nucleic acid. In a growing child, is there any adverse effect in cross-linking other proteins and cells compared to -- I know you're looking at the immediate adverse events. I'm looking more as a long term.

DR. CORASH: You are correct in that, first of all, it's the amotosalen, not the InterSol. Amotosalen is a psoralen.

It creates cross-links only when illuminated with ultraviolet A light. So post-transfusion, first of all, the peak plasma levels are extraordinarily low, because we use a compound-absorption device to remove the excess compound down to very low levels. And it is also rapidly excreted. Unless you had some way of exposing to intense ultraviolet light, there would not be a nucleic acid interaction taking place.

One of the reasons that amotosalen, which is a psoralen, interested us as a methodology is because the average person eats a couple of milligrams of psoralen a day, and it has a good chronic exposure history.

In terms of studying long-term effects, particularly in children, platelets are going into children, by and large, who have malignancies, and they are getting treated with a variety of other antineoplastic



agents which themselves have potential for creating long-term effects.

Certainly the first step in doing an evaluation of this was we did a carcinogenicity study using a sensitive P53 knockout model and showed that the compound itself and the treated platelets and plasma did not result in an increased incidence of events.

We've also done what are long-term studies in the life of an animal by exposing neonatal and juvenile animals to very long-term doses -- that is, 9 months' worth of dosing three times per week at five times the clinical dose based on maximum volume that you can transfuse -- to look for effects on development and growth, and we have not seen any.

We are trying to look at how to recognize a registry of pediatric patients in Europe where the product is already being used such that one could follow these. But you would need a control cohort, and you have many confounding factors. So it's an important but big challenge for us.

DR. SIEGAL: Dr. Fleming?

DR. FLEMING: There are many issues for discussion when we eventually get to talking in depth about the Phase 3 and Phase 4 trials. But Dr. Christie just mentioned one of the really critical issues that I think,

since he has brought it up, maybe we should amplify at this point.

Non-inferiority trials for safety, which is what we're talking about here, ruling out unacceptable increases of risk, are complicated to design and are more complicated to conduct than a superiority trial would be to conduct, for the exact reason he mentioned.

If there is noise entered into the definition of the endpoint or ascertainment of the endpoint, that noise tends to dilute you towards seeing no difference. In a superiority trial, if you still show a difference, you would say (foreign phrase) it would be even more apparent if I didn't have that noise. But in non-inferiority, it's diluting away a true signal into the appearance of a non-signal.

Furthermore, if you are adding other events that are less clinically relevant than certain events that were driving your original signal, the argument could be it's making me more sensitive, but it's actually diluting away your sensitivity.

So a lot of the principles we'll talk about this afternoon when we get to talking about the design of the Phase 3 and Phase 4 trials from a safety perspective, they're not new principles. We've had an enormous amount of discussion about these issues in an array of other

clinical settings with FDA over the last 5 years.

I will just illustrate one. A classical situation is in type 2 diabetes or with Cox-2 inhibitors, ruling out the endpoint of cardiovascular death, stroke, and MI. We don't count silent MIs. We count clinically apparent MIs. We don't want to be diluting away the true clinically relevant signal. So I think all the criticism of physicians here earlier today might have been premature, because, indeed, the clinicians may be missing some subclinical or less-relevant events. I'm not sure about that, but it readily could be the case. What the clinicians were observing in the 5 against zero could be the most important element of that signal.

Yet we do want adjudication. So if we say 12 against 5 -- it wasn't said today, but in the briefing document the argument was it's no longer statistically significant, and that raises one of the other issues.

The goal here is not to do a trial and show lack of significant excess means you're safe. No, the goal here is to get sufficient precision to rule out an unacceptable safety risk. Nonsignificant increases doesn't mean you're safe. Absence of evidence is not evidence of absence. You're only safe when you have sufficient evidence to rule out definitively an excess which, if real, would be unacceptable.

So in fact that 12 against 5 is still problematic because it's a suggestion for a 2.5 percent increase consistent with a 7.5 percent increase, which clearly would be inappropriate or unacceptable for ARDS events in this particular setting.

So two critical issues when we're thinking about designing this trial, principles: You cannot dilute out more clinically relevant events with other events, or you may in fact be losing the signal; and you have to do safety trials with higher quality than you have to do efficacy studies, because noise is diluting you away from being able to detect what it is that you're trying to rule out.

DR. SIEGAL: I have a question. There is a phrase in the briefing document, "To reexamine the data, Cerus consulted a panel of three experts. The experts restricted their review to medical charts of patients who had only pulmonary events," and I would like to understand the rationale for that. These are very complicated patients, and probably a lot of the patients had lots of events, including the pulmonary ones.

DR. CORASH: They did. These patients had a broad spectrum of events. The expert panel designated an array of adverse-event terms that were not only in the pulmonary system but also in the infectious system/organ class and also the cardiac class as well as terms to

identify patients who would be selected for review. So they used a broader array than just from the respiratory and thoracic disease system/organ class.

Now, if they had patients who had adverse events only in the skin class, they would not have selected them for review. So there was a focus on either the primary system organ/class of pulmonary disease or secondary organ classes that could overlap, such as infections that might have been coded as pneumonia but not have shown up in the respiratory system/organ class.

So in that sense it was felt to be comprehensive, and they went down to Grade 2 events. So they weren't limited to just the most severe events; they cast a very wide net to select these patients.

DR. NELSON: I have a question. One of the reasons for this product is we're trying to prevent a serious infection, bacterial or even unidentified infection from another organism that may be carried with the platelets. Since they are not refrigerated, they are fresh, they can't be screened as well as blood that's stored for a quite a while, they are a critical component with regard to infection.

But do we really know what the infection rate is in people now under current situations who, let's say, have a transplant or are profoundly immunosuppressed? One would

think that a marginally pathogenic organism or a lower rate might increase the risk, but yet there have been other -- I would like to get a sense of what is the rate of infection that occurs that we're trying to prevent, to get a sense of -- my view is that this is still an important problem in transfusion-transmitted infections, but is there any reliable estimate that you have or that you have been able to find?

DR. CORASH: I think it is an excellent question, and I think the problem is that transfusion-related sepsis -- so a septic event that occurs as the result of a transfusion -- is essentially passively reported in the United States and in most other places, and I think there are a few studies that have been done, notably the study by Yomtovian and colleagues from Case Western Reserve, which have shown that there is serious underreporting of transfusion-related sepsis.

If you talk to the people from the ARC who have collected a lot of data on contamination of platelet components, they, I think, will tell you that the system of reporting transfusion-related septic events from the clinicians is not an active system, it is a passive system.

I think the data which are most interesting are actually the PASSPORT data. PASSPORT is a study which I know this committee is familiar with because you've had it

presented to you. The PASSPORT data show that even with current methodology of bacterial detection, one in 1,500 platelet components will have bacteria which can be cultured.

Another way I think that you have to look at this is that we always talk about the risk of a contaminated transfusion on a per-unit or per-donation basis. But an acute leukemic patient needs to have eight components transfused, let's say eight platelet components, during acute induction therapy, on average. So that patient has a risk that is actually one in 1,500 divided by eight to see a contaminated product.

I think that low levels of bacterial contamination, although they may not cause an immediate fatal septic transfusion event or be recognized, can lead to colonization of a catheter or can lead to a delayed event in an immune-suppressed patient that presents many, many days after the transfusion and is never linked back to the transfusion.

So to me the most important information is actually the rate of bacterial contamination of a platelet component, and I think that is the risk we are trying to ameliorate.

DR. SIEGAL: Are there any other questions?

DR. ALLEN: Are we going to have time a little

bit later to discuss the actual clinical trial design? I have a couple of questions about that. But it is break time, or past break time.

DR. SIEGAL: There are two more sessions with the FDA before we actually get back to the discussion.

So if there are no objections, let's take a break at this time but only 10 minutes. It's now about 27 after.

(Brief recess.)

DR. SIEGAL: We are now going to hear from Dr. Nisha Jain of FDA on their review. Dr. Jain.

DR. JAIN: Good afternoon, Mr. Chairman, committee members and colleagues. I am going to present Cerus' proposed Phase 3 and 4 study designs intended to support the licensure of pathogen-reduced platelets using the INTERCEPT blood system for pathogen reduction.

I am going to briefly recap the design of the SPRINT study, outline the concerns with the outcome of the SPRINT study and the need for new studies. Finally, I am going to present the outline of the proposed Phase 3 and 4 study designs.

The total number of subjects enrolled in the SPRINT study was 645, equally randomized to the two arms, 318 in the test arm and 327 in the control arm.

Apheresis platelets were used in this study.



The primary efficacy endpoint was the proportion of patients with Grade 2 bleeding, evaluated on a WHO bleeding scale during the entire period of platelet support and lasting up to 28 days.

The primary safety endpoint was to capture all adverse events recorded by the blinded study personnel according to an NCI toxicity scale, which were then coded by blinded Cerus personnel according to MedDRA medical definitions. Please note the study lacked prespecified monitoring for pulmonary adverse events.

As you have heard before from both Cerus and my colleague, non-inferiority was established for a primary efficacy endpoint of a proportion of patients with Grade 2 bleeding between the control and the pathogen-reduced platelets. However, all of the secondary endpoints such as mean number of days of Grade 2 bleeding, interval between platelet transfusion, number of platelet units transfused per patient and clinical platelet refractoriness, not due to immune factor, were all against the test products, raising concern about their efficacy when compared to the conventional platelets.

The safety database of the study revealed 11 adverse events, MedDRA terms, that were statistically different and went all against the PR platelets. Four of these were Grade 3 and 4 events and included hypocalcemia,

syncope, pneumonitis (not otherwise specified), and acute respiratory distress syndrome. Of these four, two events of clinical significance occurred with low frequency exclusively in patients who received test platelets. These were acute respiratory distress syndrome, five versus zero, and pneumonitis (not otherwise specified), five versus zero.

Please note that Cerus attributes these above findings to under-reporting of ARDS and the extensive specificity of the adverse event coding dictionary used in this trial, which may or may not be true.

From the data generated from the SPRINT study, FDA concludes that the pathogen-reduced platelets are not as effective as conventional platelets, possibly due to the damage during the PR process, and raises safety concerns due to the imbalance between Grade 3 and 4 adverse events; specifically, the increased reports of ARDS in the test arms when compared with the control. Cerus' post-hoc review of safety data and European hemovigilance data does not alleviate FDA's concern regarding safety and efficacy of the pathogen-reduced platelets.

In addition, from the risk-versus-benefit assessment, it may be concluded that if the imbalance in ARDS is true, relative minor improvements in transfusion-transmitted diseases safety -- i.e. reduction in 1 to

86,000 incidents of sepsis -- would potentially offset an increase in incidence of serious pulmonary events compared to the reference platelets. That is 1.6 percent or 1.2 percent, depending on whether you take into consideration the original reports or the reports after post-hoc analysis by the expert panel.

In order to fully understand the balance between risks and benefits of this product, FDA concluded that a randomized control study with careful pulmonary monitoring to assess acute lung injury was needed. However, while designing the study, the feasibility of conducting such a study, especially with regards to sample size and the time frame within which it could be completed and the appropriateness of the use of acute lung injury instead of ARDS as the safety endpoint, has to be taken into consideration.

In considering whether ALI would be appropriate as a safety endpoint, let's review the definition and the difference between ARDS and ALI. This has previously been presented by Dr. Rubenfeld, so I am just going to briefly go over the definition as defined by the American-European Consensus Conference held in 1994. It is defined as a syndrome of reduced pulmonary gas exchange caused by diffuse inflammatory processes with increased vascular permeability. The associated clinical, radiological and

laboratory abnormalities are not explained by elevations in left atrial or pulmonary capillary pressure.

ARDS is a catastrophic form of ALI with a high mortality rate. The only difference between ARDS and ALI is by the degree of hypoxemia. ALI, the ratio of partial oxygen pressure over the fraction of inspired oxygen pressure is less than 300 as compared to ARDS where it is less than 200 in stable state.

All of the SPRINT studies showed an imbalance in ARDS. ALI can be considered an appropriate endpoint to be studied in the new Phase 3 study because ALI and ARDS exist as a continuum of lung damage. If the pathogen-reduced platelets truly cause pulmonary injury, then careful pulmonary monitoring should be able to detect both ALI and ARDS. ARDS will be captured as a secondary safety endpoint. Finally, the sample size is more feasible using ALI rather than ARDS.

With the low background rate of ARDS as seen in the SPRINT study, and if that is true, then a total sample size of about 3,500 to 10,000 will be needed depending on the assumptions and what would constitute an acceptable safety endpoint and also the risk-benefit assessment.

Upon negotiation, FDA negotiated the following path forward for the licensure of the product:

A new premarketing study that is prospectively designed and is randomized, controlled, and blinded to evaluate both hemostatic efficacy and safety.

All AEs will be captured with enhanced monitoring to focus on detection of pulmonary adverse events.

The primary efficacy endpoint would be mean days of Grade 2 bleeding instead of the proportion of patients with Grade 2 bleeding, because we consider the number of days of Grade 2 bleeding to be a more sensitive measure of efficacy.

The primary safety endpoint would be the incidence of acute lung injury.

Based on the control ALI rate of 6 percent seen in the SPRINT study, FDA would accept a less-than-5-percent increase in the overall ALI rate compared to the control arm and less than doubling if the control arm was less than 5 percent. However, on further negotiations with Cerus, it is now agreed that both assumptions will be evaluated, and this will be later presented by Dr. Jessica Kim.

The premarket study will be followed by a postmarket study to obtain additional safety data. This study will be powered to rule out a 1 percent excess of ALI when compared to the control arm. The initial commercial launch of the product will be a staged rollout of the product, so that until the Phase 4 study is completed

successfully, the product will be only used by centers participating in the Phase 4 study.

The design of the proposed Phase 3 study, please note that FDA has only reviewed the synopsis of the protocol. The details of the protocol will be reviewed and negotiated when it will be submitted.

The outline of this Phase 3 study protocol is as follows: It will be conducted as a prospectively designed, randomized, controlled, double-blind, multi-center study in the U.S. The inclusion and the exclusion criteria of the subjects enrolled in the study will very closely match the SPRINT study.

The total sample size is powered primarily for safety evaluation and will consist of 1,024 subjects. The subjects will be randomized in a one-is-to-one fashion and will receive platelets for 28 days, a 28-day period or until they become transfusion-independent, whichever comes first.

The minimum threshold for transfusion will be 10,000 platelets per microliter, and the platelets will be prepared to attain a targeted minimum mean dose of three times  $10^{11}$  per liter of platelets.

The primary efficacy endpoint of this study will be mean days with Grade 2 bleeding during the entire period

of platelet support and 72 hours following the last platelet transfusion.

A number of secondary endpoints to evaluate the efficacy of platelets will also be assessed. These are: proportion of patients with Grade 2 bleeding, proportion of patients with Grade 3 or more bleeding, the total dose of the platelets transfused per total days of platelet support and the number of RBC units transfused per total days of platelet support.

With regard to safety endpoints, the primary endpoint will be proportion of patients with ALI during the study period as measured 48 hours after the last study platelet transfusion.

Some of the other secondary endpoints that will be evaluated are those that showed statistical significance in the SPRINT study; for example, respiratory events of more than Grade 3 including ARDS, 28-day mortality, syncope within 24 hours after a platelet transfusion, Grade 1 hematuria during 24 hours after each platelet transfusion, and hypocalcemia during the period of platelet support and one week after the last platelet transfusion.

Please note that 28-day mortality was not statistically significant in the SPRINT trial.

In addition to the daily assessment of bleeding status for the 28-day treatment period and three days after

the last transfusion, the study subjects will be specifically monitored for pulmonary adverse events. Respiratory assessment at base line and on-study by trained study personnel will include oxygen saturation and clinical respiratory status for all patients each day.

If signs and symptoms of a pulmonary adverse event is noted, then chest x-rays, oxygen, saturation and FiO<sub>2</sub> and arterial blood gasses will be obtained. If ALI is observed, then the evaluation for evidence of left atrial hypertension will be undertaken.

ALI diagnosis by the treating physician will be recorded in the CRF. The final assessment of the ALI will be made by a panel of physicians with expertise in pulmonary medicine who will evaluate blinded data from patients who have had pulmonary signs and symptoms using the AECC criteria. Throughout the course of the study, a blinded review by independent DSMB of all of the AEs and SAEs will be undertaken at regular intervals.

The synopsis of the proposed Phase 4 study: The study will be done as a staged rollout. A minimum of five study centers in the U.S. will participate, and these study centers will be preferably those who have participated in the Phase 3 study.

The endpoint of this study will be a safety endpoint; i.e., proportion of patients with mechanical



ventilation and acute lung injury during the entire period of platelet support and 48 hours after the last transfusion. It will be powered to exclude adverse-event rate increases above one percent of the observed control rate for acute lung injury.

Thank you. Now Dr. Jessica Kim will present the statistical analysis of this Phase 4 study.

DR. KIM: Good afternoon. My name is Jessica Kim. I am a mathematical statistician at FDA/CBER.

The title of my presentation is Statistical Considerations of the Phase 3 Study: Non-inferiority Study Design with Binary Outcomes.

Here is the outline of my presentation. First, the statistical analysis of the plan proposed in the Phase 3 clinical trial will be presented. Then the corresponding FDA statistical evaluation on the proposed Phase 3 study, focused on safety analysis plan will be discussed.

There will be three major factors related to the safety analysis plan that will be discussed, and those are non-inferiority margin issues, the study hypothesis issue, and then futility criteria and the stopping-rule issue.

Then I am going to summarize my presentation providing a summary table including all of the discussion items.

The proposed Phase 3 clinical trial is a clinical trial protocol to assess the efficacy and safety of routine use of platelets prepared by the photo-chemical treatment (PCT) INTERCEPT system.

To summarize the statistical analysis plan included in the proposed Phase 3 clinical trial protocol is, first, that the study objective is to demonstrate the hemostatic efficacy and safety of PCT platelets.

The study design is a randomized, double-blind, active control, multi-center and non-inferiority study.

The active control is the conventional apheresis platelet concentrates that is an FDA approved product.

The primary efficacy endpoint is days with Grade 2 bleeding during the period of platelet support and for 72 hours following the last platelet transfusion.

The primary safety endpoint is the proportion of patients with acute lung injury, defined by the American European Consensus Conference criteria during the study period.

The corresponding FDA's statistical evaluation on the proposed Phase 3 study is as follows: FDA recognizes the study size is based on the primary safety endpoint; that is, proportion of subjects with ALI as determined by a blinded expert panel.

FDA recognizes that the study design as a non-inferiority study to show that the efficacy and safety of the treatment is not worse than the control by more than a pre-specified non-inferiority margin.

The active control ALI rate is obtained from the SPRINT study to estimate the initial study size, and an interim analysis is going to be conducted to re-evaluate the control ALI rate.

As far as safety-related concerns, stopping rules need to be pre-specified in order to stop the trial for safety-related concerns.

Continuing the FDA's statistical evaluation of the safety analysis plan, for the control ALI rate, an estimate of 6 percent was obtained from the SPRINT trial post-hoc analysis to calculate the initial study size. This rate may not be accurate for the proposed Phase 3 study, mainly due to the differences in study designs, the SPRINT study versus the proposed Phase 3 study. Also, almost always a potential bias exists when a hostile analysis is conducted.

FDA recommended an interim analysis to re-estimate the study size based on the control ALI rate at the interim look. The following two items FDA especially emphasized about after the interim-analysis look: study size re-estimation method needs to be pre-specified and

also downsizing the study size as a result of the re-estimation is not allowed, mainly because we want to keep the minimum safety data base.

The following is a more detailed explanation of the evaluation of the safety analysis plan. There are three major factors of the discussion. These three factors are all very closely related in designing the study. The most crucial factor in analyzing the safety analysis of the study design is the limited knowledge about the control ALI rate. That raises a concern on determining the study hypothesis.

Consequently, the non-inferiority margin needs to be discussed before a non-inferiority trial and also futility and criteria and stopping rule and sample size re-estimation need to be discussed when conducting an interim analysis.

The graph of this slide explains relations between two selected study hypotheses. One is the risk-difference approach and the other one is the relative-risk approach. The abbreviation RD represented the risk difference and the RR represented the relative risk. The graph of the horizontal line indicates the control ALI rate and the vertical line indicates test ALI rate. The red line shows the points satisfying all of the test ALI rate are equal to the control ALI rate. The blue line shows the

points satisfying the test is 5 percent or more than control. The green line shows the points satisfying the test is double the control.

The vertical line that you see indicating 5 percent of the control ALI rate separates the graph into two parts. The left side of this graph shows the magnitude of the difference between the using the risk difference from the test and the control value is more than the magnitude of the difference when you use the relative risk of the more than doubled criteria. The right side of the graph shows the magnitude of the difference using the relative risk as more than the magnitude of using differences using the risk-difference approach.

Keeping in mind this graphical interpretation of the two selected hypothesizes, there are two options that can take care of determining the study hypothesis of the safety analysis plan. One is named single hypothesis testing and the second one is named co-primary hypothesis testing.

In the single hypothesis testing, if the risk difference with a 5 percent margin was used, there may be a risk of approving more than double the test ALI rate if the control ALI rate is low. That is the left side of the graph that is separated by the 5 percent that you have seen in the previous slide.

If the relative risk with a margin of 2 is used there may be a risk of approving more than 5 percent higher test ALI rate if the control ALI rate is high.

To avoid the risk that may be encountered by using single hypothesis testing FDA recommended using the co-primary hypothesis testing; namely, at the end of the study, test both risk difference with a 5 percent margin and the relative risk with the margin 2, and then non-inferiority will be met when both hypotheses are satisfied.

Regarding the non-inferiority margins, 5 percent for the risk difference and the 2 for the relative risk are suggested based on potential risk and benefit consideration along with the feasibility of the study with respect to the study size. The initial study size was determined based on the control ALI rate, approximately 6 percent estimated from the SPRINT study, and the larger study size using the co-primary study hypothesis which ended up with 512 per arm.

This slide shows study power; that is, the probability of concluding non-inferiority margins if in fact the test ALI rate is equal to control ALI rate with a fixed study size. The highlighted portion of this table with the pink color shows that if the study size is 512 per arm and the estimated control ALI rate is 6 percent, using the risk difference with a 5 percent margin would satisfy

about 91 percent power. Using the relative-risk approach with the margin 2 would satisfy about an 80 percent margin. So depending on the defect(?) size at the interim, to satisfy at least 80 power of one of these study hypotheses, either the study size needs to be increased or stay as it is to maintain the minimum safety database.

Taking all of the discussion items into consideration, the study hypothesis for the safety analysis is agreed and the following co-primary hypotheses will be evaluated to demonstrate the safety of the treatment compared to the active control.

The non-inferiority is met if both the null hypothesis for relative risk with a non-inferiority margin of 2 and the risk difference with a non-inferiority margin of 5 percent are rejected at the final stage.

FDA also has an important message to the sponsor regarding the futility criteria and the stopping rule. At the interim analysis, only stopping to claim the study success is not allowed, and futility criteria should be pre-specified, and the study should be stopped if there is a safety-related concern, and the stopping rule with respect to the safety-related concerns must be pre-specified.

As a summary this table shows the discussion items with respect to the proposed Phase 3 protocol. The

first bullet says about the study hypothesis, both null hypothesis for relative risk and the risk difference must be rejected at the final stage.

Regarding the non-inferiority margin, there will be a discussion and questions before the committee members with the -- for now, the 5 percent for the risk difference and the 2 for the relative risk is going to be used for the non-inferiority margin.

The initial study size is based on the ALI rate estimated from the SPRINT study. The study size re-estimation method at the interim must be pre-specified. No downsizing the study as a result of the interim analysis is allowed.

The study will be stopped if there are any safety-related concerns based on the pre-specified futility criteria at the interim.

Thank you for your attention.

I think there are questions that I am supposed to read to you. There are two questions --

DR. SIEGAL: Excuse me. Why don't we have a little discussion at this point and then go to the questions?

DR. KIM: Sure.

DR. SIEGAL: Questions from the committee?

Dr. McComas?



DR. MCCOMAS: Thanks. So I am sitting here and I am putting myself of the shoes of a potential participant in such a trial. I am wondering about the recruitment of such participants and the informed consent process.

Given that we have heard a lot of concerns about the SPRINT trial, I am just wondering, if we are going to go out in the interest of full disclosure and allowing people to make an informed judgment, present the options as being fully equal, are we saying that that is indeed what is happening, that these are fully equal? Or would somebody might wonder if they should go the platelet route as opposed to the treated platelet route?

It seems to me that we have heard a lot about the risks and not about the benefits, and in seeking informed consent, we have to play the risk-versus-benefit question. What are the benefits for people to enroll in this trial? Are they going to get paid for it? Do they have a choice in it?

DR. NELSON: Bacterial infection is the theoretical reason.

DR. FLEMING: Just to follow up on that comment, if we could have Dr. Jain's slides again, maybe slide 7, where I think she begins to touch on that really key point. So as Dr. Nelson just indicated, what we are hearing, one of the benefits is the reduction in the incidence of

sepsis. So what we are seeing here as one of the benefits is essentially, per 100,000 people, we would be reducing one case of sepsis.

We do not know whether or not the risk of serious pulmonary events is an absolute 2 percent higher. If we really thought it was, how would you possibly join this trial, because 2 percent would be 2,000 events per hundred thousand people.

DR. NELSON: I do not know that the risk of sepsis is 1 to 86,000 either. I think that there has been quite a bit of data suggesting that it is quite a bit higher than that.

DR. FLEMING: But it would have to be -- basically, if it is of this order of magnitude, you are preventing one event for 2,000 induced events. So even if it were tenfold higher, it would be ten events for 2,000.

So let's go to slide four.

In slide four you are presenting essentially what we know from the SPRINT trial. The SPRINT trial has been put forward in one sense as a paradox because the primary endpoint has been met, and yet when you look across the board at the other endpoints, there is consistent evidence of concern as recognized by the agency both from declined efficacy as well as from safety issues.

Essentially, I would put forward that it is critical to properly justify the non-inferiority margin. I think in this case the choice of the endpoint in the non-inferiority margin was in essence a straw man; i.e., you were using an endpoint -- i.e., the percent of people who had a Grade 2 -- that was not capturing the totality of the severity and importance of the events. So, for example, when you looked at the number of days, it was one-third higher. You also have a substantial increase in the number of people with platelet units.

If you choose a really large margin, what you have to be able to say -- in this case a 12.5 percent margin -- what you have to be able to say is per hundred thousand people it is okay if up to 12,500 more people on this intervention are going to have at least one day of Grade 2 events. Where did that come from? My sense is maybe where it came from was feasibility of what would keep the trial size down at this particular stage, and yet we cannot use that as the basis for arguing a margin or we will end up with this exact paradigm. So you are going to end up with the appearance of safety when you drill down to the data and you find that there are substantial -- there is the CCI as well as the clinical excess.

One thing that has been, or two things that have been substantially discussed here. One is the appearance

of reduced efficacy and the other is the indication of the increased safety risks. But one thing that has not been discussed a lot is there is one-third more platelet units transfused. Isn't this also clinically important? We have talked a lot about needing to address the reduced efficacy. We have talked a lot about needing to address the enhanced increased safety risk, particularly ARDS, but isn't the need for one-third more platelet transfusions also a major problematic feature?

DR. ZIMRIN: Actually, these discussions reminded me to some extent of the discussions that were held around the PLADO trial. I think that in the PLADO trial there were -- there are other people who can speak with more authority about this than I can -- but there were more platelet units used. There was felt to be, however, a greater good that was obtained from that which is that overall fewer platelets in general in the system were transfused.

I think here we are focusing again on a risk-versus-benefit ratio. It does look like there are more platelet units being transfused. Maybe if we heard a little bit more about what Grade 2 bleeding is, we might have more of a feeling for the risks we are asking patients to assume, because the more serious bleeding, the Grade 3

and Grade 4 bleeding, from what I understand, was not significantly different.

Would other people find that helpful? Because it does seem to be something that has come up as a day of Grade 2 bleeding is something that people find difficult to accept.

DR. FLEMING: Just to extend on that, when Dr. Vostal was presenting his summary, he was showing us the relative numbers of Grade 2 events, Grade 3 events, Grade 4 events, and then Grade 2-to-4 events, and it was an increase from 34 percent to 43 percent in Grade 2-to-4 events, and it was contributed by each of those levels. To look separately at Grade 3/4, it is not statistically significantly increased, but absence of evidence is not evidence of absence. This is a safety access here. We cannot conclude safety by absence of statistically significant increases.

The pattern for almost everything except the straw man non-inferiority margin, which is completely insensitive to lesser efficacy the way it was set up, everything else that we are looking at is suggesting an increase in compromised efficacy, most clearly when you look at the Grade 2 events but not exclusively the Grade 2 events.

DR. ZIMRIN: I agree 100 percent that there is no proof of efficacy or safety here. The question is whether it is safe enough to ask the question.

DR. TROXEL: My main question is related to all of these. We have heard a lot about the SPRINT study, and it seems to show pretty clearly the inferiority with respect to efficacy and, equally worrisome if not more so, the increased safety concerns. So in many circumstances we would consider ourselves finished at this point, and yet we are discussing not only the possibility of another Phase 3 trial but a possible Phase 4 trial.

I understand that we have had some nice summaries by Dr. Kim about the attention to the safety that has been increased in the design of the new Phase 3 study, the proposed Phase 3 study, and I understand that is one primary difference with what has been done before. But it would be helpful if we could hear a little bit more about what might be expected to be different in terms of efficacy and safety in this new study that is being proposed. Has there been some problem that has been addressed and is now expected to have improved performance, or are we simply repeating the same scenario with not much evidence that we are going to have any increased performance?

DR. GOLDING: The risk-benefit analysis clearly should also take into consideration the question of

emerging infectious diseases. When you are talking about informed consent for an individual patient, and we do not currently have an outbreak of some terrible disease, or we cannot say for that particular patient that it is going to be a big difference; but down the road it is likely that sooner or later we are going to have some new emerging infectious diseases and that there is going to be a lag period before there is a screening test and before we can really make sure that the products are safe again.

This has happened over and over again so this should enter into any risk-benefit analysis. From our point of view, it has been very difficult to calculate that and assess it.

The other thing, we have talked about adverse events, but we realize that in the initial trial, we and the sponsor did not anticipate those pulmonary adverse events and the patients were not carefully monitored. So we think there is a reason to want to do this in a way that you can really assess this more accurately and determine to what extent this is happening.

DR. FINNEGAN: Before you sit down, one of the things that has frustrated me is that you are going to be having the same theoretical risk-benefit discussion at the end of this study unless somebody looks at the reduction in pathogens while you are doing the study. I do not

understand why there is not a culture of the platelets as they are given and then follow-up association of that with any infections that the patients might have.

DR. GOLDING: We do know from in vitro studies to what extent this removes pathogens. But it is true that we have not asked for in previous studies, and we could consider in this study, that you actually look at the platelets. But I am not sure you need to do this on every single platelet. I think once you have shown that this process can remove, say, ten to the six lots(?) of nearly every bacteria that they test and every virus that we know is highly pathogenic, do we really need to do that for each platelet sample that is being given to a patient?

DR. FINNEGAN: But wasn't the PASSPORT study that a good number of those pathogens, quote/unquote, were not actually infectious to the patient? In other words, there was not a significant problem to the patient?

DR. GOLDING: Yes, but the organ --

PARTICIPANT: You can look at the contamination rate of platelet products and then you can look at the rate of transmitting disease to patients, so it's septic rate. Not every contaminated product goes on to sepsis. The only data that we have, or the most recent data about septic reaction rates, is the data from the American Red Cross, and their frequency is about 1 in 86,000 septic reactions.



DR. FINNEGAN: But don't you think this -- I mean this would give you the perfect risk-benefit. If you can show that the sepsis rate decreases significantly and there is even a less inferiority rate than the risk benefit, you can calculate directly rather than trying to take it from somebody else's study.

PARTICIPANT: Yes, that is a very good point. This was discussed early on in the development plan years ago. We decided that the frequency of the contaminations and the pathogens is so low that a study that could prove that you actually are reducing that in terms of reducing transfusion-transmitted disease would be enormous. The company could not afford to do a study of that size.

DR. NELSON: The other problem with doing it that way is that the frequency of contamination is unpredictable. We have had epidemics of West Nile Virus, of chikungunya, of dengue, and this technique will theoretically negate that whole risk.

So you might, during a period, find a rate of 1 in 100,000, but it could easily go to 1 in 1,000 over a quick period. Theoretically, this technique, if it is safe, could be effective for any unknown future epidemic or contamination event which could not readily be predicted. We have new epidemics all the time.

DR. FINNEGAN: But I would maintain those are two separate things. You are still using theoretical risk-benefit, whereas he has an opportunity to do direct risk-benefit. I think that is really important.

Then there is this which you would use every day as compared to this which you would use when we have an epidemic and a problem with the blood supply. I think those are two separate issues.

DR. ZIMRIN: But the study is not going to be big enough. That is the problem. You do not want to include all of this extraneous stuff in a study that is big enough because then it would be too expensive, and if you include something where you cannot possibly see a benefit, then it is just a waste of resources.

DR. FINNEGAN: I am sorry, how do you do your risk-benefit? It is going to come out, say it's right on the border, everybody is iffy. You have not risk-benefit ratio to compare it to.

PARTICIPANT: I think that is what Dr. Golding said, is that it is very difficult to compute the benefit for things out there that we don't -- we have experienced outbreaks, we do not know what the next one is, we do not know how dangerous it is going to be. We do not know how quickly we are going to find a test for it. I think that

is the point that he was trying to make. So you are right. It is hard to put a number on that.

Back to Dr. McComas' point, I think that we sort of dismiss the risk of infection with HIV and with some of the other viruses because we say that they are so low. I think for patients that is not trivial. So even though we know that the bacterial infection is much more significant, I think they are concerned about viruses, about unknown agents.

Not that I at all wish to play on anyone's fears, because I want them to enroll in the clinical trial, but I do think that there is concern about the safety of the blood supply and that efforts to making it more safe would be appreciated by patients.

DR. HOLLINGER: Just to keep the record straight, this pathogen-reduction technique, as is true for the riboflavin and some other techniques, does not inactivate most non-envelope viruses like HAV, HEV, colisi(?) viruses, and so on. So it is not something that will wipe out all viruses. You mentioned the ones that are important, dengue and chikungunya and so on, West Nile, but there may be other ambuloviruses(?) because it does not penetrate the nucleic capsule where it can get in to intercolate with the nucleic acid.

DR. FLEMING: I wish I could quantitate the full benefit, and yet I agree with the comments of several that when, at this point in time, we would project that the risk might be 1 in 100,000 for bacteriological sepsis and viral complications, an order of magnitude less than that. Maybe some day there will be a new HIV, but at this point if we do this trial to rule out a doubling for a baseline rate of ALI of 5 percent, basically for 100,000 we are ruling out 5,000 additional events. If ARDS is half of that we are ruling out 2,500 additional events.

In essence, the margin needs to be sufficiently small, but anything smaller than that is clinically acceptable. Non-inferiority does not prove you are the same. It rules out you are unacceptably worse. So we do need to project efficacy in order to come up with the rational margins.

I am coming back to Dr. Troxel's points that she was making. Essentially, if we follow what is being proposed here, the margin is going to allow us to rule out, per 100,000 people, that we have 5,000 treatment-induced ALI cases or 2,500 treatment-induced ARDS cases which are pretty profound, too.

I am hearing worst-case scenario could conceivably be a new HIV coming along where the upside is not 1 in 100,000, it is 100 in 100,000, a 1-in-1,000 rate,

or even 1 in 100, 1,000 in 100,000, but it seems highly implausible that that would be the case, and that is all hypothetical against what is not hypothetical here in terms of what we are trying to rule out.

But on top of that, you also have evidence of diminished efficacy, which is not irrelevant because we are intervening here in a way to try to restore a deficit relating to platelets, and we are having to use, if this estimate is correct, and maybe it isn't, one-third more platelet transfusions, which alone does not concern me, but in the context of the safety risk, the diminished efficacy signal and the additional need for additional platelets, even if I grant full efficacy, which I have not proven in the 1 in 100,000, how does that offset 5,000? How does the non-inferiority margin that we are proposing here remotely begin to rule out an unacceptable increase?

DR. ALLEN: This is very complicated. The people who are most likely to be receiving platelets in most situations are quite severely ill with a lot of underlying issues and complications. If you look at the risk of hospital-acquired infections or other complications these are patients that are ideal setups for them. The risk of sepsis in one of these people from multiple other causes other than intrinsic contamination of platelets or blood or anything else, the risk of other causes is enormous. So

given that, what you want to do in all of these patients is to reduce their exposure to events, to hospital intrusions. You want to get them out as quickly as possible and minimize their exposure to things occurring in a hospital.

Going back to what Dr. Fleming was saying, you really have got to show that what you are doing is absolutely safe in order to have an equal balance. Most people that come in and their families do not know anything about acute lung injury or any of these other complications. They do know about HIV infection from blood. The risks are not anywhere close to being comparable. I think it is up to us to keep that kind of perspective in balance.

DR. BALLOW: Let me come back to the number of platelet packs because there is a real difference, eight versus six. Even though there may not be an effect on Grade 3 or 4 bleeding, the question I had was whether the exposure to these additional alloantigens -- maybe Dr. Siegal can answer this -- what effect might that have on the transplant process? Remember these are patients undergoing stem cell transplantation. So is there a potential problem by increasing the number of platelet packs as far as survival of the graft or the "take" or the engraftment of the graft because of the increased number of

platelet packs? I mean that is on an outcome that I have heard that was going to be examined in this study.

DR. SIEGAL: I certainly agree that it should be, but I cannot give you an answer.

DR. SIEGAL: Mr. Templin.

MR. TEMPLIN: If there is a need for one-third more platelets, would there be a potential platelet shortage down the road because everybody would be using one-third more platelets? Is the system able to handle that extra increase in platelets?

DR. SIEGAL: We will have to give you back more than Mexico.

(Laughter)

DR. BIANCO: If I could say, I do not think that is the issue that we are discussing here. This system has been able to produce the platelets that are needed and will be able to produce more if we need them.

DR. CHRISTIE: It sounds like a lot of what we are talking about is basically public policy, right?. There seems to be a big belief that sterilizing -- that is the wrong word -- making less risk of the platelet transfusee population for the nation is a good thing to do. But then there is also this risk of giving too many people acute lung injury. Maybe these things balance each other off in the middle.

So one question that I had, since we are starting to talk about policy things, the one question is platelet availability and the second question is cost. I mean if these things are roughly equal, are we just going to go ahead and -- I mean if the risks are roughly equal, has anybody thought about whether it is worthwhile pursuing?

DR. SIEGAL: Anyone else? Tom, you were going to say something?

DR. FLEMING: I was just going to say the issue with additional platelets is not just whether or not the system can evolve to being able to provide it. It's things like Dr. Allen was referring to, which is the more transfusions you have to have, is that exposing you to a medical system that could be exacerbating your vulnerabilities for people who are already vulnerable? To me that is a third dimension. It is not irrelevant. I do not raise it as the sole concern. It is a third dimension.

The first dimension was the off-target effects. There were 11 significant differences and they all went in the wrong direction. Some of them seem to matter. I do not know if they are real but they are of sufficient concern because of their clinical importance that if they are at all close to being real, I would think they would trump the benefit.



The second dimension is -- and there is evidence to really suggest that the efficacy could readily be less. I do not know if it is true, but the evidence that it is there according to multiple measures says it is less.

So then it is the third dimension, that in fact also takes one-third more platelets.

I come back to what some were arguing before. It's an interesting informed consent. I think it is conceivable still that this product could have a favorable benefit to risk, and yet I am really skeptical when I consider all of that evidence, and I am not sure how to change that skepticism except to say that it is imminent that a new, unrecognized pathogen is on the horizon that could make it much more favorable to have an intervention like this.

Coming back to Dr. Troxel's question, is it possible to learn from what we have experienced to improve somehow the method, the delivery, et cetera, to give us a sense that when we then went into a new Phase 3 trial we could expect to see a better efficacy and a better safety profile than was seen in SPRINT? Is that possible?

DR. SIEGAL: Does anybody want to answer that from the company or anywhere else?

PARTICIPANT: What we saw from the SPRINT study is that those patients that are getting transfused in the

treatment arm, their platelet counts are always lower because the survival of those platelets is a lot shorter and you get a less of a bump for transfusion.

Being in the treatment arm, you also had increased bleeding. Is that because those platelets do not work or is that because there are not enough of those platelets? One way to try to resolve that is you could actually even increase the dose further and transfuse more treated platelets so you would have equal levels of platelets circulating in the control arm and in the treatment arm and then compare the bleeding rates. That way you would look directly at the efficacy question and not necessarily at the platelet count question.

DR. FLEMING: It is an interesting theory. That theory -- it is almost like a higher-dose kind of theory in a cancer trial. It could improve the deficit in efficacy. It would, though, exacerbate the excess in platelet transfusions needed, and it might exacerbate the off-target effect concerns.

DR. ZIMRIN: Not necessarily. Platelets come in small, medium, and large, as we found out, I mean the apheresis units. So if you used a larger apheresis unit and treated it, you would get, I don't know, a medium sized, smallish, I have no idea. So you would not

necessarily increase the exposure to donors by -- or you could not if you did it the right way.

PARTICIPANT: Yes, and if there was an adverse even associated with the treated platelets, this would actually increase the chances of seeing that adverse event further because you would have more damaged platelets on board.

DR. TROXEL: I do not want to belabor the point too much but it does seem that this is a very tough sell from an equipoise standpoint, and I think there are a few things that are conceptual ideas that might make it seem doable, but they are both extreme and unlikely.

So I think that we should think very hard about whether or not it is even plausible that we could be in a setting, given the evidence that we have seen so far, which is really quite compelling in the other way.

DR. ZIMRIN: One other point that we have not heard a whole lot about is the experience in Europe. I know they are not looking as carefully at the adverse events. I mean it is a totally different setup, there are differences in how they process blood components, but the idea that there is a huge imbalance in the number of people with catastrophic respiratory events would seem to me to be less likely given the fact that this has been in use there for a while, and they do have a hemovigilance program.

Again, it is not a substitute for what I think needs to be done, but it might allay some concerns about the product.

DR. CHRISTIE: They presented the European data. You cannot tell that statistically, but there seemed to be more TRALI in the group that had been getting it. So you just do not know. It is a rare event.

DR. ZIMRIN: I agree. I think the question is out there.

DR. CORASH: May I try to clarify some things? First of all, around the issue of the number of transfusions -- and this is very much driven by dose in part -- during the conduct of the SPRINT trial, as I attempted to show, we had many small doses. We had more smaller doses that drove more transfusions because they were smaller doses and you got lower count increments. In the European experience, where we have been able to see more consistent production of doses when you are in routine production, we are not seeing increased consumption of platelets on a per-patient basis. I think that is one of the things that Dr. Andreu tried to show in his data, and we have additional data from Belgium from a blood center that does apheresis platelets using exactly the same type of system that would be used in this clinical trial that

has characterized the use of platelets per patient per day of thrombocytopenic support and not seeing a difference.

I think some of the difference in numbers of transfusion is dependent upon the dose which is contained in individual units of platelets, and that needs to be improved in the management of this clinical trial.

A second point, I think, doing a clinical trial to demonstrate the benefit of reducing transfusing transmitted sepsis unfortunately is not feasible due to the size of the trial that would be required. But the PASSPORT data I think do show convincingly, along with the ARC data, because the dataset is so very large, that there is residual bacterial contamination of platelet components.

I think people have raised the issue that transfusion of these platelet components, even though they may be contaminated by bacterial culture, do not cause transfusion-related sepsis as the event of great interest. But it is based on a passive reporting system, and the question is, is any bacterial contamination suitable for a patient who has no neutrophils? I think it would be better as a hematologist not to have any bacteria in these products as opposed to having bacteria. Cultures could be done obviously with these products and are being done on a quality surveillance basis. That is one possibility to

look at. Potential benefit would be residual bacteria in contaminating platelet components.

DR. NELSON: One of the things, in thinking about it, informed consent is going to be pretty tough here, if you use the quantitative figures of acute lung injury with a mortality of 29 percent over ARDS with a 41 percent mortality and a several-fold increase over the possible risk of bacteria or sepsis prevented and maybe not.

I just wonder how the -- I guess the FDA will anticipate approving the consent procedure. That might actually affect the ability to do this trial. I can see some real difficulty, because acute lung injury is a pretty serious outcome.

DR. TROXEL: The question is, is a small reduction in a theoretical and already low risk worth an increase in something very serious?

DR. NELSON: The majority of the cultures have shown anaerobes like propionibacter which are probably not a pathogen, certainly not a high-level pathogens and may not be pathogens at all. But occasionally, there are other certainly more serious concerns, and we do not know what is around the corner. So preventing infection, as an infectious disease person, I am in favor of.

DR. EPSTEIN: I think there is a perspective that has been missed here which is that essentially what has

been contended is that the adverse findings of the SPRINT trial were not real, that they were artifacts of the limitations of the design. That is argued more for the pulmonary toxicity than anything else, but it is the pulmonary toxicity that has us most worried.

Really the question is whether we can exclude serious adverse events. I think one way to look at this is you had findings of the trial and we are not sure if they are real or not. What do you do? Do you just say, well, that is the end of that product development, or do you say repeat it with better monitoring and let's see if we can get closer to the truth? I think that is really what is going on here, that the attempt to figure out the risk-benefit from SPRINT as the basis to decide if you have equipoise in essentially repeating the trial is doomed to failure, because you are supposing that you know those results to be valid when that is the very thing that is being asked.

FDA essentially has been asked, what if these are not real? Is this still the end game?

DR. McCOMAS: Just to follow up on that, I get that. Okay, let's replicate it. Let's see if we find those similar results or if we find something different.

But perhaps what I have taken a pause at is the focus on, all right, let's talk about Phase 4 then and

let's talk about this going to market, which sort of assumes that it was wrong, and therefore we are going to find that it is a great product, and so we are going to go forward there.

I don't know again if that is part of the whole process in terms of going through. You would not want to go through all of the trouble of this Phase 3 without looking at sort of the end goal, which is getting it to market. I guess that is what I find myself reacting to.

DR. EPSTEIN: Right. Let me try to address that. I think Dr. Fleming hit the nail on the head when he said, not that that is unusual, that these safety margins or non-inferiority margins are not adequate to rule out levels of adverse events that would concern us. That is absolutely correct.

The problem is that there is no feasible trial large enough to do that. What basically the FDA is saying in concurring with the trial proposal is that if, within feasible non-inferiority margins, we do not see the excess and adverse events that were seen in SPRINT, then we are prepared to allow a limited rollout in which a more narrowly constructed trial could rule out adverse-event accesses at a much, much tighter margin.

You could say, well, shouldn't you know that before you allow any commercialization of the product? I



would say, ideally, yes and always. But in the real world, in this situation, we cannot.

So the question is, if you allow a trial to be repeated with albeit wide margins and you do not see the findings that you saw in SRPINT with much more detailed and directed prospective monitoring, is there then a basis to say, well, it is shown safe and effective within the limitations of clinical trials, but we want additional safety data. We are going to constrain rollout until we have seen that in controlled trials in Phase 4. So that is what is underlying it.

Again, it all comes back to the question of whether the serious adverse events are real or not real. We are not sure. We are all worried, but we are not sure.

DR. ALLEN: The discussion of pathogen-reduction technology has been around for a long time, and I have real concerns based on what I have read and heard about this. Nonetheless, it is exciting to see that the technology has moved forward fairly significantly, and I certainly would want to see -- I would anticipate that we will be discussing it a decade from now and that the technologies will have moved on. But that also implies that we do need to have appropriately, carefully designed clinical trials to understand what is going on within the patient population.

So, Jay, I think your point is very well taken and I appreciate your perspective on that in talking to it.

DR. BIANCO: I want to just follow up on Dr. Allen. It is true it has been going around for a long period of time, and there is less and less enthusiasm on the part of manufacturers to spend more in order to develop those technologies, in order to bring them to market. My fear and the fear of many of us involved in transfusion is that if we say no too many times, people will give up.

We have recent examples of West Nile Virus in Italy, chikungunya in the Reunion Island just a few years ago that stopped transfusion in the whole island, and where the French rushed to use the INTERCEPT to be able to provide platelets to patients there. There was chikungunya in Italy. So we were talking about dengue this morning here in the United States and all of that. There are other viruses, other things that we know are very close to us here. We would like to be prepared and we want support from the manufacturers in terms of having those products at the point where we can use them.

I am very happy to see that there is an open door still, that FDA is willing to work with the manufacturer to bring another trial that is designed to answer to the doubts that we have from the initial SPRINT trial. I really do hope that we pursue that.

DR. ADAMS: One of the things that I think that many of us agree on is that if you get acute lung injury and you end up on a ventilator, that is a bad thing to have, and that the mortality rate is quite high in these patients. In the original trial it sounds like those patients who ended up on a ventilator, the five patients compared to zero, that all of them were on a ventilator and all of them died.

So if we are worried about -- I know this is not a large simple trial -- this is probably the furthest thing away from there -- but if there are very wide margins when we are looking at safety, is there a way to design a safety margin that is not so wide where you do not have to worry about quite so many people having adverse events for something that may or may not be real, because admittedly there are major problems with how we diagnose people with acute lung injury? Maybe some of the things we are struggling with are, yes, we do not want to prove beyond a shadow of a doubt that lots of people are going to be hurt, but maybe we can figure out, maybe some smart people who will be able to think a lot about trial design who might be able to come up with a better measure.

DR. FLEMING: I think that is an important point for us to pursue. Just to follow up on what Jay was saying, I understand a lot of what you are saying, Jay. In

fact if the essence of the concern that occurred in SPRINT was ARDS, I totally agree with what you are saying. It is a suggested concern. I do not know if it is real, and yet I need to understand it because it can so meaningfully influence benefit to risk.

The problem that I am having is that is not the totality of the concern. As FDA and others have clearly indicated there is diminished efficacy of those increased numbers of transfusions, et cetera, that in totality are enhancing the level of concern. Some of those things, though, are still not well understood from SPRINT, although I strongly discount the data that we get on these kinds of issues from non-randomized control, particularly pharmaco-vigilance programs that have more passive surveillance. It is not possible to understand the causal relationship when factors are 1.2 to 1.5, even 2. Where that pharmaco-vigilance works well is if I have Tacaribe and I have PML and it is a 1,000-fold increase, I do not need a randomized control. Pharmaco-vigilance is going to show it to me. If I have the rotavirus and it is in its inception, it is more than a tenfold increase, I can get that.

We are talking here though about relative increases of, at most, 50 percent that we are concerned about in days with Grade 2 events and relative increases that I would argue have to be less than two, because 1.5 is

surely problematic as well for ARDS or for ALI. Those kinds of effects cannot be understood from pharmacovigilance. You have to have a randomized comparative trial, which has two implications. One is how important the Phase 3, the proposed Phase 3 that the agency and the sponsor have put forward, and the Phase 4, if it is going to be done, I do not understand how it can be done without a randomized control.

Two examples that I think could be relevant to thinking forward, is there a measured next step? The two examples that I can think of are when the Cox-2 inhibitors in OA and RA patients were discovered to have the off-target effect of increasing cardiovascular death, stroke, and MI, Vioxx and Bextra came off of the market but Celecox if it was not sufficient clear, and the agency left the product on the market. It is now being studied in the precision trial which is randomizing 20,000 people, following them two and a half years to determine whether one can rule out a one-third increase in the risk of cardiovascular death, stroke, and MI.

Why one-third? Because the background rate in OA and RA patients is ten events per 1000 person-years. One-third increase is an extra three events. Why is that acceptable? Because you're getting rid of GI ulceration

and you are enhancing the analgesic opportunities for patients. That is the tradeoff.

Another setting, type 2 diabetes. Until July 1st and 2nd of last year we were using hemoglobin A1C effects over six months, and it was discovered with emerging data that there was a lot we did not understand about benefit to risk, particularly cardiovascular risks based on what happened with muraglitazar, with rosiglitazone, with other trials that emerged.

So what the agency has put forward is a two-step plan that in a certain sense parallels what the FDA has talked about here, a premarketing ruling on a 1.8 excess risk and then a postmarketing ruling on a 1.3 excess risk. Why 1.3? Well, that is a 2-percent-per-year annual event rate, which is 20 events per thousand person-years. Ruling out a 1.3 is ruling out an excess of six events, six cardiovascular deaths, strokes, and MIs per thousand person-years.

Why allow that? Because you have got agents that are understood to provide long-term positive effects on microvascular complications -- blindness, neuropathy, nephropathy, and potentially long-term positive effects on cardiovascular death, stroke, and MI, which is the major cause of morbidity and mortality for diabetes patients. It is because of that sense of the long-term benefit occurring

in substantial fractions of people that it is judged that if you can rule out a 30 percent increase, you can stay in the market. If you can rule out an 80 percent increase, you can get into the market.

By the way, those studies contrast what the story used to be: 300-patient studies followed for 6 months where you do five or six or seven of those, to now needing to do a 5,000-to-6,000-person study following people for 5 years to accumulate 600 events, 120 of them before you get into the market. You need 500 events from the Celecoxib trial.

These are examples where there is the possibility that a product that provides important on-target benefits and yet could achieve off-target effects that could trump that could still be studied where you could rule out what would be unacceptably high.

In this setting it is not fundamentally different if the ALI rates or the ARDS rates are real, if they are real. Those kinds of excess events would be meaningfully offsetting the benefits of what we are hoping to achieve here. My concern is what is put forward here are margins that are difficult to justify, a margin of two. Basically a margin of two for ALI with a baseline rate of 5 percent would be ruling out 50 excess events per thousand person-years or per thousand people. Even for ARDS, ruling out

two would be 25 to 30 events. Those are much more than what have been viewed in the Cox-2 setting or in the type 2 diabetes setting for excess events. It is not clear to me why we should be allowing more here than in those kinds of settings.

An approach could be to essentially -- so essentially the way it is proposed as you have got it right now by my calculations, it takes 65 events, ALI events, 65. About half of those are going to be ARDS events, about 32. That is not going to give us a robust, extended insight about what we already have. Essentially, as I have already mentioned, that is only going to rule out a doubling. If instead you were ruling out a 50 percent relative increase ultimately, and an 80 percent relative increase to get into the market, then essentially you would be cutting in half the number of those excess events that you could be allowing.

It seems more balanced. It is still really aggressive when you can talk about what is known about what is known about the upside of preventing bacterial sepsis. But it does seem more balanced with what is going on moving forward in other clinical settings where one is saying, yes, there is the potential for benefit, but what is the downside? I think it needs to be quantitated in



terms of numbers of events per thousand people or numbers of events per hundred thousand people.

If you did this, I think you would have to do it the way it is being done now in type 2 diabetes. You set a higher bar. You are allowing 1.8, which is what is happening in diabetes in premarketing, but in postmarketing there is 1.3; maybe you could justify 1.5 here. But the postmarketing is a randomized, controlled trial. You cannot go into postmarketing trying to discern differences of a 5 percent rate against 6. You have no chance of discerning that, whether it is true signal or whether there are selection factors that account for it.

It would seem you have to parallel what is happening now in type 2 diabetes, where you would do an extended safety assessment in Phase 4, if a Phase 3 assessment -- it would be 190 events of which 90 of them, 90 of them would be ARDS. So that would substantially enhance your understanding about whether, as you correctly note, Jay, it could be a chance event that that occurred. But you would have a substantially enhanced insight.

It seems to me that the margins would have to be more in this order. What is the price of it? It is 3,000 people. It is not the 1,000, it would be 3,000. It is still a lot less than the 20,000 that we are doing to keep Celecoxib on the market or the 5,000 to 6,000 people we

followed for 5 years that every single new agent in type 2 diabetes is having to do. Why is it so large in those settings? Because those are highly common settings. OA, RA, and type 2 diabetes, they are highly common settings. We owe it to the public to understand adequately benefit against risk.

This is not an orphan indication here either. This is a very significant setting that seems to need the same level of balanced insight.

DR. CHRISTIE: How common is this? How big is the market for platelet transfusion -- I am just trying to get some idea because that helps us balance the type 2 diabetes versus the acute myelogenous leukemia or Reye's syndrome.

PARTICIPANT: I believe there is 4 million apheresis platelets doses collected per year.

DR. CHRISTIE: So that is really big. So the question is it is not feasible because it would take too many. I mean if you're giving 4 million, that is a lot. So it does fit in more closely to Type 2 diabetes paradigm than the Reye's syndrome paradigm.

DR. CORASH: If I could just comment, it is not 4 million patients a year. Hematology-oncology patients, who comprise about 60 percent of the population getting

transfused, there are about a quarter of a million patients a year, we believe, who get platelets in the United States.

DR. ALLEN: I am changing the subject a little bit, although it does follow along a bit with some of the other discussion. I was going to ask questions but I will just make a simple comment.

During her second presentation, Ms. Moore talked briefly about the preparation of the platelets in anticipation of the trial. That is not -- at least I could not find it in any of the materials that were provided to us -- there is not sufficient detail about the study plan.

I think that is a very critical aspect of it, however. I do not know exactly how it was set up in the earlier studies, and maybe it is adequately covered. I think it is an area that needs attention to assure that there is not only blinded randomization of the patient population but of the way in which the platelets are done. You do not want the INTERCEPT platelets, let's say, to be an average of 2.5 days of age and the control platelets to be 3.5 days of age because that might have a significant difference in and of itself. Platelet preparation just needs to be looked at very carefully as part of the study design.

DR. ZIMRIN: With regard to -- I am sorry. I was struck by your point and I totally lost my thought. Give me a second and I'll get it back.

DR. SIEGAL: In the meantime, let me ask if there is anyone who wants to speak in the open public hearing. Okay, we do have a volunteer, so I think I have to read a statement.

DR. ZIMRIN: Before I lose my thought again, with regard to your -- I guess the point that was made about doing a larger study afterwards and how many patients were available, we heard a lot about how difficult it was to make the diagnosis if you are looking specifically at a diagnosis of acute lung injury. Expanding that and trying to get everyone who actually transfuses platelets into patients with leukemia without adequate training and without the unbelievable detail that we were hearing about, which I think is essential -- I mean it seems to me that the crux of this is that we are actually going to define this and we are going to be very careful, because otherwise it would sort of be garbage-in/garbage-out kind of a result.

DR. CHRISTIE: To clarify, my question was not necessarily the size of the study and what it takes to diagnose acute lung injury. I mean we do that in a lot of other studies that are quite large scale.

The question really was the impact on the public. If this was something that was rare and that we were only transfusing platelets to a small number of the people, would it not necessarily fit an orphan paradigm but would that kind of justify the potentially smaller size of the trial and the more rapid progression toward a postmarketing surveillance paradigm, as opposed to the type 2 diabetes paradigm which you know has more stringent premarketing conceptual framework due to the fact that it is so common, there are so many people exposed to it. I was just trying to get a sense for how big it was.

In terms of the trial, I do think at some point in time we have got to talk about some specific feedback on the outcome of the study and how you are actually going to do that and whether you can handle spectrum bias and misclassification and so forth, which I think might be helpful, because this is very, very difficult stuff to do.

I know that Dr. Sevransky and I spent a lot of time talking about this on the side because it is really hard. So I am glad to talk about that when people want to talk about it. So we have the public to hear from first.

DR. ALLEN: Just very quickly. Given the aging of our population, the development of new technology such as human stem cell transplants and so on as part of therapies, this really is an expanding area.

DR. FLEMING: Just one other quick thought following on all of this. These are great added issues around the reality around what we are facing. Just to quote what the sponsor said when they talked about ALI, rigorous protocols needed to identify ALI cannot rely on physicians to identify them. It takes a lot of training. I would also say, when it is that subjective or that complicated, it takes a blinded assessment. How could you possibly do that without a randomized control? How can you possibly, in that scenario, going beyond the fact that you want to detect relative risks of 1.2 to 1.5, when you have that level of subjectivity and the complexity at the endpoint, you have got to have a control arm.

DR. SIEGAL: Let me just read this before the open public hearing.

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**Agenda Item: Open Public Hearing**

DR. SIEGAL: We have two speakers, one of them I recognize, the first one please identify yourself.

DR. AEBERSOLD: The first one is Paul Aebersold from Quintiles. One of the things that is unusual that was presented today is that there were something like 11, I believe that was mentioned, adverse events that all were against the test platelets. Those were statistically significantly different against the test platelets and none against the control. That is 11 out of Lord knows how many hundreds or two hundred adverse events in the MedDRA coding terms. There must be tables and tables of adverse events, and 11 of them were different, statistically all one way.

If there were equal safety, you would expect about half of the -- and there will always be statistically

different ones out of that number -- you would expect half of them to go against the control and half of them to go against the test intervention if the safety is equal.

I do not know how you can design this as part of your analysis, but it would be part of my analysis in doing a trial that would not repeat SPRINT but, as Dr. Corash pointed out, would probably solve this problem of a lot of low platelets that were delivered and lower platelet counts on board and so forth.

If you are testing, as Dr. Troxel pointed out, in doing this new trial that you are going to correct for some of these perhaps deficiencies in platelet delivery and SPRINT, then what you would want to see as a safety outcome in the adverse events is, above and beyond any particular thing -- I mean ARDS is bad and that is why it is focused on, but what about the -- how do you get 11 out of 11 going one way? You want to see, if you have equal safety, that you would have half going one way and half going the other way. I don't know how you could prospectively write this as an analysis. I would ask Dr. Fleming about this.

Personally, I would expect just by random chance to see half one way and half the other way. If that is the way that it came out, then you would get a better feeling of, oh, it looks like it is kind of equal safety all the way around, and then maybe you would accept a little bit



more uncertainty about any particular one of the adverse events.

DR. SIEGAL: Dr. Alter.

DR. ALTER: Harvey Alter from NIH but I am not speaking for NIH. I have no financial relationships; in fact I have no money.

(Laughter)

But this was an understandable but frightening discussion, because until Jay came in and turned the tide, I saw this concept of pathogen reduction slipping away here. I think there are concerns about the previous trial, but I am not sure they are real, and I think they have to be repeated. I think Jay expressed that very well.

But there is something bigger at stake here. This is a chance for us to change the paradigm of blood safety in terms of infectious diseases. There are other measures that are important in blood safety, but in terms of infectious diseases, we have had this continuous reactive strategy where we have to see disease before we develop a test, so we are accepting the risk of a new disease over the emergence of an old disease, and we are always behind the agent.

Pathogen reduction is our chance to be preemptive, to make platelets as safe as plasma. We have had tremendous comfort with plasma as new agents emerge

because we know we already have pathogen reduction in place. This is the hope, to do the same for platelets, ultimately for red cells. Once you can do it for red cells and platelets, then there is a lot of economic savings that would make this whole thing fly.

I do not know if we will get to red cells but that would make this whole thing wonderful. It is a magic bullet if it does not have major toxicities. I think that we have to find out if there really are major toxicities.

MS. CARDO(?): Lisa Cardo from the U.S. Army, not speaking for the Army.

We are assuming, or a lot of the discussion assumes, that we always exist in the same low-risk category. But I think that there are times, for example, when the military cannot test and we have to transfuse untested platelets. That is one time when we have a different risk. Another time might be during a major epidemic, like if the flu became pandemic and we had no blood.

So assuming that the studies show that the treated platelets might be inferior, do we still want to say that we can never use this? Because I think that there may be times when we want to use it in spite of the fact that the platelets might be a little less efficacious or a little more dangerous.

DR. SIEGAL: Are there any other open public hearing speakers? If not, let's finish our conversation and proceed to the vote. Is there anyone else who wishes to speak at this point?

(No response.)

With that in mind let's have the questions.

**Agenda Item: Questions for the committee**

DR. FLEMING: While we are putting the questions up, as is typically the case when you are designing a trial, there are enormous complexities. It is not a dichotomous outcome: yes, this is fine; no, it is not fine. And yet, it looks as though we have more dichotomous kinds of questions here. What is your advice? Do we say okay, but, and then clarify the buts if all of these things are addressed? Because these are fundamental design issues that are highly complicated, and I think it has been a great discussion bringing out many of what they are. How does this lend itself to yes/no answers?

DR. SIEGAL: Could we ask that of the FDA?

DR. EPSTEIN: Well, FDA has to decide whether to allow a trial. That is a yes/no question. So to be advised by the committee, I think we want to ask you the question of whether the Phase 3 study as proposed is adequate to determine safety and efficacy, taking into account all of the nuances that have been heard; in other

words, under the current circumstances, with the available data and with a plan for Phase 4. That is the bottom line, really.

We can talk about design. If the answer is no, we can talk about is that no, not ever, or is that no, but it could go forward with modified design? But the bottom line really needs to be whether we think the Phase 3 study as designed is adequate.

So I think the way out of the conundrum you are proposing is to ask the blunt question first and see where the committee is.

DR. HOLLINGER: So, Jay, again, and I think you spoke about this earlier, can you summarize again why you think the first study was either poorly designed or why you have some problems? Because you come down to the second thing, you do another study. Let's say you got just the opposite results. Are you then going to say, well, gee, I do not know if the study was designed that way and now we have got these results, so I am not sure? But you may have some specific things why you think that this might have resulted in something that concerns the FDA or the agency.

DR. EPSTEIN: Okay, well, first, we do not think that the SPRINT study was inadequately designed. It was well designed. However, we knew from the early results in Phase 2 that there was reduced recovery and survival of

platelets. So there was a fundamental question of whether to adjust dosing up front to eliminate it as a potential confounder. The company elected not to do that.

The particular toxicities that were found were unexpected, and prospectively the monitoring had not been designed to carefully assess that. Particularly, this is about lung injury, and we have heard abundantly that it is difficult to assess. So I think that the logic behind repeating the trial is to improve the monitoring so that we get a more reliable result.

Now, the issue of adjusting dosing I think is still on the table. FDA's preference still would be to adjust dosing. However, absent that, if the core question really is whether the serious toxicity, particularly ALI/ARDS, were real or not, the study as redesigned would enable us to answer that question, albeit with wide margins, wide non-inferiority margins.

So that is the rationale. The principal difference between SPRINT and what is being proposed is really the clinical monitoring.

DR. SIEGAL: I actually have a technical question for the pulmonologists here. I am puzzled as to why there is a pulse oximetry on room air of 92 percent as the cutoff for action. Where did that come from? That seems awfully low to me.

DR. CHRISTIE: I have no idea where that came from. If you are talking about the screening portion for acute lung injury, I think that is tricky. I think they have to cut it off somewhere. I will tell you that if I were thinking about acute lung injury or ARDS diagnosis, you can think of other cutoff points that have to do with  $\text{FiO}_2$  because somebody on room air with a pulse oximeter of 92 percent cannot have acute lung injury by definition because of the way that the ratio goes. It would be almost impossible.

That said, because it is a weird ratio, this  $\text{FiO}_2$  ratio, you can actually get down to where it's a double(?) criteria, but many experts have put certain limits on the degree of oxygen people are expiring to avoid sort of artificial cases; for example, a  $\text{BO}_2$  of 60 on 21 percent  $\text{FiO}_2$  or  $\text{BO}_2$  could be acute lung injury. So most people would say generally we think 35, 30 percent  $\text{FiO}_2$  as a trigger and then -- so I didn't have a problem with that.

DR. ADAMS: The only thing I would add is that if you're looking to screen early, I know this is not used for the diagnosis, if I recall from the study, but rather to start looking at the patient more closely, so you start getting to the steep part of the saturation and oxygen dissociation curve just a little bit below there, so it

seems reasonable, if you're trying to pick people up early. I just don't know where that came from.

DR. SIEGAL: I know that as a clinician dealing with people who might have *Pneumocystis carinii* pneumonia that anything under a pulse-ox of 95 would worry me. Is that inappropriate?

DR. ADAMS: It means they're sick, but it doesn't mean they have ALI. So, yes, it should worry you, but it doesn't necessarily mean that they fulfill criteria for acute lung injury or ARDS.

DR. SIEGAL: But I'm not really asking whether you're looking for ALI per se. I'm asking whether you're looking for something in the lung that might be a precursor and might indicate lung damage.

DR. CHRISTIE: Yes. For early monitoring, again I think maybe 92 got picked out of the air again, as John said, because that's where, for most people, depending on their pH, you start to drop off the saturation curves.

DR. ZIMRIN: These are also patients, they're often relapse patients with leukemia and lymphoma who have gotten drugs, who have gotten radiation. So they are not novice patients. So a certain amount of hypoxemia would not be unexpected given what they might have been exposed to.

DR. SIEGAL: No, but the protocol calls for a base line anyway prior to platelet transfusion.

(Comment off microphone.)

DR. SIEGAL: I'm sorry, we would have a point of reference because there's a base line called for prior to platelet transfusion. So you would pick up those people before they got their platelets.

DR. CHRISTIE: Are you advocating a change to trigger or --

DR. SIEGAL: Yes.

DR. CHRISTIE: Because a lot of people are going to be on oxygen and a lot of people are going to be a little bit sick or a lot sick but not ARDS sick, and so there are going to be people on oxygen. Are you advocating changing or suggesting a potential modification of the protocol such that it would be more -- as John said, you're talking about a real screen, and I think that 92 percent on room air in sick people is a pretty liberal place to start for a screen. Liberal might be the wrong word -- a broad enough net for an initial screen.

So I was fine with it, quite frankly, but I'm a critical-care doctor, so that doesn't seem that sick to me.

DR. SIEGAL: Okay, good.

DR. FLEMING: Just to follow up to see if I'm interpreting Jay's response, to be explicit, the kinds of



numbers that I was mentioning before are if the premarketing study was 3,000 people rather than 1,000, we would be getting 190 events of ALI overall, rather than the current proposed 65, and half of those ARDS, there would be 90 of them rather than 30.

That would give you a much more robust -- in fact it would allow you, as we do in type 2 diabetes, to rule out a 1.8. An 80 percent relative increase for ARDS would allow you to rule out a 1.5 for ALI.

Then if the postmarketing was 6,000 people, basically you would be ruling out at that point 1.5 rather than just 1.8 on ARDS and 1.33 rather than 1.5 on ALI, and 1.33 is more parallel to what has gone before us with the Cox-2 inhibitors in OA/RA as well as in the type 2 diabetes.

Now, with this setting, in a sense the answer to your question could be yes because it would be going forward with the trial, it would be allowing ALI to be a principal measure, but it's powered to also look at ARDS, which was the signal-driving result, and it would also greatly enhance our sense about the efficacy issues, because that's a pretty big margin too where you're saying 2.1 days, it's okay to be up to a one-day increase. You would be substantially more powered to a more subtle and reasonable increase.

So if that was one's perspective, is that a yes to your question?

DR. EPSTEIN: That's a year for the caveat, sure.

DR. FLEMING: Okay.

DR. CHRISTIE: Tom, I hate to be a little bit of fly in the Vaseline there, but one of the issues is that, as Dr. Sevransky and I were talking about, this is really hard to diagnose, and so there is a lot of uncertainty. You saw from what Gordon Rubenfeld showed -- I'll come back to that question of are those numbers handling the potential -- there are two pieces to it. One is the potential for misclassification and the other piece is this sort of spectrum effect in handling people who are willingly equivocal.

For example, in observational studies where we're trying to do, say, genetic risk factors for acute lung injury or something, we routinely pull people out who, when people like John or I are looking at chest x-rays, we just say we really just don't know. They might be obese, there may be underlying hardware, there may be a messy film. There may be a lot of things going on. Even though it's protocolized, there are things where you just look at it like that's right on the borderline.

So I am wondering, those numbers are really great for a clear, clear cut. Again, given that this is non-

inferiority, and whereas misclassification or spectrum effect would bias toward a result that would -- toward one, which is what they're trying to prove here, how would you factor in the potential either for, A, misclassification, or B? The misclassification rates are probably 10 to 20 percent. That's just anecdotal, but Gordon showed that, we presented that, John, and when you look at these, that's probably about the right number. So how do you factor in that sort of equivocation if that's appropriate?

DR. FLEMING: I agree with everything you said. It's a great point, and some of these are inherently incredibly challenging to address. The approach to addressing it, first of all, is the margin that you're having. It forces you into a more conservative margin, to address the point you're making. It also, I think, requires you to be looking at the more substantial events separately, which is why I asked Jay if I could say yes to his ALI as long as these numbers are adequate that I can also address the ARDS separately.

So I am going to get rid of some of this noise by not only looking at ALI, I am going to look at ARDS separately. Secondly, I'm looking at a more moderate hazard ratio than what was proposed by the FDA and sponsor, partly because of what you're saying.

Thirdly, this study has to be planned out extremely carefully to ensure that we are building in the best possible event ascertainment that we can that minimizes the noise but still leaves us in a real-world setting. I don't want to come up with something so artificial that it's not generalizable to the real world, but I want to minimize the noise.

But I think these numbers are moving us to a direction of being more robust than what was originally proposed, for the reasons that you're concerned about.

DR. CHRISTIE: I think one other way to handle it is to just build into the characterization protocol a definite probable characterization. Because, remember, there is spectrum effect and then there's misclassification. So even the people with severe hypoxia, where you're looking at a film where there may be a unilateral infiltrate from their leukemia or something, or their Aspergillus or whatever they have, and then they've got something that grows on the other side on their film, and you're scratching your head and looking at it, you can say definite or probable. That's very different than the person who had a clear chest x-ray who whites out, and you're like that is clearly something really bad.

Then there are these borderline things that Gordon called 'tweeners and we call them equivocal. I

don't know what John calls them when he is doing these studies. That's a different thing where you allow the event adjudication committee or the ALI adjudication committee to say these are definite or these are probable. It's no different than strokes or no different than multiple sclerosis or other diseases or MIs, exactly. So I think that that would be important.

But then you also have to really think about the classification even within ARDS. So you address the spectrum effect, which I agree with. But the misclassification even within ARDS is an important thing to add to the power calculations as well.

Do you want to talk about those questions now?

PARTICIPANT: That's why I'm here.

DR. FINNEGAN: Could I ask a question? Actually, this is a dumb orthoped question. Will an MRI pick up the subtleties?

DR. CHRISTIE: Wow, that's a great question. It's exceedingly non-routine, number one. Number two, the death rate from going to a CT scanner in somebody who is that critically ill is, what, about 5, 10 percent, John?

DR. FINNEGAN: I'm at Parkland. I don't think so.

DR. CHRISTIE: But still, people with ARDS who are critically ill, when you move them and go down to CT

scanners or even MRIs, at Parkland, Penn, wherever, it is a pretty high complication rate associated with that, a major complication rate.

Number one, there is no precedent for ever using MRI in ARDS. Number two, getting somebody down to the scanner would not justify the potential benefit from it.

DR. FINNEGAN: But do we know if it shows changes?

DR. CHRISTIE: Go ahead, John.

DR. ADAMS: Because the case definition is not built on that, we don't -- you've heard from a number of people here, we don't have a gold standard. The gold standard is built on a chest radiograph. So I don't know what an MRI would show. You wouldn't be able to do that. There's no biomarker for this syndrome, unfortunately. It would probably cut out an hour's worth of discussion here if there were.

DR. GOLDING: I have a question to the pulmonologists. What you're talking about in your misclassification is that this is very difficult, especially based on a single chest x-ray.

My question is what is stopping us from having more than one snapshot? For example, when you mentioned increased left atrial pressure, well, you treat with

diuretics, and if the pulmonary edema or whatever is in the lungs goes away, you know it was not ALI.

DR. CHRISTIE: I think that's a great point. The question was sort of the longitudinal aspect of it. I'm going to take each of those one at a time.

The first is a single chest x-ray. I agree with you that a cap on a single chest x-ray for ALI, as Gordon showed, is .5. We are all in agreement it is 80 percent. So, with that in mind, many people look at multiple chest x-rays along the way.

The 10 to 20 percent I'm talking about is actually on the individual basis. I don't know how many John has reviewed, but I have reviewed about 7,500 chest x-rays in the last 5 years on people with major trauma and sepsis to adjudicate ALI as part of a process that we have for studies that we do.

Even with that, within an individual, five, six x-rays in a row, again you have somebody with a unilateral process and then you start seeing something that kind of waxes and wanes, blossoms and goes away. If you diuresed it and it went away and their oxygenation got better, does that mean that they didn't have real acute lung injury? Was it not clinically significant even if it leads to mortality? These time-course things are tricky. So the

first part is yes, you look at every x-ray. It's not just that that misclassification is inherent to the individual.

The second point of it is now you're starting to talk about endophenotypes, because there are people with heart failure who also have acute lung injury. The numbers from Gordon there with all the mortality and the ARDSNet studies -- you know, ARDSNet excludes people with cancer, and so there are going to be a lot of people in here but nothing to do with an ARDSNet study or have never had anything to do with an ARDSNet study.

Some people believe that TRALI is a completely different acute lung injury endophenotype than ARDS following trauma, sepsis, or any of these other things. So your question of if it waxes and wanes with diuresis I think leads to a little more complex thought about what this syndrome is rather than just saying we can throw them out. Those might fall into the probable rather than definite.

DR. GOLDING: The other point that you raised I think might also improve the classification, and that is we're talking about an event that is time-related to a transfusion, within that time period. We're not talking about any event, any time.

DR. CHRISTIE: Agreed.



DR. ZIMRIN: I have a question. If the mortality from ALI is substantial, why is it important to be powered to differentiate between ARDS as well as ALI? Maybe I misremembered, but I thought it was like 28 percent or something. It would seem to me that that was an important event in its own right.

DR. ADAMS: If I can just make a point about diagnosis, there is a lot of confusion between the definitions that people have. The data that Gordon presented on the mortality with acute lung injury were people who required mechanical ventilation. With ARDS, they also required mechanical ventilation.

The case definition that we've seen six or seven times up there by the American-European Consensus Committee does not require mechanical ventilation. It might be reasonable to think, if we're worried about finding the right patient requiring for the case definition, to require mechanical ventilation might be one way to -- it won't eliminate all of these other problems about making the diagnosis, but it might select out the more severe forms.

DR. NELSON: Can you make this diagnosis with an autopsy? Because, you know, 40 percent mortality --

DR. CHRISTIE: The answer to that is maybe.

Just to come back to Ann's point, you were getting to the concept of paradigm, right? I mean, this is

a syndrome. It's lupus, it's a syndrome, it's not a disease. That's why I said maybe with the autopsy.

The point about the ARDS, though, is that that's a spectrum-effect issue. One is more severe, one is less severe. So that's why it's probably worthwhile to look at the one, both because the misclassification will probably be less and also because it's probably the more severe end of the spectrum.

But to second John's point, I think that's a great way of getting out of the sort of fuzzy people on the fringes of this.

Then the third thing to come to is just why not ARDS with mortality, because that's really what you want to know? But that's a whole, much smaller population.

DR. FLEMING: I agree with his exact answer. Again, he gave two fundamental reasons why it would be relevant to look at ARDS in addition to the broader ALI. One is that it's more robust to the misclassification, it's more severe, and I would add a third: It's where the signal was. There were 12 against 5. The deaths were 9 against 5. It's one of the reasons that I think having triple the number of events than was currently proposed, we're not powering for mortality, but you're going to have more robustness to be able to look at things like mortality. But it's where the signal is, it's where more

sensitivity may be, because it's less subjective to the misclassification and it's in general where you would expect the higher risk.

DR. ZIMRIN: We actually had a discussion related to mechanical ventilation, I think it was with regard to snake bite, snake bite venom, anti-venom. I guess part of the question there was that people had different thresholds for intubating patients, so that might introduce some subjectivity. I don't know if you agree. Maybe snake bite -- I'm not a pulmonologist -- is different than -- and we know it's different than ARDS.

DR. ADAMS: I think the distinction is whether or not you require positive pressure. Some people don't have a plastic tube shoved down their trachea, they get mechanical ventilation delivered through a tight-fitting mask that fits over their face.

Usually, in most studies, and in Gordon's epidemiologic study, either of those two fit the criteria.

DR. CHRISTIE: And in fact in leukemia patients most people will try non-invasive ventilation first because it has been studied and it reduces mortality, particularly with acute hypoxic respiratory bilateral infiltrates, which is what we're talking about.

DR. SIEGAL: Any more discussion?

PARTICIPANT: Should we address the points?

DR. FINNEGAN: Actually, I have a question for Dr. Epstein. Where it says, "If yes, the proposed magnitude," can we do with caveat, or will you let us vote on that? With Fleming caveat?

DR. EPSTEIN: Well, what I'm hearing -- and we don't know the sense of the committee; only certain people have spoken up -- is that there is some discomfort with the non-inferiority bounds that have been proposed. So the answer to that question would then be no, and then the comment would be, alternatively, here are better bounds.

But again, I don't know the sense of the committee as a whole. An opinion has been expressed that these are not adequate non-inferiority bounds.

Likewise, for 1a the opinion has been expressed that ALI inclusive of ARDS is not an adequate endpoint; that the study should be powered on ARDS.

DR. FLEMING: But I thought you said we could answer a yes if we then followed up a(i) with a no, clarifying that the margins have to be tighter such that you're going to get enhanced insights so that when you answered yes to a, you're not only going to get the ALI answer, you're going to get a great insight for ARDS and for the Grade 2 days, and you said yes. You could say yes to 1a but then you would alter 1a(i).

DR. EPSTEIN: I think one could do that. It's a question of what's the message you're telling us. I guess there's a nuance between saying that you can design the study to look at ALI inclusive of ARDS but only if it's adequately powered to get a, quote/unquote, good look at ARDS. It's really just lumping 1 and 2, a and b.

DR. CHRISTIE: The number thing was not only the ARDS signal, it was also that 5 percent for ALI is inadequate. So it seemed to me, Tom, I'm putting words into your mouth, but it seemed to me that that was sort of killing two birds with one stone.

DR. EPSTEIN: Again, I think it's understandable that to answer it your way -- it's just different answers in the two scenarios.

DR. FLEMING: For those people who believe that we can go forward -- now, we can go forward under some non-trivial refinements, and it seems like that's something you would need to hear, if some of us, if the majority of us believed you could go forward, with refinements that we would get to when we look at (i) and (ii).

DR. EPSTEIN: Maybe the way to go about this is first to vote the subparts. In other words, if there is agreement to reject the non-inferiority margins in favor of tighter ones, then it's clear what you're saying. Just reverse the order and then it's clearer.

DR. JAIN: So the overall product development plan includes both pre- and postmarketing studies to resolve the safety and efficacy concerns raised by the outcomes of the SPRINT study.

Question number one: Premarket study is designed to provide sufficient information to evaluate safety and efficacy.

So, reversing the question, the subpart of question a now is, Is the proposed magnitude of the differences between the treatment and control arms acceptable; that is, a difference less than 5 percent and less than doubling of the rate?

DR. HOLLINGER: So I think, if I may state, I think what you're saying is the second part is, Is the proposed magnitude of the differences between the treatment arm and control arms acceptable? And then you can vote on that.

DR. JAIN: Right, and then we go back to the number a.

DR. FREAS: Could we just have the second part of that slide up there? Right now it says, "If yes --

PARTICIPANT: We are just voting on 1 now?

DR. JAIN: We are voting on 1-a-subpart.

DR. FREAS: Is the proposed margin acceptable is what we're voting on.

PARTICIPANT: I'm sorry, can you just remind us which key we hit?

DR. FREAS: Please don't vote yet until we get the question up on the screen.

DR. JAIN: So we are deleting, "If yes." The question is right now, "Is the proposed magnitude of the differences between the treatment and control arms acceptable, namely, number 1, a difference less than 5 percent, and 2, less than doubling of the rate?"

PARTICIPANT: Those are two questions.

DR. JAIN: One question.

DR. FREAS: Before you vote, there are 16 voting members at table. One is yes, two is no, three is abstain. You can go ahead and vote now.

(Committee members voted.)

DR. FREAS: Would you let us know when everybody is done?

Could we have the names of those not voting?

There are three yes votes and 12 no votes. I will read -- there are 16 voting people at the table. I will read the names of the three yes votes for the record: They are Dr. Zimrin, Mr. Templin, and Dr. Kulkarni.

We're ready for the next -- we're going back to the first question.

DR. JAIN: The first question is, "Is acute lung injury inclusive of ARDS an appropriate safety endpoint?"

DR. FREAS: Before you vote, could we have that posted on the slide, please, so everybody knows exactly which one we're voting on?

DR. FLEMING: And now, Jay, following your logic for the reversal, can we now answer this in the context of having said we would revise the margin?

DR. EPSTEIN: For clarity of the record, I believe we should revise this question to say, "Assuming narrower non-inferiority margins, is ALI inclusive of ARDS an appropriate safety endpoint?"

DR. FREAS: Go ahead and vote.

(Committee members voted.)

For the record, there are 15 yes votes.

Unanimous, no abstentions.

We are ready to vote on the next question.

DR. JAIN: So then the second part of question one, "For the premarket study, is mean days of Grade 2 bleeding an appropriate efficacy endpoint?"

DR. FREAS: The question is displayed. Please go ahead and vote.

(The committee voted.)

This is a time when it's best to be a committee member as opposed to an AV tech.



(Laughter)

DR. BIANCO: Or a non-voting member. It's even better.

DR. FREAS: There were 12 yes votes, zero no votes, and four abstained votes. To simplify the process, I'm going to call out the abstained votes, and then we'll take questions. The abstained votes are -- I don't see any number 3s up there.

DR. JAIN: Three.

DR. FREAS: Okay. And make sure I'm calling out the correct names. The abstained votes for the 1b that we just voted on, the names of the abstainers are:

Dr. Edwards, Dr. Finnegan, Dr. Sevransky, and Dr. Christie.

Next question.

PARTICIPANT: You didn't count abstentions on the first two votes.

DR. FREAS: Everybody voted. There were no abstentions on the first two votes.

Ah, I think we'll start voting by show of hands from here on out. I will -- for tomorrow I will give you the list of names of who voted what. Everybody who voted, we will make sure your vote is correct. The numbers do not tally with the people at the table, and I believe it's a technical error as opposed to a voting error, which we won't take any more time to discuss.

Would you read the next question?

DR. JAIN: "With regard to the postmarketing study, does the committee agree that, A, the conduct of a postmarket study to exclude a 1 percent increase in ALI compared to the control group would provide meaningful additional safety data?"

DR. FLEMING: We're going to vote -- so I think two of us are just asking the same question. You make it easy for us if you don't add a substantive part to the question, which is, "Does the committee agree that a randomized controlled trial postmarketing study" -- do you want to know that added level? That makes a big difference to some of us. Is that an acceptable amendment to the question?

DR. EPSTEIN: Again, it changes the landscape. Some may believe that that's absolutely necessary because there is no alternative certainly at that level of margin. Others may think that a surveillance-type study, for example, looking at cohorts, similar hospitals in the same city, one hospital is doing it because they're in the Phase 4, the other isn't -- you know, baseline demographics. I understand. Some people might accept a case-cohort design; others would reject it prima facie. So I think it might be better to ask independently would a randomized controlled trial be required. We'll add a part.

We'll start with the question of whether ruling out a 1 percent increase in Phase 4 is the appropriate target, and then we can ask whether a randomized controlled trial is needed.

DR. FLEMING: How wedded are you to the 1 percent?

DR. EPSTEIN: Well, it's what we were contemplating. Maybe we can just take discussion on this point, because again, we're barely able to design Phase 3, and we don't know the results, and that may condition what we want to do in the Phase 4. So I think maybe what we should do here is, do we accept in principle a Phase 4 trial with a smaller non-inferiority margin? and stop there. And we're not sure exactly how to design it or how far to go, because it will depend on what we see in Phase 3.

DR. FLEMING: Although it would be very good for the agency to attempt to lay out a perspective that would guide the sponsor before they launch Phase 3 so they have a sense of what it is that is globally to be expected, even though I understand that it could be tweaked based on what you see in Phase 3. But the example that I gave, which was for ALI, premarketing 1.5, postmarketing 1.33, translates to about 1.5 percent. So it's a little more liberal than what you have laid out, but it's even more rigorous than

what you would have in premarketing. So do you want to be explicit at 1 or do you want to say a more rigorous --

DR. EPSTEIN: I am suggesting that we be a little bit more general here because we may need a debate when the time comes over the right margin. I think the concept that has been put forward is a narrower margin. The question is should FDA obligate the sponsor to a Phase 4 study, or if the Phase 3 succeeds with given endpoints, should we obligate the sponsor to a Phase 4 study with a significantly narrower margin of non-inferiority?

DR. FLEMING: So I think we are agreeing, or at least I think I'm agreeing with what you're saying, that this question would go forward but it wouldn't be as rigid as saying 1 percent. It would say that when you get to the postmarketing, a more rigorous non-inferiority margin would need to be ruled out.

DR. EPSTEIN: Right.

DR. FLEMING: And that would be determined as you go forward.

DR. EPSTEIN: Yes. Again, if the committee is comfortable with that revised question, I think we can ask it.

DR. SIEGAL: Are there any objections to that? So let's proceed.

DR. FREAS: I've been told that we're going to try the electronic voting one more time. So please use your electronic vote and we'll try it one more time.

PARTICIPANT: What are we voting on?

DR. JAIN: I think the revised question would be, "For the postmarket study, does the committee agree that the conduct of a postmarketing study to exclude an increase in ALI compared to the control group will provide meaningful additional safety data, and that the exclusion to rule out the increase in ALI will be dependent on the results of the Phase 3, outcomes of the Phase 3 study?" Did I get that right?

DR. EPSTEIN: Well, in general, but I think we need exact language for the record. I'm suggesting: "The conduct of a postmarket study with a narrower non-inferiority margin compared to Phase 3, to exclude an increase in ALI compared to the control group," da, da, da, da.

DR. JAIN: Okay.

DR. FREAS: Did you all hear that or do you need it reread? We will go ahead and vote at this time.

PARTICIPANT: He didn't say that it was double-blinded or --

DR. FREAS: No. That's the next question.

DR. EPSTEIN: Deferring that to a separate question. Shall I repeat it?

(Committee members voted.)

DR. FREAS: Do you have a record vote for everybody? Does anybody need to revote?

We'll call off the names with the votes, and if the vote is incorrect, we'll go back to showing hands.

DR. JAIN: Unanimous.

DR. FREAS: So that's 16 yes votes for the modified question that was just read into the record.

Would you read the next question?

DR. JAIN: The next question is, "For the postmarket study, does the committee agree that a staged rollout is a prudent and necessary approach to the initial commercial launch of the product and the design of the study be randomized control?" Is that how we're linking the two up?

DR. EPSTEIN: I think we just phrased an alternative second question, which is, "Should the postmarketing study be a randomized controlled trial?"

DR. FREAS: Are we ready to vote, even though the question is not on the board? Please go ahead and vote at this time.

(Committee members voted.)

DR. FREAS: We have added another question. You don't have it recorded yet.

We're going to vote by show of hands on this. Again, could you just reread it one more time?

DR. EPSTEIN: It now says, "Two, does the committee agree that" -- and this is new part b -- "the postmarketing study should be a randomized controlled trial?"

DR. FREAS: We have to vote simultaneously. I think it will be faster just to have a show of all the yes votes. Could I have a show of all the yeses? Please keep your hand up until your name is called. The yes votes are Dr. Nelson, Dr. Allen, Dr. Edwards, Dr. Bower, Dr. Sevransky, Dr. Siegal, Mr. Templin, Dr. Finnegan, Dr. Hollinger, Dr. Troxel, Dr. Fleming, Dr. Kulkarni, Dr. Christie, and Dr. McComas. Thank you.

Could I have a show of hands of the no votes? There are zero no votes.

Could I have a show of hands of the two abstentions? There are two abstentions: Dr. Ballow and Dr. Zimrin.

We're ready to have the next question read.

DR. JAIN: That's already up. "Does the committee agree that a staged rollout is a prudent and

necessary approach to the initial commercial launch of the product?"

DR. SIEGAL: Dr. Fleming?

DR. FLEMING: Just to make sure at least I, for one, know exactly what you mean by the staged rollout, would a staged rollout, for example, be that we would have the premarketing assessment using these tighter margins but then the postmarketing would be a randomized trial with a further tightening of the margin? Would that be called a staged rollout? Or do you mean something more than that?

DR. EPSTEIN: Exactly what was proposed was that the commercialization of the product be limited initially to the centers participating in the Phase 4 trial. That was the exact proposal.

DR. FLEMING: Could we have some discussion? Is there anyone who could comment to give their perspectives on that?

DR. NELSON: I thought it also was supposed to be the incidence of the acute lung injury would be measured in the control, and if it might be different than what was in the clinical trial. You know, it was 6 percent. It could be 3, it could be 12 when it was commercially -- was that part of it, Jay, or not? That the incidence or what you're measuring the treated platelets against the standard apheresis platelets might be a different standard. That



would be part of the staged rollout, too, right? That they would sequentially measure what the incidence of acute lung injury is with the standard platelets.

DR. EPSTEIN: Again, the concept is to get more accurate measures in both the treatment group and the control in order to achieve a tighter non-inferiority margin before there's widespread clinical use. That's the concept.

It recognizes the fact that the initial results of a much smaller trial might be misleading or non-representative. So you have more study centers, more patients. Of course, the tradeoff is whether you can achieve comparable rigor, and that's always an open question.

DR. FLEMING: I certainly see advantages to doing that. One of them is sense of urgency. Sponsors are, through experience in these types of safety trials, not exhibiting the same sense of urgency in getting a postmarketing study done as they do a premarketing study, and if you had restriction, there would be obviously a substantially retained sense of urgency, because your market is limited to the people that would be going into the postmarketing trial.

It's not the way it's being done in type 2 diabetes, just as an example in context. If you are

approved in the premarketing step, it is allowed to have broad marketing where, of course, everybody is saying we're really committed to make sure we get that postmarketing study done in a timely way. But it will be harder to do so.

But at least by analogy in the type 2 diabetes setting, once you get the premarketing step successfully completed, if you're approved, then you're marketing the product and still doing the safety study in the context of marketing.

DR. ALLEN: This one may be a bit different than type 2 diabetes, however, because you don't have an individual physician deciding to order the INTERCEPT-treated platelets versus non-treated platelets. It's going to be made on a system-wide basis, whether a blood center will decide all of the platelets we deliver will be treated or a hospital will decide that.

So I think the rollout, the implementation, is going to be very different than it will be in a standard clinical setting where a clinician is deciding whether or not he wants to offer a certain treatment, and that has to be taken under consideration.

DR. FLEMING: As you do so, what is your sense? What is your sense then?

DR. ALLEN: You know, I haven't really thought about it before today, and I would let somebody from the FDA who has had more experience with a rollout respond.

DR. HOLLINGER: But if you're going to do a randomized controlled trial, it almost looks like it's a third -- the Phase 3 trial again, except for tighter margins. You're going back to the same centers. They're going to be doing the same randomized control, so it's not a decision that they're going to make except as it is randomized.

I am just not sure, Tom, about what -- how this is going to play out. I think postmarketing is important. I think one of the problems that the FDA has had in the past is they said, oh, we want postmarketing, but then nobody really follows through often to make sure that it has really been done.

So I like the idea that there's a little bit more authority put to this, but I'm just wondering about the staged and other things, how this is going to play out.

DR. FLEMING: My sense is that, at least in the type 2 diabetes setting, the idea was to try to make this as user-friendly or as accommodating as possible to those developing interventions while still being responsible to the patient population to get a timely insight. So there it was you've got to hit at least a first-pass level of

rigor in the margin. Then you can start marketing the product, but we still want a timely assessment in a more rigorous way.

My sense is again to make it user-friendly. I don't want to compromise the integrity of that postmarketing study, but I do see the need to try to think creatively how the sponsor could start marketing the product. I would actually be more comfortable saying they could stop marketing the product, but we have a 5-year window or some defined window to say in that time period, once you get into the postmarketing, you've got to finish the postmarketing trial. But the point is to allow for the marketing to occur then to make it more user-friendly and to get this product to the public sooner if it passes that Phase 3 screen.

DR. SIEGAL: Celso?

DR. BIANCO: We have a recent experience with the PASSPORT study, and it was very effective as a Phase 4, even if it showed that it didn't work. But I think that that's a similar thing here, and I think more liberal marketing after the Phase 3 if the Phase 3 is concluded appropriately and safely will be the encouragement for the manufacturer to go ahead and do it.

DR. FINNEGAN: Dr. Fleming, don't you think that we're trying to sort of look into the future a little bit?

Because some of this postmarket is going to depend on what they find on the Phase 3, and we're not happy with what they found initially. So I don't think we can actually give them anything more.

DR. FLEMING: That's a great point. All of this is contingent on reliably passing each step. So the question as I understand it, at least the way I'm interpreting it, is if the Phase 3 step is completed meeting appropriate, more stringent margins that we've talked about, and the ultimate benefit-to-risk is assessed to be sufficiently favorable to justify approval, then in that context you would approve and you would then need to finish the postmarketing study and you would be marketing the product.

Same idea in type 2 diabetes. If you don't pass, though, that Phase 3 benefit-to-risk, then bets are off. You're not going to get the approval of the product and then the postmarketing. It's still going to back in premarketing. In fact, to be explicit, FDA has said if you don't have a sufficiently favorable result in that premarketing, then you have to extend that premarketing before you get further approval or in fact discontinue.

So this whole issue of postmarketing is contingent on meeting a favorable benefit-to-risk

assessment using the bar for favorable that these margins will be specified to be for the Phase 3 step.

DR. SIEGAL: Jay, do you want to say something?

DR. EPSTEIN: No, I agree. I was going to say a similar point is that the whole concept is that we cannot in Phase 3 have a large enough denominator to be confident of a tolerable ratio of risks. So there is no other way except to monitor it in Phase 4. What we're really just talking about is what's the rigor of the Phase 4 study.

DR. FREAS: We are ready to go ahead and vote on question 2b as shown on the screen. Go ahead and enter your vote.

(Committee members voted.)

There still should be 16 votes when we get done.

There are 14 yes votes, zero no votes, and two abstained votes. I will read the names of the two abstained votes. They are Dr. McComus and Dr. Edwards.

That's the end of the voting for today.

DR. SIEGAL: Does anyone wish to say anything intelligent at this hour?

(Laughter)

We are adjourned.

(Whereupon, at 7:10 p.m., a recess was taken until 8:15 a.m. the following day.)