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Center for Biologics Evaluation and Research (CBER)
121st Meeting of the Blood Product Advisory Committee (BPAC)

OPEN SESSION

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This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

ATTENDEES

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Monique Gelderman, Ph.D.	Food and Drug Administration
Christina Vert, M.S.	Food and Drug Administration

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CALL TO ORDER AND OPENING REMARKS/INTRODUCTION OF THE COMMITTEE

DR. RICHARD KAUFMAN: Okay. Good morning. We're going to go ahead and get started. It's a pleasure to welcome everyone to the 121st Meeting of the Blood Products Advisory Committee. My name is Richard Kaufman. I'm the medical director for the transfusion service at the Brigham and Women's Hospital, and I'll be serving as chair for this meeting.

So, I'd like to welcome the members of the Committee, participants, the public as well as the audience joining us via the webcast. So just to start, I'd like to go around and ask the members of the Committee to introduce themselves. And I'd like to ask that they please provide their institutional affiliation as well as their expertise. So, why don't we start with Dr. Perez.

DR. ELENA PEREZ: Good morning. My name is

Elena Perez. I trained as a pediatric allergist immunologist at Children's Hospital of Philadelphia and was in academia for a while. And now I'm in private practice in Jupiter, Florida -- sorry, in North Palm Beach, Florida.

DR. JUDITH BAKER: Hi, good morning. Judith Baker. My background is public health. I am with the Center for Inherited Blood Disorders in Orange County and also an assistant adjunct faculty at UCLA in Los Angeles.

DR. JACK STAPLETON: Jack Stapleton. I'm a professor at the University of Iowa of internal medicine and microbiology, and I'm an infectious disease physician.

DR. ALFRED DEMARIA: Al DeMaria. I'm a medical and laboratory consultant to the Massachusetts Department of Public Health, Bureau of Infectious Disease and Laboratory Sciences and expertise in infectious disease and epidemiology.

DR. BARBARA BRYANT: I'm Dr. Barbara Bryant. I'm a professor and Medical Director of the Transfusion

Medicine Department at the University of Texas Medical Branch in Galveston, Texas.

DR. SUSAN STRAMER: Good morning. I'm Susan Stramer. I'm with the American Red Cross as Vice President of Scientific Affairs. I'm trained as a public health microbiologist. And on this committee, I'm the industry rep.

DR. KENICHI TANAKA: Good morning. My name is Ken Tanaka. I'm a professor of anesthesiology at University of Maryland. And I'm also a practicing cardiac anesthesiologist.

DR. JOEL BENNETT: I'm Joel Bennett from the University of Pennsylvania. I'm a hematologist. I study platelets and focusing on platelet integrin and structure and function.

DR. ANDREI KINDZELSKI: Good morning. Andrei Kindzelski trained as hematologist. I am a program director in blood division NHLBI, NIH.

DR. AMY SHAPIRO: Hello. I am Amy Shapiro. I'm a pediatric hematologist from the Indiana Hemophilia and Thrombosis center and also have an

academic appointment at the Blood Research Institute in Milwaukee.

LCDR JEFFERSON JONES: Hi, good morning. Lieutenant Commander Jefferson Jones. I'm a pediatrician and preventative medicine physician. I'm a medical officer with the Center for Disease Control Office of Blood, Organ, and Other Tissue Safety.

DR. RICHARD KAUFMAN: And I'd like to introduce three additional members that are calling in. Dr. DeVan?

MS. CHRISTINA VERT: He may be joining us later.

DR. MICHAEL DEVAN: Hello?

MS. CHRISTINA VERT: Dr. DeVan?

DR. MICHAEL DEVAN: Yes, hi. I'm the medical director for Blood Services at Walter Reed National Military Medical Center.

DR. RICHARD KAUFMAN: Thanks. Dr. Ortel?

DR. THOMAS ORTEL: Hi. This is Tom Ortel. I'm Chief of Hematology at Duke Medical Center.

DR. RICHARD KAUFMAN: Thank you. Dr. Morgan?

DR. CHARITY MORGAN: Hi. I'm Charity Morgan. I'm Associate Professor of Biostatistics at University of Alabama at Birmingham.

DR. RICHARD KAUFMAN: Well, thank you and welcome.

CONFLICT OF INTEREST STATEMENT

MS. CHRISTINA VERT: Good morning everyone. My name is Christina Vert, and it is my pleasure to serve as the Designated Federal Officer for the 121st Blood Products Advisory Committee, known as BPAC.

The Committee Management Specialists for this meeting are Ms. Joanne Lipkind and Ms. Monique Hill. The Committee Management Officer for this meeting is Dr. Jeannette Devine, and our Director is Dr. Prabhakara Atreya. On behalf of the FDA, the Center for Biologics Evaluation and Research, and BPAC, we would like to welcome everyone to this meeting.

Today's session has one topic that is open to the public in its entirety. The meeting topic is described in the Federal Register notice that was

published on October 2, 2019.

The FDA CBER press media representatives for today's meeting are Mr. Paul Richards and Ms. Megan McSeveney. Can both of you stand if you are here so that members of the press can identify and reach out to you as needed? Okay. If they're not here, they may be here later. The transcriptionist for the meeting today is Andrew Del Bene.

I would like to remind everyone to please check your cellphones. Please make sure they're either turned off or are in silent mode. When making your comment, please first state your name and speak up so that your comments are accurately recorded for transcription. Please keep in mind that a few Committee members are joining us remotely, and we would like everyone to be heard for the benefit of the FDA staff here in the room, members of the public, and those listening via webcast.

I want to remind members all formal discussions have to be done while the meeting is on and not during breaks. I will now proceed to read the

conflict of interest statement for this meeting.

The Food and Drug Administration is convening today, November 22, 2019, for the 121st meeting of the Blood Products Advisory Committee, BPAC, under the authority of the Federal Advisory Committee Act of 1972. At this meeting in the open session, the Committee will discuss considerations for cold stored platelet products intended for transfusion, including product characterization, duration of storage, and clinical indications for use.

The Committee will hear presentations on available characterization and functional studies of cold stored platelets, clinical studies, and the potential role of cold stored platelets in clinical care in military and civilian patient populations. The Committee will also discuss the clinical studies needed to support the indication for use of cold stored platelet products stored beyond three days.

The following information on the status of this advisory committee's compliance with federal ethics and conflict of interest laws, including, but

not limited to 18 U.S. Code 208, is being provided to participants at this meeting and to the public. The conflict of interest statement will be available for public viewing at the registration table.

With the exception of the industry representative, all participants of the Committee are special government employees or regular government employees from other agencies and are subject to the federal conflict of interest laws and regulations. Related to the discussions at this meeting, all members and consultants of this committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them, including those of their spouse or minor children and, for the purposes of 18 U.S. Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employee. FDA has determined that all members of this advisory committee are in compliance with federal ethics and conflict of

interest laws. Under 18 U.S. Code 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. However, based on today's agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code 208.

Dr. Susan Stramer is currently serving as the industry representative to this committee. Dr. Stramer is employed by the American Red Cross. Industry representatives act on behalf of all related industry and bring general industry perspective to the Committee. Industry representatives are not special government employees and do not vote and do not participate in the close sessions, if held.

Dr. Judith Baker is serving as the consumer representative for this meeting. Consumer representatives are special government employees and do

have voting privileges. And they are authorized to participate in the closed sessions, if held. They are screened for their financial conflicts of interests and cleared prior to their participation. Today, we have three temporary voting members: Dr. Joel Bennett, Dr. Kenichi Tanaka, and Dr. Charity Morgan via phone. They have been appointed as special government employees for the Agency, and they have been screened for potential financial conflicts of interest and cleared for participation.

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

FDA encourages all other participants to

advise the Committee of any financial relationships that you may have with any firms, its products, and, if it's known, its direct competitors. We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest that participants need to exclude themselves from such involvement. And exclusion will be noted for the record.

Additionally, I would like to provide specific items regarding this BPAC November 22, 2019, meeting. Please note that the topic of this meeting is determined to be a particular matter of general applicability and as such does not focus its discussion on any particular product, but instead focuses on the class of products under discussion. Therefore, BPAC's role is to discuss the available characterization and functional studies of cold stored platelets, clinical studies and the potential role of cold stored platelets in clinical care in military and civilian patient

populations as related to the class of products being discussed. Speakers will provide data on the clinical development of blood products that serve only as examples for the Committee to have a scientific discussion while considering cold stored platelets products.

This BPAC meeting is not being convened to recommend any action against or approval for any specific cold stored platelet product or clinical trial. This BPAC meeting is not being convened to make specific recommendations that may potentially impact any specific party, entity, individual, or firm in a unique way. And any discussion of individual products will be only to serve as an example of the product class. This meeting of the BPAC will not involve the approval or disapproval, labeling requirements, post-marketing requirements, or related issues regarding the legal status of any specific products.

This concludes my reading of the conflicts of interest statement for the public record. At this time, I would like to hand over the meeting to Dr.

Kaufman. Thank you.

DR. RICHARD KAUFMAN: Thank you. So, the topic for today's meeting is scientific considerations for cold stored platelet products intended for transfusion. At this time, I'd like to invite our first speaker, Dr. Carolos Villa from FDA, who will be introducing the meeting topic.

INTRODUCTION TO THE TOPIC

DR. CARLOS VILLA: Good morning. Thank you to the Committee. Thank you to all our participants and our speakers today. I'd like to welcome everyone to the 121st meeting of the Blood Products Advisory Committee. My name is Carlos Villa. I'm a medical officer in the Division of Blood Components and Devices in the Office of Blood Research and Review at CBER. Today I'll be providing an introduction to our topic, which is the considerations for cold platelets intended for transfusion.

Today, FDA is seeking advice from the Committee to advance the safe, effective, and efficient

development of cold stored platelets. As part of this, the Committee will hear presentations discussing available data on cold stored platelets, including characterization and functional testing, clinical studies, and their potential role in clinical care.

The Committee is asked to consider the available evidence and provide advice on studies needed to support the use of cold stored platelets intended for transfusion and stored beyond three days. With that, I'd like to switch to some background on platelets and platelets in transfusion medicine in general.

Platelets have an important role in normal hemostasis and control of bleeding. We can see on the righthand side of the slide, in the top left panel, what a normal platelet has a discoid or plate-like shape. Following activation, platelets will assume a spiny shape with cytoplasmic projections, or filopodia. And it's important to remember that platelets are metabolically active and contain a variety of intracellular granules and components that participate

in various physiologic processes, such as hemostasis and cytokine signaling. Platelets are transfused to prevent bleeding in patients with thrombocytopenia, to treat active bleeding, and to treat patients with dysfunctional platelets.

Platelets for transfusion are collected by apheresis or prepared from whole blood donations. And these platelets can be stored in plasma with or without additional platelet additive solution. We can see on the righthand side of the slide what a typical platelet product would look like. These platelets may undergo additional modification, such as pathogen reduction. Following my introduction, Dr. Darrell Triulzi will provide a more detailed look at platelets in clinical medicine.

Conventionally, platelets are stored at room temperature for a period of up to five or seven days. These are referred to as room-temperature platelets, or RTP throughout my talk. For room-temperature platelets, agitation facilitates oxygen utilization and helps to maintain their morphology, their function, and

their pH during storage. Nonetheless, platelets undergo a series of physiologic and biochemical changes during storage, which is commonly referred to as a storage lesion.

We'll hear a lot about those changes that occur during storage from several of our speakers today; but as a visual example of some of those changes, we can see on the righthand side of this slide, in the left panel, a fresh platelet with a discoid shape and normal intracellular contents. And then five days after storage, it has assumed the spherical shape with disruption of its intracellular contents.

Alternatively, cold stored platelets can be stored -- platelets can be stored in the cold, which I'll refer to as cold stored platelets. This is a temperature range of one to six degrees centigrade. However, although studies show decreased circulatory -- although cold stored platelets were commonly used prior to the 1970s, studies did show decreased circulatory recovery and survival when compared to room temperature

platelets. Historically, storage has been limited to 72 hours from the time of collection of the source blood. And because metabolism is slowed under cold conditions, agitation is optional per the Code of Federal Regulations. And I'll get to that third point in terms of the storage period in a moment.

At this point, I would like to review some of the regulatory history provide some context on the storage duration of cold stored platelets and to introduce the idea that some of the questions around the optimal storage period for platelets in the cold are not new. In fact, in 1974, the preamble to the proposed rule concerning the additional standards for platelet concentrates included the following statements and noted that there was differing medical opinion with respect to optimal storage temperatures. It included statements such as "Platelets stored at 20 to 24 exhibit a longer posttransfusion survival time. Platelets stored between one to six degrees centigrade, which on the other hand, appear to be more potent during the initial stages of producing hemostasis" and

finally stated that “the Commissioner proposes that a licensed manufacturer may store the product at either temperature.”

Subsequently, in 1975, the regulations were finalized and included both cold storage and room temperature storage. In 1982, this storage period was shortened to 48 hours and was, again, restored to 72 hours in 1985. Fast forward to 2007, a final rule changed the dating period regulations to allow for flexible dating periods depending on the type of collecting, processing, and storage system used to produce the platelets. For cold stored platelets, this meant that the storage period became up to 72 hours from collection of the source blood or as specified in the directions for use for the collection system and storage system.

Most recently, in 2016, a final rule amended the regulations for consistency with updated practices in the biologics products industry. And for cold stored platelets and all platelets outside room temperature, the dating period became as specified by

the instructions for use. And this is where the storage period stands today. That has some implications which I will touch on later in my talk.

Going back to the 1970s, although cold storage was included in the standards for platelets at that time, given the prevalence of platelet transfusion for prophylaxis in thrombocytopenic patients, the decreased circulatory recovery and shorter survival of cold stored platelets led the transfusion medicine community to shift almost entirely to room temperature platelets. Nonetheless, some attributes of cold storage have drawn renewed interest in cold stored platelets. Some of these include no agitation. As a result of their slowed metabolism, cold platelets don't require agitation. This provides some logistical benefits -- limitation of bacterial growth as compared to room temperature and, finally, the potential for a longer storage period while maintaining hemostatic efficacy when compared to room temperature platelets of similar storage age. And it is this last point which will be the focus of much of today's discussion.

Now, many studies have characterized cold stored platelets in vitro. And these in vitro characterization studies have demonstrated that cold stored platelets undergo a unique set of cold induced changes in platelet physiology, frequently referred to as the cold storage lesion. This includes changes in their physical characteristics, biochemical and metabolic status, their platelet activation state, generally an increase in activation, and changes in physiologic responses to stimulate or agonists, for example changes is hemostatic function as measured in vitro of which aggregometry and viscoelastic testing are two examples. And we'll hear much more about all of these particular changes from several of our speakers today.

And although there have been many in vitro characterization studies of cold stored platelets, clinical studies with cold stored platelets remain limited. In the 1970s, limited and sometimes conflicting studies showed that cold stored platelets may better correcting bleeding times in aspirin-treated

healthy volunteers or thrombocytopenic patients. More recently, studies have examined cold stored platelet circulation in healthy volunteers and cold stored platelet function in cardiac surgery patients. We'll hear it from investigators involved in both of these studies later today. And finally, additional cold stored platelet studies have been proposed to determine their safety and efficacy after different storage durations, and we'll hear about such a proposal again this afternoon.

Having provided some of the background in vitro data and clinical experience with cold stored platelets, I think it'll be instructive to consider some of the regulatory considerations for cold stored platelets. While FDA regulations permits storage at one to six degrees centigrade, commonly used blood collection processing and storage systems do not include cold storage in their instructions for use. Therefore, to comply with the applicable regulations, blood establishments have requested approval of exceptions or alternative procedures as described under

CFR 640.120. This is commonly known as a variance.

Now, approval of a variance is based on data showing that the alternate process ensures the safety, purity, potency, and effectiveness of the blood component or blood product. And request for a variant includes specific circumstances and may require a submission of supporting data unique to the circumstances under which that variance is requested. As two examples of this, in 2015, FDA granted a variance to a blood establishment that allowed for storage of cold stored platelets without agitation for up to three days for use in resuscitation of actively bleeding patients. And most recently, in 2019, FDA granted a variance to the Department of the Army that allows storage of cold stored platelets for up to 14 days for the treatment of actively bleeding patients when conventional platelets are unavailable, or their use is not practical.

And before I conclude with the agenda and our questions before the Committee, I'd like to highlight some of the points for the Committee to consider today:

first, the design of clinical studies to evaluate the safety and efficacy of cold stored platelets stored beyond three days; the predictive value of in vitro studies on the clinical efficacy and safety; the impact of differences in product manufacturing variables, for example, different collection platforms, storage media, or the use of pathogen reduction, on the quality and efficacy of those products; and finally, the benefit-risk profile of cold stored platelets, considering their reduced circulation, potential adverse events, and the intended patient population. With that, I'll provide an overview of today's agenda.

Following my introduction, we'll hear about platelet transfusion in clinical medicine from Dr. Darrell Triulzi, followed by an introduction to in vitro characterization of platelets and regulatory approaches to the evaluation of platelet products by Dr. Monique Gelderman from here at FDA. Dr. Moritz Stolla of Bloodworks Northwest will provide an in vitro, preclinical, and in vivo recovery and survival studies of cold stored platelets. And this will be

followed by a short break.

After the break, we'll hear about a clinical trial of cold stored platelets in cardiac surgery from Dr. Geir Strandenes of the Norwegian Armed Forces Medical Services. Dr. James Stubbs will provide blood establishment considerations for cold stored platelets. And finally, Dr. Donald Jenkins from University of Texas San Antonio Health will provide the role of cold stored platelets in clinical care in the general population. And this will be followed by lunch.

After the lunch, Colonel Andre Cap of the U.S. Army Institute for Surgical Research will provide the evaluation of cold stored platelet function and military experience with cold stored platelets. And Dr. Philip Spinella of Washington University will describe a proposed clinical trial to evaluate the efficacy of cold stored platelets in surgical patients and potential endpoints for cold stored platelet clinical studies. Following a break, the meeting will conclude with an open public hearing and our open committee discussion.

And finally, our questions before the Committee today: number one, please comment on the available data on cold stored platelets, including discussion of knowledge gaps and potential need for preclinical or clinical studies with respect to the following: the length of storage beyond three days, indications for use such as treatment of active bleeding, differences in collection platforms and storage media, and pathogen reduction. And our second question is to please comment on the design of any additional clinical studies needed to evaluate the safety and hemostatic efficacy of cold stored platelets to support their widespread use in the United States. With that, I'd like to again thank the Committee, our speakers, and all of our participants today. And I look forward to today's discussion. Thank you very much.

DR. RICHARD KAUFMAN: All right. Thank you, Dr. Villa. So, we'll hold questions until the first four speakers have given their presentations. At this time, I would like to introduce Dr. Darrell Triulzi

from the University of Pittsburgh.

PLATELET TRANSFUSION PRACTICE IN THE US

DR. DARRELL TRIULZI: Good morning. Thank you to the FDA and the Blood Product Advisory Committee for inviting me here to speak this morning. As Dr. Kaufman mentioned, I'm the Director of Transfusion Medicine at the University of Pittsburgh. And we oversee about 80 doses of platelet transfusions a day, so this is something that I do live and breathe every day.

I would like to mention that my purpose today is to give the Committee a general overview of the general clinical standards by which platelets are used and a little background about the platelet products themselves.

I do have two disclosures to mention. One, I serve on the Medical Advisory Committee for Fresenius Kabi, and I also have a grant from Cerus Corporation. Okay.

So, this is what I'd like to cover. I'll briefly talk about the national statistics and the trends in platelet collection and distribution and transfusions on a national basis. All right. This has a mind of its own. Can you go back two slides?

I briefly want to cover the differences between whole blood and apheresis platelets, the risks of platelet transfusion. And then the bulk of the talk will be on the epidemiology of who's getting platelets in the U.S. and the indications for platelets with an emphasis on the difference between prophylactic and therapeutic platelet transfusion.

So, the distributions of the platelets in the U.S. are shown here. Now, the 2017 data are the most recent national blood collection utilization survey data, which I understand has not yet been published but was presented at the AABB meeting. And you can see it's relatively flat over the last few years. There's about a five percent increase, and distribution is a reflection of collections. So, there's a slightly increased number of platelets being collected. Next

slide.

However, we continue to see a decline in platelet transfusion, so it's down almost 15 percent since 2013. And I attribute this to the patient blood management and more attention being paid in the hospitals to the appropriate use of platelet transfusions. So, it's now below 2 million doses a year. For many years it was above 2 million doses in the U.S. Now, as you can see, it's below 2 million doses a year.

The other thing to point out is, over the years, whole blood platelets have become less and less of the total platelet doses being given, and it is now below five percent, which is the lowest in probably a decade. So, for all intents and purposes, 95 percent of the platelet doses in the U.S. are from apheresis platelet collections.

So briefly to discuss just the differences between whole blood and apheresis platelets, so apheresis platelet donation requires a dedicated donor to be willing to donate for anywhere from 60 to 90

minutes on an apheresis machine. There are a number of devices that are approved in the U.S. They basically function in the same principle that whole blood is removed. In the device, generally through centrifugation, the blood is separated. And then the component of choice, in this case platelets, is kept in the device, and the red cells and plasma are returned to the donor.

The devices today are so efficient that, on average, you can collect two adult doses from each donation. And that's where the term single donor platelets comes from. It means that all the platelets from that dose came from one donation.

So, this is what apheresis platelets look like. You can see they basically look like plasma. There's very little red cell contamination, and they're all leukoreduced. So, they are suspended in plasma. The volume is 2- to 400 mls, although not many are as high as 400 mls. They contain a minimum of three times ten to the eleventh platelets. On average, it's closer to 3.5 of 3.6. And that's equivalent to about five

units, four to five unites of a pool platelet.

The storage is five to seven days, depending on the bag and the conditions. And the therapeutic dose is one apheresis per transfusion episode. And that generally results in a platelet increment of 20 to 30,000. And as I said before, about 95 percent of the doses of platelets in the U.S. are derived from apheresis platelets.

The alternative whole blood platelets, as the name would suggest, each unit is derived from one unit of whole blood platelets. And there's not enough platelets that are obtained from one unit of whole blood for a therapeutic dose in an adult, so we have to pool several together. And generally, transfusion services that use them will pool four to five units to make a therapeutic dose. Whole blood platelets are stored under the same conditions: room temperature, constant agitation, up to five days. There's no seven-day option for pooled platelets. The dose for pediatrics is one unit per 10-kilogram body weight with four to five units as a standard dose in an adult. And

that gives you a similar increment of approximately 20 to 30,000. And again, this is a small minority now of platelet doses in the U.S.

I next want to cover the risks of platelet transfusion. I'll be doing this briefly, but it is relevant to the discussion of cold stored platelets. This is a table that is from the AABB platelet practice guideline that was published a few years ago. You can see that the vast majority of reactions to platelets are fever, chill, or allergic reactions, not over 90 percent, probably more than 95 percent. And these are mild, generally self-limiting, and don't result in major morbidity or mortality.

TRALI, you can see at one in 138,000, is much lower due to TRALI mitigation strategies that have been implemented over the last decade and is actually now quite common. And the infectious risks are all very low. You can see here far less than one in a million. So, what's really driving substantial risk from platelets is bacterial contamination, in this particular table one in 75,000. And that's why it's

relevant to the cold stored platelet. In fact, it's not advancing. Believe me. I'm trying.

This is, of course, the FDA's own data, which you're all familiar with, showing that there are still deaths being reported from bacterial contamination of platelets. These are pheresis over the last five years and one from pooled platelets. In 2017, five deaths from contaminated platelets reported. And then behind that tip are a larger number of cases in which bacterial contamination did not result in death but may have resulted in significant morbidity from a septic reaction. So, it is still a recognized problem, and that's prompted the FDA guidance document from September of this year with guidance on what we can do to further lower the risk of bacterial contamination.

And I am most definitely not going to go through this slide. I only show it to you to emphasis the complexity that the blood centers and transfusion services are facing in order to reduce the risk of bacterial contamination. There's one and two step interventions here. And again, this is relevant to the

cold stored platelets, which would be a potential way to avoid the complexity that we're faced with implementing in order to deal with this residual risk of bacterial contamination.

I'll now talk about transfusion recipients for platelets. And fortunately, we were just -- I'm now able to discuss data on probably the largest epidemiologic study in the U.S. of platelet transfusion done by the Recipient Epidemiology and Donor Study III, REDSIII, network. So, this study took 12 hospitals in the U.S., a mixture of academic medical centers and community hospitals, and collected basically the entire EMR on every platelet transfusion recipient at these 12 hospitals for a four-year period. So, there's over 30,000 patients, 163,000 individual products, and 130,000 platelet transfusion episodes. So, you can see some episodes get two doses. And this has given us some really useful information that I think will be relevant to the Committee's deliberations.

So, who is getting platelets? Twenty-three percent, or about a quarter of the patients who get

platelets are undergoing cardiac or vascular surgery. Another quarter have hematologic diagnoses, which an ICD9/10 are designated as neoplasms or diseases of blood. And despite the fact that they are only a quarter of the patient, they accounted for over 50 percent of the products. And that's because these patients tend to get multiple doses, which makes complete sense.

Now in CMS, trauma fits under injury and poisoning. So, they accounted for 16 percent of the doses and then basically GI bleeding another nine percent. So about 75 percent of the patients that get platelets are non-hemonc patients and presumably getting because they have active bleeding or they're undergoing a procedure. So, half the platelets go to hemonc, half go to non-hemonc patients.

What are the platelet transfusion triggers that we observed? They're pretty much all over the board. You can see it's about evenly divided between those who have counts less than 10,000, 10 to 20, 20 to 50, and more than 50,000. And to be honest, the use of

platelet transfusions above 50,000 are not likely to be evidence based. There's only a relatively small portion of patients who would have an accepted indication with counts above 50,000, mainly patients who are on anti-platelet drugs. And we did have that data, and it accounts for only a small portion of the patient transfusion episodes.

So, one of the things we observed is there's probably a lot of excess platelet transfusions still going on. The other thing at the bottom is to look at the doses. Seventy-eight percent, so the vast majority of time, the transfusion episode is one dose of platelets. Another 17 percent were two doses. And it's quite unusual to have multiple doses of platelets at the same transfusion episode. These are likely to be the major hemorrhage or major surgery patients who need multiple doses.

I'll then move to discussion of the indications for platelet transfusion with the emphasis on prophylaxis versus therapeutic dosing of platelets. So, the clinical indications for platelets are either

thrombocytopenia or platelet dysfunction. One of those two things needs to be present. And the indications then fall into one of these two buckets. Either they're getting the patients prophylactically to prevent bleeding or therapeutically to treat bleeding. And with the prophylaxis setting, there's the risk of spontaneous bleeding.

So, what is this? This is where we're giving platelets because the patient's platelet count is so low that we're concerned about spontaneous hemorrhage into a critical organ, meaning the brain, the eye, or the lungs primarily. And so, platelets are given to prevent spontaneous bleeding. The other prophylactic use would be a patient having a procedure where we're giving platelets to prevent bleeding from the invasive or surgical procedure, which could be an interventional radiology procedure or an OR procedure.

Now, the therapeutic indication are patients who have active bleeding. So that's the trauma, bleeding during a surgery, medical bleeding which would be something like GI bleeding or even obstetrical

hemorrhage. Those would fit into the therapeutic bleeding. And I'm going to talk about the indications in each one of these settings, but I emphasis -- go back a slide, please -- that 50 percent of the platelets fall into that spontaneous bleeding and hemonc patients. And then the 50 percent left fall into all the other indications. Okay.

Now, when we talk about the quality of evidence, the quality of evidence has been largely heavily weighted towards studying the platelet transfusions in hemonc patients, particularly in the prophylactic setting. So, we have good moderate to high level data in that setting to know when to use platelets. However, in the other settings, the levels of evidence are quite low. So, we'll come to that in a moment.

So, when we talk about it in the prophylactic setting of platelets, there's an important biologic phenomenon to be aware of. And that is, as your platelet count drops, particularly below 50, the survival of platelets is shortened. And you can see

that graphically shown here that, in patients or individuals with a normal platelet count, the half-life of the circulating platelet is five days, which would mean ten days for their total survival. That makes sense. That's what we teach in medical school. But when the platelet counts are below 20, the half-life is two days, and the total circulating life is about four days. So, it's greatly reduced in severe thrombocytopenia.

And if you take this data and you plot it on this curve, this is what it looks like. You can from it derive that we use 7,100 platelets per microliter per day to maintain endothelial integrity. So, the lower the platelet count, the greater proportion of it that is used to maintain our endothelial integrity and prevent spontaneous bleeding. So that's important when you talk about the use of prophylactic platelets. So, this principle has been known for decades and is supported by clinical data.

So, this is early studies just showing that as the platelet count is low, below 10,000 -- in fact,

below five -- in this study, there's increase GI blood loss. This study from Lancet's European transplant center showing in red major bleeding is not observed until platelet counts are below 10,000. And this led in the '90s to a number of randomized trials comparing a prophylactic threshold of 10,000 versus 20. And these studies uniformly supported the safety of using 10,000 as the prophylactic platelet transfusion threshold in hemonc patients. And that remains today, I would say, the standard of care. So clinical trials today studying platelets in the hematologic malignance or transplant setting would be designed to use 10,000 as the prophylactic threshold for platelet transfusion.

Now, a relatively recent study called the Platelet Dosing Study looked at different doses of platelets. And in fact, despite the fact that we're using platelets at a 10,000 threshold, there's still a high incidence of bleeding. And in this study you can see 70 percent of patients still had a bleeding episode despite the use of prophylactic platelets. Now, fortunately, the great majority of that bleeding is

grade 2. And grade 2 bleeding is clinically significant but not life-threatening. Something like epistaxis or mild hematuria or a severe ecchymosis, not enough to require a transfusion, which would put it in grade 3, and not life threatening, which would be grade 4. So, we still have bleeding despite the use of prophylactic platelet transfusion.

This is also from the Platelet Dosing Study, and it's showing you the morning count is shown on the bottom. And the Y axis is percent of days with bleeding. You can see when the platelet count is below 5,000, there's a much higher chance of having a grade 2 or higher bleeding episode that day. But once you get the patient above 5,000, the risk is basically unchanged, and that's a baseline risk of about 16 percent per day. So, this data would support the prophylactic threshold of 10,000 and the fact that, when you don't have enough platelets below 7,000 to maintain endothelial integrity, your risk of a bleeding episode is higher.

The other slide from the Platelet Dosing Study

that I think is informative is this is over 1,300 patients with leukemia, lymphoma, or transplant that we had daily information on transfusions that the time between transfusions in the medium dose arm, which is what one pheresis would be -- that would be kind of the standard -- or higher dose would be equivalent to two pheresis -- that the time between transfusions is two days to three days. So that's important to realize. That with our current products that we use in the hemoncs transplant population, every two to three days they're getting a platelet transfusion. If we used a product that had a shorter circulating half-life, that probably would impact patient care that you'd be probably needing to transfuse every day and maybe even more than once a day. So, it's important in this population to see what the use of standard platelets is resulting in the platelet transfusion interval.

Now, does it make a difference whether you use pheresis or pooled platelets? This was studied in this Platelet Dosing Study. And there is about a ten percent higher correct account increment. In other

words, there's a -- one to four hours after transfusion, the platelet count does go about ten percent higher with apheresis platelets versus pools. However, when you look at what's more important is the hemostatic effectiveness, this is the time to a bleeding episode. These curves completely overlap. So even though there is a slightly lower correct account increment with whole blood platelets, it doesn't translate into any difference in achieving hemostasis in the prophylactic setting in hemonc patients.

The last slide in prophylaxis I want to mention is refractoriness. What this means is the patient is not responding to platelet transfusion as expected, which would be in green dotted line where their platelet count goes up, again, 25-, 30,000. And most of those platelets are there the next day, and they may not need to be transfused until two days or three days, which is what we saw in the study.

But there are frequently, anywhere from ten to 30 percent has been reported, of patients develop refractoriness where the platelets do not result in the

expected increment or do not survive normally. Most of these patients have clinical reasons to consume platelets. They're febrile. They're septic. They have DIC. They have splenomegaly. They have fungal infections.

And what do those all have in common? They shorten platelet survival. So, in the refractory patient, using a platelet that has an even shorter half-life would not be ideal. That would be suboptimal.

So, let's talk now about what we know about the use of platelets in the non-hemonc setting in surgical patients and in active bleeding. So, this is the AABB practice guidelines for platelets published in 2015. And I would love to be able to show you four or five large randomized trials of when to use platelets in surgical or bleeding patients. But the fact of the matter is that they don't exist. So, what we have are basically observational studies and expert opinion. The AABB used a grade methodology, which is a formal methodology, to evaluate the literature and provided

these guidelines to us for the use of platelets.

So, the first one is prophylactic platelets in hematology/oncology patients, which we just talked about. And the grade recommendation was strong, and the quality of evidence is moderate, which is as good as it gets. When we talk about for procedures, here's the recommendation for central line placement, 20,000 platelet count, but the recommendation is weak, and the quality of evidence is low. What about for lumbar puncture? Same. Grade recommendation is weak and now very low. What about just for major surgery, such as a colectomy or a lobectomy or a splenectomy? What would you need for that? Well, the recommendation is 50,000, but the evidence is very low. We just don't have good randomized control trial data to support whether it should be 50 or 30 or 70. How about for cardiac bypass? Well, they did not give a specific platelet count.

Basically, it's when there is bleeding perioperatively with thrombocytopenia not defined or platelet dysfunction, not defined how that's measured

either, weak or very low. And then intracranial hemorrhage, uncertain, very low. So, you can see there's a dichotomy in balance of quality of evidence. We have a pretty good idea how to use it in hemonc patients and a very poor knowledge of how to use it in the non-hemonc population.

This was a paper that was published recently by our critical care and surgical colleagues who did a review of the literature, not as formal as grade methodology, and provided some recommendations on when platelets should be used. For acute traumatic hemorrhage, so this is in the trauma population, in their analysis they recommended 50,000. For patients having major surgery, 50,000. More minor procedures like line placements, 20 to 30,000. For neurosurgery, 100,000. So, you can see there's a wide range there, and the quality of evidence for this is low. This is based on observational studies, expert opinion. Prophylactically, in the non-hemonc setting in critically ill patients, 40 to 50; sepsis 20,000; and active bleeding you can see 50,000; intracranial

bleeding, 100. So, it's kind of all over the map, which tells you that we don't have good data to know what truth is and what it should be.

So, to summarize, in the non-hemonc population, it accounts for a large portion of platelets, approximately 50 percent. It's commonly given prophylactically for invasive procedures and surgery, typically at 50,000. That would be what I would say, if we were to survey most hospitals, that's what they would be using as their guideline. About 15 percent of cardiac surgery patients get platelet transfusion. So, I mentioned earlier that 25 percent of the patients who get platelets or cardiac surgery, among them, it's about 15 percent.

So primary CABGs don't use platelets. It's the redo aortic arch surgery, valve plus CABG that get platelets. So, it is very common that we use platelets in cardiac surgery. Platelet transfusion is the standard of care for massive transfusion protocols. So, every level one trauma program in the country is accredited, and they look at what your massive

transfusion protocol is. And they expect there to be platelets as part of that. So that's part of the standard of care as well. And then early platelet transfusion is increasingly being associated with improved outcomes in severe trauma.

And I just want to show a couple slides of this. So, this was observational data in the combat setting showing that patients who have the highest amount of platelets have the best 24-hour survival, and that's also true at 30-day survival. But this is an observational study and could be confounded by survival bias. That's certainly true.

Similar data are seen in civilian trauma. So, this is John Holcomb data again showing that the best survival at 24 hours and at 30 days are those who get the most platelets. But the same potential confounding could be occurring since it's observational data.

Now, just recently, the PROPPR study, which is a randomized trial of two strategies for component ratios, one to one to one versus one to one to two -- a secondary analysis was done of this randomized trial in

patients with severe trauma. And they looked at the incidence of death in those who did not get platelets with their first cooler of blood versus those who did. And you can see at six hours there's already a substantial difference in mortality, much higher in the group that did not get platelets than the group that did.

And this is also true at 30 days. So, there was lower mortality, also greater probability of achieving hemostasis if you've got platelets in your first cooler. And many fewer died of exsanguination if you got platelets in your first cooler. So, the body of evidence is growing that early platelet intervention is important in severe trauma. Next slide.

And how early is early? This table is showing a number of studies that were randomized trials in severe trauma. They may have been studying hemoglobin substitutes or something else. But the point is that they all looked at time to hemorrhagic death. And you can see it's very short, on the order of two hours, which is similar to what was shown here in this paper

with over 1,000 trauma related deaths. The time to hemorrhagic death median was 1.65 hours.

What is that telling you? That's telling you that we need to achieve hemostasis quickly, and it needs to be maintained in hours, not like days which are needed in the hemonc setting. It's an acute situation. Even traumatic brain injury, head injury deaths are occurring in less than 20 hours. So, these are all less than 24-hour time spans we're talking about when we're using it for acute bleeding.

So, in summary, the key differences between the use of prophylactic versus therapeutic platelet transfusion are shown here. So, prophylaxis for the hemonc setting, the clinical effect needed for in-patients is generally two to three days. The more extended effectiveness would be desirable in the out-patient setting, which accounts for about ten percent of the patients transfused. So that's still a big chunk that we would need to have platelets that the longer they last, the better.

Most bleeding events in this situation are not

life threatening. They're mostly grade 2 bleeding. So, we're not dealing with a severity of bleeding that we are in the non-hemonc setting, except for rare exception in the hemonc setting. Another key difference is it's hypoproliferative anemia. So, they're not making their own platelets. So, there's no opportunity for them to start supplementing the platelet transfusions with their own platelets until they're ingrafted or recovered from their myeloablative therapy. And refractoriness is an issue.

Now, contrast that with the use of platelets in surgical or acutely bleeding patients, that the clinical effect is needed quickly and the ideal is lasting for hours. We don't need it to last two to three days. We need hemostasis over a 24-hour period, quickly and lasting for hours -- that the bleeding is much more severe and much more likely to run into risks of morbidity and mortality. The patients are generally capable of making platelets, and, in addition, about a third of your platelet mass is in your spleen.

So, unless the spleen is part of the site of

trauma, you do have the ability to replace what's lost in the intravascular space with stores of platelets in the spleen. So that's where this short-term support is important because they're making their own platelets and can replace what is being lost with the splenic reserves. And then lastly, refractoriness is generally not an issue in the non-hemonc population. And I will stop there. Thank you very much.

DR. RICHARD KAUFMAN: All right. Thank you very much, Dr. Triulzi. Our next speaker will be Dr. Monique Gelderman from FDA.

REGULATORY APPROACHES TO THE EVALUATION OF PLATELET PRODUCTS AND IN VITRO CHARACTERIZATION OF PLATELETS

DR. MONIQUE GELDERMAN: Good morning. My name is Monique Gelderman. I am a staff scientist in the Division of Blood Components and Devices. And today I will be providing an overview on regulatory approaches for the evaluation of novel platelet products and the in vitro characterization of platelets.

I will start out with a brief summary on the process of changes that platelets undergo during storage, followed by general approaches for the evaluation of novel platelet products, and the in vitro tests used for the evaluation. And lastly, I will highlight in vitro assay results of two separate studies on extended cold stored platelets that were conducted in the Laboratory of Cellular Hematology at the FDA.

As my colleague, Dr. Carlos Villa, already mentioned in his introduction of today's topic, platelets undergo changes during storage, which is referred to as the platelet storage lesion. This figure shows you the platelet storage lesion in a nutshell. And as we know, as soon as the platelets are collected and processed, they undergo metabolic and physiological changes. And these changes continue to occur during storage.

So, let's take a quick look at this figure. Let's start at the bottom left, right here, and move clockwise. So, starting at the bottom left, as I told

you, several of the changes that occur are shown here; such as changes in morphology, activation, et cetera. And examples of the factors that may influence these changes could be the storage temperature, respiratory capacity of storage containers, and of course we evaluate these -- we look at these changes by evaluating them with in vitro assays. And as we know, no single test can be effectively predictive of the clinical performance of platelet products.

Many studies have been conducted and are being conducted to find ways for preventing or overcoming the effects of platelet storage lesions. And a couple of examples could be improvement of preparation, processing, and storage techniques. Here you see on this slide examples of novel platelet products and future platelet products and technologies such as pathogen reduced platelets, new storage solutions, new storage containers, new storage conditions such as cold stored storage.

So, with that said, let’s turn our focus on evaluating novel -- on the evaluation of novel platelet

products. The evaluation of novel platelet products involves in vitro testing, and these tests are classified in the following categories that you see here: physical characteristics, biochemical status, activation, and physiological responses. In addition, the evaluation also involves clinical studies.

Here are several examples of possible studies that may need to be conducted. The Phase 1 studies are radiolabeling studies in healthy volunteers to investigate platelet survival and recovery. The Phase 2 and 3 studies are safety and efficacy studies conducted in patient populations to determine efficacy in hemostasis. Sometimes there is a need for a Phase 4 study, which is a post-market surveillance study. And of course, the need for all stages of evaluation varies with the type of platelet product.

So, let's put the platelet evaluation into perspective by looking at this schematic presentation of the progressive evaluation of novel platelet products. It's a three-tiered approach, and, depending on how much the novel platelet product differs from a

conventional platelet products -- and of course the concerns about the differences -- determines the necessary evaluation of a novel platelet product. For example, when there are minimal levels of concern, conducting only in vitro studies is usually sufficient. However, when a new apheresis collection device is evaluated, usually in vitro and radiolabeling studies are appropriate.

But if platelets are very different, and you see examples provided here at the top, then probably all three levels of evaluations are necessary. So, all levels of the evaluation, as I've just showed, are important and need to be addressed when necessary. But from this point on, I will focus on the in vitro studies.

So, let's take a look at the in vitro tests used to evaluate novel platelet products. On the next four slides, including this one, I will briefly go over the four categories of in vitro testing and the tests that fall under each category. These tests have been developed over decades of research and represent our

understanding of the changes that take place when platelets are stored or processed differently. There are no standards for these laboratory results. Therefore, when testing novel platelet products, the results of these tests are compared to conventional platelet products.

So, let's start by taking a look at the first category that you see here, physical characteristics. Since time is of the essence, I will highlight only the first two listed tests of each category because these are considered the core tests. So that does not mean that these are the only tests that need to be conducted because, when a novel platelet product is very different from a conventional platelet product, it is suggested that the majority, if not all, listed tests are performed. This decision is usually made on case by case basis, and this applies to all four categories of the in vitro testing.

So, the first one that you see here is a count. So, when a reduction in platelet count is observed, it can indicate storage damage, or it could

also be a result of platelet aggregate formation. Of course, morphology is self-explanatory. We look at their discoid shape and if there is a change into a spherical form.

So next, let's take a look at the category that you see here, biochemical/metabolic status. This is usually assessed throughout storage. So, the first one is pH. And pH, of course, is considered the surrogate marker for the quality of platelets because it has been demonstrated that platelet viability is not effective as long as the pH remains at or above 6.2. Since platelets remain metabolically active, therefore we measure glucose consumption and lactate production.

So, our third category is platelet activation and apoptosis. As shown here, p-selectin expression is the platelet activation marker. And annexin V binding is the marker of apoptosis.

So last but not least, this is the fourth category, physiological responses. So, the first two tests, hypotonic stress response and extent of shape change are the two tests that correlate with in vivo

viability. So, with that said, it should not come as a surprise that the in vitro evaluation of platelet has its limitations, and here you see the reasons.

Evaluation of a single parameter alone may not be informative. In vitro results may not be predictive of the hemostatic efficacy of platelets in vivo. And the applicability of the current in vitro parameters for all novel platelet products is unclear, for example, cold stored platelets. All right.

So, it's known that cold stored platelets undergo a series of changes in response due to cold, and that has been referred to as the cold storage lesion. Here you see just a few examples of these changes. By no means is this an all-inclusive list. So, an increase of intracellular calcium can be observed. There are shape changes, microparticle formation, increased p-selectin expression, and externalization of membrane lipids.

The figure below this short list shows a timeline of when these changes occur. And let me just highlight a few changes. So, for example, within five

minutes of cold storage, there is an increase in cytosolic calcium. And within 20 minutes, spontaneous fibrinogen binding may occur. Within four hours, the discoid shape is lost, and pseudopodia are formed.

So, when you look at the timeline, the 18-hour time point is highlighted here. And this is considered the point of no return. And what that means is, if the platelets are not rewarmed before this time point, the changes that you see are irreversible and become permanent.

So how do the changes that platelets undergo when stored in the cold affect the in vitro test results? Well, here you see a few examples for each of the four categories based on the published in vitro observations of cold stored platelets compared to conventional platelets. So, it has been observed that cold stored platelets can demonstrate lower platelet counts due to aggregation. And there can be an increase in microparticle formation because cold storage slows down the platelet metabolism, which delays the decrease in glucose consumption and the pH

levels. Of course, the activation and apoptosis is also amplified, and several physiological responses are affected.

So that leaves us with the question which in vitro tests are the most appropriate tests for the characterization of cold stored platelets? So, with that said, let's switch gears, and let's take a look at the results of two different studies on cold stored platelets stored beyond three days that were conducted in the Laboratory of Cellular Hematology at the FDA. So, for the first study, I will show you highlights of the in vitro assay results of apheresis platelet products that were used in a radiolabeling study in health volunteers. These platelets were stored for seven days at room temperature or cold in 100 percent plasma.

These three graphs show you the results of several morphology and functional responses on day seven. As shown in the graph in the top left corner, the mean platelet volume was similar for both the cold and room temperature stored platelets. However,

morphology scores and hypotonic shock response and extent of shape changed measurements were statistically significantly reduced for the cold stored platelets compared to the room temperature stored platelets. As you can see here for the morphology scored, it was about a fivefold reduction. HSR is six-fold reduction. And for ESC, a fivefold reduction.

Here you see the agonist-induced aggregation on day seven. The dual agonist-induced aggregation resulted in a better response from the room temperature stored platelets when compared to cold stored; whereas the use of the single used agonist resulted in comparable responses for both storage conditions. Lastly, as you can see here, the cell surface expression of p-selectin and annexin V binding was significantly elevated in cold stored platelets, and we observed a fourfold increase for CD62 and a threefold increase for the annexin V binding. Just in case you were wondering about the recovery and survival of these platelets in vivo, here you can see that the room temperature stored platelets, shown in black,

circulated longer than the cold stored platelets, shown in blue in this graph.

Next, I will show you highlights of a different study, which was an in vitro study characterizing human platelets stored in the cold and at room temperature for up to 21 days. These platelets were also evaluated in our SCID mouse model of platelet transfusion. So, the focus of the next three slides, including this one, will be on a few in vitro platelet function characterizations that show statistically significance between cold and room stored platelets on days 14 and 21. All three slides are set up the same. The left column shows you the parameter. The next column shows the storage period and followed by the storage conditions.

So, let’s take a look at pH. As you can see here, the pH value dropped below 6.2 for the room temperature platelets by day 14 and continues to decrease. For the cold stored platelets, the pH also decreased. On day 14, it decreased to seven, and, by day 21, it was 6.73.

So, looking at the glucose consumption/lactate production, on day 14, the glucose levels were less, and the lactate levels were greater for the room temperature platelets when compared to cold stored platelets. And this trend continued for day 21. So we saw a tenfold reduction in glucose level and tenfold increase in the lactate production.

Moving on, so when looking at the results of the hypertonic stress response measurements, on day 14, a 25-fold reduction in HSR measurement was observed for the room temperature platelets and a fivefold reduction for the cold stored platelets. And as you can see, by day 21, the HSR response for both storage conditions is pretty much lost. Taking a look at the aggregation results, the dual agonist-induced aggregation resulted in a better response for the cold stored platelets on both day 14 and day 21 compared to room temperature platelets.

On day 14, the p-selectin expression of the room temperature platelets was greater than the p-selectin expression of the cold stored platelets. So,

as you can see, the values for cold storage were, for day 14, about 63 percent and, on day 21, 77 percent. So, may I remind you that annexin V is commonly used to detect apoptotic cells by its ability to bind to phosphatidylserine. And as you can see here, on day 14, the annexin V binding increased to 72 percent for the room temperature stored platelets, which is great enough for the cold stored platelets. For the cold stored platelets, the results we observed for day 14 was about 26 percent; whereas day 21, it was 41 percent. All right.

So, the previous slide concluded the in vitro data highlights, so let's take a quick look at the in vivo recovery of these human platelets in the SCID mice. So, the SCID mouse model of platelet transfusion was validated against the radiolabeling study in healthy volunteers, which I just highlighted on slides 15 through 19. So, the graph that you see on the left shows the initial platelet recovery in the mice. The X axis indicates how long the platelet products were stored; whereas the Y axis indicates that initial

percent recover of the human platelets in the mice.

So, the surprising finding of this study is that the cold stored platelets showed a better recovery when compared to room temperature platelets for both day 14 and 21. So there's a clear switch after day seven because, what is shown here on day seven, that's what we used to see. But as you can see here, there is a total switch between day seven and 14.

So, the graph on the right shows the calculated area on the curve. The AUC encompasses both the recovery and survival of platelets and indicates how long they remain in circulation. And as I have circled here, on day 14 and day 21, you see that there are still more platelets in circulation compared to the room temperature stored platelets. So, the conclusion of this study was that the in vitro data showed that the cold stored platelets performed better when compared to the room temperature platelets on matching days. And the results generated using the mouse model suggests the same.

So, with that said, let me summarize this

presentation. So, the evaluation of novel platelets products includes in vitro and in vivo studies. In vitro studies provide information on platelet biochemical, physiological, and activation status. Cold stored platelets show changes in in vitro parameters when compared to room temperature stored platelets. However, it is not clear which in vitro tests are the most appropriate for the characterization of cold stored platelets. And that concludes my presentation. Thank you for your attention.

DR. RICHARD KAUFMAN: All right. Thank you, Dr. Gelderman. And I would now like to introduce the next speaker, Dr. Moritz Stolla from Bloodworks Northwest.

IN VITRO, PRECLINICAL, and IN VIVO RECOVERY AND SURVIVAL STUDIES OF COLD STORED PLATELETS

DR. MORITZ STOLLA: Good morning, everyone. I would like to thank the Committee for inviting me to present our data here. I should mention I am the site

PI for a Terumo trial for pathogen reduction and also run a study for Cerus for pathogen reduction.

So, I'm talking today about in vitro, preclinical, and in vivo recovery studies that we did with cold stored platelets over the last three years in Seattle.

And I would like to start with a brief overview. You've already heard a lot about cold stored platelets. Overall, it's well-understood that the circulation half-life is severally reduced compared to room temperature stored platelets. In a couple of very elegant studies, Karen Hoffmeister and colleagues showed how they are cleared by hepatic macrophages and hepatocytes were the actual Morell receptor.

They have potential advantages by prolonging the storage time while limiting bacterial growth. And most in vitro studies show that they perform better than room temperature stored platelets. And interestingly, they also retain the response to naturally occurring inhibitors.

So, this is from the study that I mentioned in

the beginning where Scott Murphy has showed that if you store platelets -- really at 18 hours he saw a significant reduction in survival here and half-life of one day compared to the half-life of three to four days for room temperature. And he then further increased the temperature to 37 and 30 degrees and actually found that the recovery goes down with the higher temperatures and the survival remains the same. And clearly, you have a higher risk for bacterial growth at these higher temperatures. So overall, it was concluded that room temperature was the best storage temperature, at least to maximize survival for prophylactic transfusions.

And this was an attempt to test the function of these platelets, also in the early ‘70s, by Dick Aster’s group in Wisconsin. And they showed that, especially after a prolonged storage here up to 72 hours, the cold stored platelets appeared to be better at correcting the bleeding time in thrombocytopenic patients. Here you have eight out of 12 that improved with cold and one out of seven with room temperature

storage. He then later in a subsequent paper claimed that the room temperature group was at a disadvantage because it was too high of a concentration that he used. It's unclear what to make out of this study.

And then this study by Dr. Slichter showed that -- again, this is in thrombocytopenic patients with bleeding time over 30 minutes and platelet counts below 10,000. So, they were all down here prior to transfusion. And then with transfusion of these room temperature stored platelets, she was able to bring them back to where you would expect them to be. And then after transfusion of cold platelets, she was able to increase the count, but she was not able to reduce the bleeding time.

Now, there are several issues. Obviously, bleeding time is not a perfect test and has numerous issues. It was done in the '70s. And even though there are a lot of data points on this slide, I think there were only three or four subjects included in this study, so also a limited number of subjects.

So, the way we approached these studies were

with three open questions. We would like to address the storage time. What is the maximum time that we can store these platelets? As we have heard already, the maximum time currently for the FDA variance is three days. Clearly, that's not helpful. Then the storage solution, is it additive solution? Is it plasma? And finally, the in vivo function, how well do they prevent or stop bleeding in patients?

So, the first question was how do we best store them, in plasma or in additive solution? And the reason why this is important is that here in this -- and this has been shown by numerous -- but the most thorough investigation, the most recent investigation is the one by Dr. Getz from Andrew Cap's group where they showed that, actually, when you store platelets in the cold, you get this additional population here. You see these visual aggregates that occur as well, and you see a drop in platelet count. This is presumably because they stick to each other and thereby are not counted as individual platelets.

And what they did is then replaced the plasma

with additive solution, here with 65 and 85 percent of additive solution. And they showed that they were able to prevent this drop in platelet count, here at panel D, and were able to reduce the aggregate count as well. And another interesting finding was that, by this way, they were actually able to reduce phosphatidylserine exposure. So, there might be some additional added benefit to this as well.

So, the first study was then called cold stored apheresis platelets in Intersol versus plasma. Here we have two different groups, 100 percent plasma and Intersol and plasma mix. We stored up to five days, so slightly longer than the current variance. We had a regular platelet concentration. We did not agitate these platelets. Actually, Dr. Slichter did previous studies where she compared agitation to not agitation. And as we heard, it's not required today either.

The comparator was one day storage where the historic room temperature control group, which was kindly provided by Dr. Slichter and Dr. Zimring. We

performed in vitro testing for platelet quality, including the platelet yield, metabolic parameters like glucose and lactate, and apoptotic parameters like Caspase3,7 and mitochondrial membrane integrity. And finally, we did also radiolabeling for in vivo testing with indium-111.

Now, the way I organized these slides is that the absolute data you can see on the left-hand and the percentage of fresh on the right. The percentage of fresh is useful because it eliminates some of the donor to donor biologic variability. And it was also promoted as the gold standard for introduction of new product by Dr. Scott Murphy. You can see clearly the recovery is significantly lower in the cold groups, but there was not statistical significantly difference observed between the Intersol plasma and the plasma group on its own. The same is here shown on the recovery, percentage of fresh.

Now, clearly survival is not the most critical question for these platelets. As we heard, they're intended for actively bleeding patients and trauma

patients. But we found that, not surprising, the survival is significantly reduced. And there was no difference here between plasma and plasma and Intersol. And in the percentage of fresh, it looked like the Intersol group -- there was a trend for a higher survival. But this is already at an extremely low level, so unlikely to be clinically relevant.

Next, we look at the platelet yield, and we were able to corroborate what Dr. Getz and coworkers showed. You can see the significant drop in the cold group. We did not see a significant difference in the absolute data, but in the percentage of fresh, you can see the significant difference here. But it did not really reach the same level as room temperature storage and plasma.

And we looked at the metabolic parameters. You can see the glucose levels are clearly lower in the room temperature group compared to the cold group. The Intersol is a little bit misleading just by the design of the experiment. By removing the plasma from the platelet, you are basically removing a lot of the

glucose. So, this is really an unfair comparison, I guess. But we looked at lactate then. And I guess corresponding to the glucose level, the room temperature group that consumed the most glucose also had the highest lactate values. Clearly, lactate was significantly lower in the cold groups here. And interestingly, the Intersol group had significantly lower lactate values compared to the 100 percent plasma group.

Next, we looked for functional data. And we already heard in the previous talk about the PAC-1 antibody. It's an antibody that specifically binds the activated confirmation of the integrin. And if you add an agonist, if a fibrinogen binds to the major platelet integrin, alpha-2-B-beta-3, anti-PAC-1 antibody can bind as well. And what we found is that you can see BL is for baseline and COL stands for collagen. You can see clearly -- nicely see the pre-activation that occurs here at the BL level in the cold in these platelets. And if you then add collagen, you actually get a significantly better response compared to room

temperature. And the same is true for the Intersol group. We did not find significant differences at four degrees Celsius between 100 percent plasma and plasma and Intersol.

Next, we looked for the mitochondrial function, and we used the JC-1 dye. This is a good dye to test this because it accumulates in mitochondria. It admits a red wavelength, as you can see here. But if the mitochondrial membrane is disrupted and damaged, it is diluted in the cytoplasm. Then it admits a green wavelength. So, you can take a red to green ratio by flow cytometry, and then you can get information about the mitochondrial health. And what we found is that clearly both groups in the cold, the plasma and the plasma and Intersol group, had significantly better mitochondrial preservation compared to the room temperature stored group. And again, no significant difference was found between the plasma and plasma and Intersol group.

We then looked at -- so mitochondrial membrane potential is a relatively early marker of apoptosis,

but Caspase 3,7 is a rather late marker. So, we looked for Caspase 3,7 activation and found, overall, if you look at the percentage of fresh on the lower panel, this was done at baseline. No significant differences -- maybe a trend for higher Intersol Caspase 3,7 activation. To promote apoptosis, we add a small molecule, ABT-737, which binds BCL-2. So, it's a BH3 mimetic and basically inhibits BCL-2 function, which is pro-survival protein, and thereby promotes cell death. And we were able to increase Caspase 3,7 activation here in all groups. But interestingly, the group with the highest Caspase 3,7 capacity to activate Caspase 3,7 was the Intersol group.

So clearly five days is not really what we are looking for in these platelets, so we then performed a subsequent study. We had extended storage and actually added another group, another additive solution, the Isoplate. So, we had three groups: 100 percent plasma, Intersol/plasma, and Isoplate and plasma. We stored up to 15 days. And at the same platelet concentration, we actually had a three-day comparator, which is the

current FDA variance, and tested for in vitro with the platelet yield, microparticles, annexin V, p-selectin for alpha-degranulation, and again metabolic parameters for glucose and lactate. And the same testing for the in vivo functioning with radiolabeling was done as well.

As you can see, at the three-day timepoint there was no significant differences between any of these groups. Again, similar to what Dr. Getz and coworkers showed, we found significantly lower platelet yield in the plasma group at ten days. We then did not see a significant difference between the two additive solutions. But it looked like the Isoplate was a little lower -- and overall no significant difference in plasma, ten versus 15 days.

Then, the metabolic parameters, again, you can see this significantly lower glucose values in the Intersol and Isoplate groups because of the removal of the plasma in these groups. And we also found a drop in the glucose from ten to 15 days at these late time points. And lactate, correspondingly again a higher

lactate level at 15 days compared to ten days and, similar to the previous study, we found lower lactate levels in the Intersol and Isoplate group compared to the plasma group at ten days.

Next, the pre-activation markers, or the activation markers of platelets, annexin V is a marker for phosphatidylserine exposure. And overall, no significant differences were observed between plasma, Intersol, and Isoplate up to ten days. Clearly, in plasma at 15 days, you can see further deterioration of the platelets. For p-selectin, it was similar. The ten-day group didn't show any differences. But at 15 days, they were higher compared to the Intersol group. And the microparticles, the same thing, no significant difference between the ten-day storage groups. But at 15 days, there were higher microparticles compared to plasma at ten days.

Lastly, the in vivo markers, you can see, much to our surprise, we actually found that the Intersol had lower recovery compared to the plasma group. And this was -- it says not significant, but it was, I

think, 0.054 or something. It came pretty close to significance. And clearly, the Isoplate group is clearly inferior compared to the Intersol and plasma at ten days. And another observation is that, from ten to 15 days, the recovery drops clearly in plasma. Again, the survival on the right side here, you can see the survival also drops from ten to 15 days in the plasma group.

So, to summarize this first part, we have a similar in vivo recovery between plasma and additive solution, up to five days of storage. When you further extended the storage up to ten and 15 days, the additive solution actually had a lower recovery compared to plasma. We have a higher in vitro yield in Intersol and Isoplate compared to 100 percent plasma. We have overall a lower lactate production in the cold, and we have comparable mitochondrial function and integrin activation in both plasma and Intersol.

So that brings me to the second question we tried to address in our studies. What's the maximum storage time for apheresis platelets in plasma? And

for this study, we used extended cold stored apheresis platelets in plasma. And we went in intervals of five days, from five, 10, 15 to 20 days. We used the same platelet concentration as before. This time we used the fresh comparator from two hours, and we had a historic room temperature control group that we used. And we had similar in vitro tests, again, the same platelet yield mitochondrial markers, integrin activation markers, alpha-degranulation, and metabolic parameters and recovery and survival studies with indium-111.

So, the yield, basically the same finding as before. You can see, compared to room temperature, the yield is significantly lower in vitro. And overall, with the whole storage time of 20 days, we did not see a significant difference here in the percentage of fresh. In the percentage of fresh analysis, you can see that there's no significant difference from time point to time point. If anything, it looks like, though, these aggregates might de-aggregate a little bit over time. But this is a speculation, I guess, at

this point.

For the in vivo markers, you can see a clear stepwise decrease from five to 20 days in the cold. This was also here in the percentage of fresh analysis. And the survival is shown over here on the bottom panel. And you can see a drop from five to ten days, but after ten days there's basically a low (Inaudible) is reached. And there were no significant differences.

Then, for the glucose and metabolic parameters, you can see these platelets are still metabolically active. They're going down step by step in their glucose levels here from five, ten, 15 to 20 days. And correspondingly, you can see a step-wise increase in lactate from five to 20 days. And overall, there's no statistical significance at 20 days cold compared to five-day room temperature.

I already mentioned the PAC-1 antibodies, so this is an activation specific antibody for the major platelet integrin. And clearly, you can see there's pre-activation. So, B is, here, baseline pre-activation, and the cold actually persists up to 20

days. It looks like it even increases over time a little bit. And they still respond to collagen at all time points, but we found that, after 20 days, they still responded significantly better compared to the room temperature group over here. And the same was true in the percentage of fresh analysis.

And here's some of the original or raw data. You can see this PAC-1 binding is on the X-axis. After 20 days, you still get this right shift here, which you do not get at room temperature. We then looked for alpha-degranulation with p-selectin. And this is done without an agonist, so this is just storage lesion that you can see. And you can see, again, a step-wise increase over time. And after 20 days, there was no significant difference to five days. And we then looked for early apoptosis with a JC-1 dye that I mentioned earlier, and you can see, very similar actually to the integrin data, that the mitochondrial membrane preservation goes down over time. But after 20 days, it still is significantly better compared to room temperature over there and the same in the

percentage of fresh group.

So, to summarize this second part of the presentation, the recovery drops continuously over time in cold storage plasma stored platelets. There's continuous metabolic activity in these platelets over time. We have shown an increase in pre-activation parameters at four degrees Celsius over time, and we so a continuous decline in mitochondrial function and integrin response. But at 20 days, they were still significantly better compared to room temperature storage. With that, I would like to thank my team who did all the hard work to generate these data and the funding agency, the Army and the DOD. And I'd like to thank you for your attention.

QUESTIONS FOR SPEAKERS

DR. RICHARD KAUFMAN: All right. I want to ask if the Committee has any questions or comments from the four speakers that we've just heard. Dr. Bennett?

DR. JOEL BENNETT: All right. Maybe this is

not relevant, but platelets have an intrinsic apoptotic pathway. So, after about ten days, they sort of commit suicide, right? The BCL-2 increases.

So, would you expect platelets stored beyond ten days to do very well when they go back into circulation because things are sort of dying off over time? Maybe those are something that could be measured. Ben Kyle has this -- there are two ways that platelets get destroyed: random and non-random. And this non-random is related to intrinsic apoptosis, so to speak.

So maybe 15 days isn't good. Maybe platelets are sort of dying on their own. You give them back to patients, and it's not clear how they get removed. But they certainly do get removed. So maybe after ten days, they just don't like to circulate, if you know what I mean.

DR. RICHARD KAUFMAN: Perhaps Dr. Stolla can comment on that?

DR. MORITZ STOLLA: Yeah. Thanks for the question. Yeah. I'm familiar with the studies by Dr.

Kyle. So, I think he mainly did his studies in mice.

But there's work from Dr. Slichter where she replaced some of the plasma with additive solution and stored them, I think, up to 14 days at room temperature and still got almost normal recovery and survival. She had to replace the plasma and had to collect them in a very gentle way. But I think this applies mainly for in vivo circulation, this intrinsic apoptotic pathway that Dr. Kyle discovered.

And I think, clearly, if you remove them out of the pathway and you manipulate them in a way, I don't think the same intrinsic clock that Dr. Kyle described still applies. Because she essentially got normal recovery and survival, and this basically means that they were functional up to -- at least circulating up to 21 days in the end, if you included the storage period.

DR. RICHARD KAUFMAN: I have a question, actually, for both Dr. Stolla and Dr. Gelderman. We'll hear presentations this afternoon from Dr. Andre Cap, whose lab reported that aggregometry to single agonist

was actually improved in cold stored platelets versus room temperature. Dr. Gelderman's data seemed to be exactly the opposite. And I was wondering maybe if Dr. Gelderman has any comments to possibly reconcile those finding and/or if -- Dr. Stolla, have you done any aggregometry on the cold stored platelets?

DR. MORITZ STOLLA: Yeah. So, from my data, I think I can say that we mostly get superior responses, but occasionally there are inferior responses. We currently don't know why that is, but I guess it's part of the biologic variability that donors show.

DR. JARO VOSTAL: Hello. My name is Jaro Vostal. I work with Dr. Gelderman. And I think I would agree that there's variability in donors that we did see a potentiation of dual agonist-induced aggregation in the cold. But we're dealing with a relatively small data set, so it's possible that that accounted for the differences otherwise reported.

DR. RICHARD KAUFMAN: Thanks. Okay. Any other questions? Dr. Tanaka?

DR. KENICHI TANAKA: I have a question for Dr.

Triulzi. What percentage of the patients received platelets for anti-platelet therapy, bleeding due to anti-platelet drugs such as Plavix or Prasugrel?

DR. DARRELL TRIULZI: So out of the 130,000 episodes, about 6,000 were for anti-platelet drugs, so about five percent or so. And that was for both bleeding or for procedure.

DR. KENICHI TANAKA: And do they usually get one dose, or do they get more than one dose?

DR. DARRELL TRIULZI: It was still primarily one dose.

DR. RICHARD KAUFMAN: Thank you. Dr. Perez?

DR. ELENA PEREZ: I'm not sure if I'm farming this correctly, but it was mentioned in one of the talks that if the longevity of the platelets was affected that, perhaps when they are infused for hemonc patient versus a non-hemonc patient, there may be a difference in efficacy. I'm just wondering if cold stored platelets are also envisioned for both applications or just the application where it might be the most helpful with the traumatic replacement --

replacement for trauma reasons?

DR. RICHARD KAUFMAN: So, I think it's fair to say that when you're talking about cold stored platelets expected to circulate for a substantially lower amount of time that the application being considered is really one of stopping acute bleeding versus being able to be used for, let's say, both populations. We will hear from Dr. Jose Cancelas this afternoon. So there has been some exploration in trying to get the best of both worlds because you have a cold stored platelet that could circulate as long as a room stored platelet.

But many of the products that we're talking about we know that the time in circulation will be lower. But the question is can that be offset by the real -- by a meaningful benefit in hemostasis. And obviously, there would also be a benefit for bacterial safety in addition by keeping them in the cold. But for the purpose of this meeting, it's really hemostatic function that's the focus versus bacterial safety.

DR. ALFRED DEMARIA: Can I ask a question

related to that?

DR. RICHARD KAUFMAN: Sure.

DR. ALFRED DEMARIA: So, are we talking about -- are we envisioning two product lines in the blood bank, one being the room temperature stored platelets and one cold stored platelets, and different indications for their use, rather than all or nothing?

DR. RICHARD KAUFMAN: Yeah. I think so. So if the FDA were to someday approve a safe and efficacious cold stored platelet product -- let's say something that could be stored beyond five days -- then I think the scenario to envision would be one where perhaps blood banks would carry room temperature platelets to be used as prophylaxis for nonbleeding patients who were thrombocytopenic related to their therapy and a second inventory of platelets stored in the cold to be used for acute bleeding.

And as I said, maybe the best would be to have something that could do everything, since there are definite logistical problems in having dual inventories. But yeah, I think that that's the

scenario that the Committee is being asked to think about. Dr. Shapiro?

DR. AMY SHAPIRO: So, I think this is for Dr. Stolla. There was some indication in some of the prereading that we were giving that there's a difference in terms of the bag collection, in terms of recovery and aggregates that are formed. Could you just comment on that in terms of the experiments you perform?

DR. MORITZ STOLLA: Yes. Generally, we did not observe as many aggregates as some of our colleagues. We're not sure why that is, but we used the regular Trima Accel machine and the Tremo bag. Maybe that has to do with it.

DR. RICHARD KAUFMAN: Oh, and actually, Dr. Stolla, I had one other question. Can you comment about ways of looking at recovery and survival for cold stored platelets? You had commented on using indium as a radiolabeling marker. Can you comment about what happens with chromium? And also, are there any options for non-radiolabeling methods to do such studies?

DR. MORITZ STOLLA: Yeah. That's a great question. So, chromium, I did not show that data, but chromium requires active uptake into the platelet. And preliminary studies actually done by Dr. Slichter -- she -- we showed that cold platelets do not take chromium up, basically. That's it. So, we had to rely on one radiolabeling agent, which was indium-111, which is very sticky and sticks to everything I guess. So that was used for the -- obviously, you have to design your experiment, then, in order.

So, you cannot do one injection basically. You have two different, one for fresh and one for the stored product. So that has to be taken into consideration. And this, I believe, biotin, biotinylation can be used. We have not done that, but I think there are other groups who are more advanced with this technology who might be able to help with that technology as well.

DR. RICHARD KAUFMAN: Thank you. Are there any questions? Sorry. Dr. Jones, first.

LCDR JEFFERSON JONES: I'm not sure who'd be

best to answer this, but for the data that's presented so far, are any -- most of this seems to be focused on the efficacy of the platelets. Are any of these markers for either a pro-inflammatory response or some risk for the recipients as the transfusions are given? Or in other words, if the largest concern is about recovery and survival, if you're giving increased doses of platelets to kind of overcome that weakness, is there a risk to the recipients based on these studies or based on other data?

DR. MORITZ STOLLA: That's a very tough question. I believe there were studies done that looked at supernatant at room temperature compared to cold. And I think generally, if I remember correctly, the cytokines in the supernatant are generally higher in room temperature stored platelets compared to cold platelets. So, my guess would be that these platelets are less pro-inflammatory compared to room temperature. So, I don't think there are any good studies that looked at this.

DR. RICHARD KAUFMAN: And just to follow up on

that, I think that there's little concern for unwanted thrombi when you transfuse a standard platelet product. I think that that is something that would need to be explored in a product that we know to be more activated in vitro, at least. I think it would be important not only to think about that is the efficacy of stopping bleeding but also ensuring that, if a cold stored platelet were to be approved, that it would not cause arterial or venous side thrombi that could cause harm. Are there any questions from those on the phone, Drs. DeVan, Ortel, or Morgan?

DR. CHARITY MORGAN: Hi, this is Dr. Morgan. No, I don't have any questions.

DR. THOMAS ORTEL: Hi, this is Tom Ortel. Richard, you actually asked my question. I was going to ask if anybody had looked at these products in any kind of thrombotic animal models.

DR. RICHARD KAUFMAN: Dr. Cap?

COL. ANDREW CAP: So actually, our lab did look at that. We published a paper in *Journal of Thrombosis and Hemostasis*. I think it was 2016. We

did intravital microscopy in a rat model of laser injury. So, the laser injuries were both sort of endothelial damage, kind of the standard intravascular thrombosis, as well transection with the laser to look at more of a bleeding model. And we tested fresh versus cold stored platelets, rat platelets, stored for up to seven days I think it was.

And we found that there was no thrombosis formed beyond the site of the laser injury. So, we were able to quantify rolling and adhesion and so forth under flow. And so, they were effective at causing hemostasis, if you will, at the site of injury when there was a transection model. And they did adhere to a laser injury site, but there was no, if you will, adventitial adhesion and thrombosis beyond that site.

DR. RICHARD KAUFMAN: Thank you. Dr. Bennett?

DR. JOEL BENNETT: -- studies in animals perhaps to look at atherosclerosis-prone mice, for example, sort of extrapolating from the Vioxx data where it looks like, if you're older and have bad vessels, you ended up having thrombi and thrombosis.

Or you did poorly if you got Vioxx, for example. So, if you give something that's partially activated, perhaps if you had bad vessels, you'd do worse than somebody who was younger, for example.

DR. RICHARD KAUFMAN: I think that's an interest comment. In particular, it's possible that some clinical studies may -- well, some have been proposed and some have actually been done in cardiac surgery patients. So, I think that that's apt. So, any other questions? All right. Well, why don't we take a break at this point for about 15 minutes. We'll reconvene at 10:45. Thanks very much to the speakers for this morning's presentations.

(BREAK)

DR. RICHARD KAUFMAN: All right. So, we're going to go ahead and get started. So, I would like to introduce the next speaker, Dr. Geir Strandenes from the Norwegian Armed Forces.

IMPLEMENTATION STRATEGY WHOLE BLOOD AND COLD STORED PLATELETS

DR. GEIR STRANDENES: Thank you very much for inviting me to this important meeting and thank you for being the only foreigner here who comes from the country where chilling is quite obvious. It's the chilled country. I'm going to tell you a little bit about our strategy for implementation of cold stored platelets and cold stored whole blood. I know we are not going to talk about whole blood during this session, but we do have to remind you that we have an approved platelet produce for storage of platelets stored cold until 21 days in whole blood. And we use it. Let's see. So, the regular disclaimer.

So just to give you a little bit of information of -- Norway is a small country, a rather large geography, 5 million people living in Norway. Bergen is a small city. We have regional level 1 trauma center, 1.1. million, 900 beds, and a national burn center in Bergen.

So, this is a small hospital compared to probably other bigger hospitals in the U.S. We have annual use of 20,000 units of red cells. I can tell you that our cardiothoracic surgical department is consuming around 16 to 17 percent of all the blood products the blood bank produces and also a little bit different in between apheresis platelets and (Inaudible) platelets. In Norway, at least 70 percent of the platelet units is still whole blood derived platelets.

That is just to tell you how the blood banking system works in Norway. It's an integrated part of the hospitals. So, all the hospitals who have trauma for general or acute function normally has also a blood collection center. This just shows you hospitals with red blood cells and plasma. And the problem that we have in our region is that a lot of the smaller hospitals does not have platelets. So, our solution to that is to place cold stored whole blood units there as their platelet solution. And hopefully, we are now seeking regulatory approval for an extended storage

solution of platelets up to 14 days.

This is just -- I just wanted to show you this because this shows you that, if you can see here, from mid-Norway to top there is only two hospitals that has platelet inventory, which poses a huge problem because these other hospitals are also assigned to be able to give a balanced transfusion. And people up north are also bleeding, so we are really looking that we need a platelet product with extended storage. And I guess that might be a similar problem that you have in the U.S.

Let's see if I can get this to work. This is just to show you the map again. If this works, I get the map of -- yeah. Here you can see the size of Norway over U.S. and over Europe, so just to get the idea of long transport line or resupply lines for blood products poses significant problems in our country. And these are not climate crisis pictures. This is the climate in Norway, and the climate also poses trouble with resupply and roadblocks and air supply where the air space is kind of no weather. And this is Bergen.

So, this is a part of a research education program that we initiated in 2010. And it's a collaboration between the military and the civilian and focusing on far forward blood product and making blood product available as close to the point of injury as possible. And there is a need for also transfusion platelet early, meaning that we need to be able to bring platelets to the point of injury.

So, this is just to show you the timeline for some of our studies. And we have done a lot of in vitro studies of both cold and room temperature platelets. And our findings is that cold stored platelets in the past has much better aggregation response if you store them for a longer time compared to room temperature. That is what other groups have shown, Cap and (Inaudible) group has shown that aggregated response is better preserved when you store it cold.

And this is the number of cold stored platelet units we have been transfusing for the last two years. This number is now 600 in 121 patients. And this is

what we use it for, emergency department surgery, obstetrics, cardiothoracic, vascular, medical, pediatric. These are all patients with major bleeding who receive this platelet containing a product called whole blood.

So, this is the age of the units given, and you see we give them up to day 21. And so far, we have found no significant hemolysis, or any other adverse reaction is reported for these 600 units that has been given so far. So, we find that the safety issue is well taken care of and is not any worse than components.

So now I'm going to tell you about the clinical study that we needed to do because the in vitro studies suggested that cold stored platelet might be beneficial for major bleeding. And this is basically the only platform we could use. Bergen is a city of about 300,000 people. We cover 1.1 million people. And we don't stab each other, and we don't shoot each other. And we have at least a 50 percent reduction in severe trauma by cars. We have the least

number of car accidents per capita in Europe.

So that means that we need to use this model, and it's a complex model because post-op bleeding in cardiac surgery is really multifactorial. And it's really hard to kind of correct the most important factor that is called the surgeon factor. That is not confounded for. So just telling you that.

So, this is at the other university hospital. We did first a study design of two-arm randomized clinical pilot study, and we followed up with a single-arm extended study from eight to 14 days of cold storage. They were non-agitated.

So, when we started this, we decided we only want to change one thing. So, we only changed the temperature of the apheresis platelet unit. So, there was no other thing though. So, the surgeons and the anesthesiologist did it exactly the same way that they've always been done. They used the same protocols, so temperature was the only thing we changed. And it was randomized week -- week randomization, so we do not waste too many products.

So, I've already said this. We were comparing room temperature to cold, and I'm going to give you some of the results. It's a little bit slow, this one.

So, we suspect cold stored single-donor platelets equally effective to conventional room temperature stored platelets intervention of post-operative bleeding in patients undergoing complex cardiothoracic surgery. This is complex surgery. This is not an ordinary bypass surgery which normally has an ex-corp time of 45 to 60 minutes. These are patients that have an extra-corporeal circulation time of above 200 minutes, so three to four times the length of extra-corporeal circulation which really, really affects especially the platelet function.

So, the first arm was a parallel arm randomized trial comparing CSP to RTP, and they were both agitated. The average time of storage of the room temperature platelet -- 50 percent of the room temperature was stored from day five to day seven. And the cold stored platelets, 70 percent of those were stored in five to seven days. So, a lot of these were

in between five and seven days of storage. And very few of them were from one to two days because we normally produced the platelets on a Friday when we're going to use it in the week. So that means it was at least stored for three days. So, it was 65 percent pass with agitation for seven days.

And then the observation study, we extended the duration of platelets stored for up to 14 days. And the storage age was from 10 to 14. So, there was no platelets that was stored cold for less than ten days, and the average storage time was 12 days.

So, this was only adult patients hospitalized at Haukeland University. Only elective and semi-urgent patients were enrolled. And we got better at selecting patients because you don't know if they need platelets or not or -- kind of percent of it was around 40 percent of the enrolled patients needed platelets. And after time went by, we got better in knowing who probably will need platelets or not. So, we were a little bit stricter at the end.

When we started making this protocol, we also

included patients who were on dual platelet inhibition, less than 48 hours prior to surgery. Then the surgeons completely changed that practice. So, all elective cardiac surgeries now have at least five days of withdrawal of dual platelet inhibitions. So, there are no patients in any of our arms who was on like (Inaudible) and other anti-platelet drugs.

So primary outcome was cumulative postoperative blood loss, measured as chest drain output. The reason for that is that the ongoing bleeding in the operating room is really hard to measure the volume. And most of that is such a fact to the extra-corporeal machine. So just output after chest closure was what we chose as the post-op bleeding volume.

This is just maybe a little bit hard to see that. We included 120 patients in the randomized arm, excluded 70 of those, meaning 70 didn't receive platelet at all. Then you have the intention-to-treat arm, which included 50. And some of these patients needed reoperation in the 24-hour window because of

surgical bleeding. Some went to ECMO and were heparinized. And when you heparinize these, you cannot actually use chest output to (Inaudible) the platelet or not that's used. So, we ended up with 21 per protocol patients in the warm and 20 in the cold. We did the same with the observational study. We actually included 21 and ended up with 10 in the per-protocol.

So, 51 patients completed frequent protocol, receiving either room temperature or cold for seven days and ten receiving up to 14 days of storage. So, the criteria for platelet transfusion, someone might say that you need to make -- use any point of care test or multiplate to decide what product to give. But we decided we will not change the way that blood products is given. This is the anesthesiologist and the surgeon together who decides what products to be given. It is based on clinical judgement, experienced people who have been doing this for a long time.

And it's based on the amount of bleeding, hematologic parameters, transesophageal echo, evaluation of the right and left ventricular

performance to decide. And when they were bleeding, we replaced bleeding by blood products, red cells, and plasma. And if there's a need for a balanced infusion, we will add platelets. So, this is eyeballing. In fact, it's the most important way of deciding when to give and when not to give. And I'll show you in the last slide that maybe it's equal to other parameters.

This is the most common type of surgery requiring platelet transfusion in our study. That is aortic arch surgery, which requires a lot of anastomosis. Some of these are in deep hypothermia. We cool them down to 16 degrees Celsius in the blood, so they are really cold. And they go into cardiac arrest and this takes some time.

This is just show you the difference in patient characteristics in the per-protocol group. If you look at the EUROSCORE here, the EUROSCORE is European System for Cardiac Operative Risk Evaluation. And none of this is actually statistically significant. You see the cardiopulmonary bypass time is above 200 minutes in each of the arms.

This is the chest tube output. You see both the intention-to-treat arm. And when you take away those who doesn't follow the protocol, you will have the room temperature arm will have a medium chest tube output of 720 milliliters. The cold stored has a median of 570. And the 14 days cold stored group is 590 milliliters of blood in chest tube output.

This is also blood component use. No statistically significant difference between blood components use and the -- we did not do a statistical comparison between the observational arm, of course, and the two other groups. So, this statistical analysis is done between the two arms in the seven-day arm.

So here comes to change in aggregation response after the first transfusion episode of the either room temperature or cold stored platelets. As you can see, there is a clear increase in aggregation response, either if it's warm or cold or even if it's up to 14 days. Remember that the 14 days patient, we limited the number of cold stored platelets used to

two, just for safety issues. If he needed more than two units of platelets, we went to standard temperature stored platelets. But only one in the 14 days platelets arm received more than two, average 1.5. So, in that group, they received less amount of platelets, also showing that their platelet increase after first transfusion episode is a little bit less. And that also affects aggregation response post-transfusion.

This is just how it looks if you take this ADP. And we think that multiplate ADP is in these patients that is the best agonist to choose to evaluate if you need platelets or not. And you see the room temperature arm and the cold stored arm show exactly the same curve. There's no difference in response.

If you look at platelet count, at least we could not find any difference in platelet increase, decrease, and platelet count the next morning. So, we couldn't find -- we should assume that cold stored platelets, they are cleared more quick in the circulation. But we could not find that just in our clinical data. There was absolutely no difference.

And the other thing here is activated trauma thromboplastin time. And also, just mark that in a lot of studies done of cardiac thoracic surgery, fibrinogen is looked upon as one of the things that drops the most. And in our study, we didn't see anyone -- none of our patients actually in average dropped below average fibrinogen level.

This is another important slide, I think, because this is actually viscoelastic testing. We introduce viscoelastic testing in cardio thoracic surgery years ago. Conclusion from the collision was that it was not very useful for us to be able to use TEG as a point of care test to decide when to give platelets or not. And if you see the data here, both adverse TEG values is actually normal, within normal range all the way. And it's a very insensitive test for evaluating platelet function. And really, we have patients who have almost zero platelet aggregation response prior to transfusion, and the had a normal TEG and RTP.

So that's just for -- it's almost my last

slide. Here you can see we compared multiplate ADP aggregation response prior to platelet transfusion. And you see the difference between the transfused versus the non-transfused. There's a clinically significant difference in ADP aggregation response. So, the conclusion is that the clinicians here were able to decide fairly good who would need platelets or not, without knowing the aggregation response prior to the study. And you see this is kind of the difference between eyeballing versus multiplate.

Important also that the one who got transfused had significant lower hemoglobin. Lower hemoglobin will affect hemostasis. It will affect platelet adhesion, and that might also be a reason why they needed platelets and the other didn't.

So adverse events, venous or arterial thromboembolism, actually length of stay, and mortality, we found no difference in between groups. Remember that these are very sick patients, and it's extended surgery. And it's kind of a high right and thromboembolic events postoperative in these patients.

So, we didn't see any difference. The number of patients is too low to conclude, but I think this is the average amount of thromboembolic events we see in these patients, even if they didn't get platelets at all. And the length of stay in the ICU and mortality no difference.

So, the only thing we actually concluded with is that it seems that up to 14 days of storage of cold stored apheresis platelets can contribute to hemostasis. And this is the basis of why we want to seek regulatory approval for stored in cold up to 14 days because all these smaller hospitals doesn't have platelets. I would rather have -- it's not a perfect product on day 14, but it's definitely better than no platelets. That's my opinion.

Then the acknowledgements of the Blood Far Forward group in Bergen and Spinella and all the other groups in tool that has been advocating for doing this study. And actually, I think the reason that we actually chose to do this study was based on the meetings we have in Bergen and understanding the

importance of at least doing a pilot trial as a basis of going further with larger randomized trial. This is the research group in Bergen that I have to thank. Without these guys, there was no possibility to do this. And do or do not; there is no try. Thank you.

DR. RICHARD KAUFMAN: All right. Thank you very much. Our next speaker will be Dr. James Stubbs from the Mayo Clinic.

COLD STORED PLATELETS HOSPITAL-BASED BLOOD BANK EXPERIENCE

DR. JAMES STUBBS: Well, thanks for the opportunity to be able to address this group. I thought I would sort of take you through what our experience has been with cold stored platelets since we've been transfusing them at our facility. We started in 2015. So, I'll sort of tell you where we've been and a little bit of where we might want to be going. I don't have anything to disclose, as was mentioned earlier.

This started as, and continues, I think, to be a collaborative project between the blood supplier transfusion service at Mayo Clinic and our Trauma Services, including our pre-hospital service lines as well. Circled there, that humongous building there is St. Mary's Hospital, where you can get lost on a daily basis. But on top of there circled is where our air ambulances take off and land. And they play an integral part in part of this story.

Well, in 2013, I had a meeting with the trauma personnel at Mayo Clinic, including Dr. Jenkins who's in the audience today, who came to me saying that, given the potential added value in bleeding patients based on the data that had accumulated to that point, they really wanted us to consider supplying them with cold platelets. So, we made a joint decision between trauma and transfusion medicine in Rochester to try to pursue and obtain regulatory and accreditation approvals to use cold stored platelets in our trauma practice.

And most of this is outlined in this article

here where we sort of went through the process. I'll give you some of the high points. I've been told that this paper sort of reads like a dark comedy, but anyway, be that as it may.

So, on November 18, 2013, we submitted a variance requested AABB Standards and Global Development Department asking -- knowing that platelets are intended for transfusion, must be stored at 20 to 24 degrees with agitation. We asked for the option of storing apheresis blood components at one to six degrees without agitation. And we asked for five days because platelets were stored for five days.

Well, after a lot of back and forth, our request was denied mainly because the program unit noted that the bag manufacturer that we were proposing to use for these apheresis platelets did not have a claim that you could support cold storage with that bag system. Therefore, they couldn't grant our request. So, they suggested we go to the FDA to determine if a variance would be needed to store platelets at the temperature described in the bag system that we

proposed using.

So, we started in with the FDA, asked for approval to store platelets in a monitored, controlled refrigerator system for a maximum of five days for specific use in actively bleeding trauma patients. And we noted that 21 CFR already stated that platelets could be stored at one to six degrees Celsius without agitation. And as we went along with the FDA, we sent a letter that included validation data. We looked at cold stored platelets up to seven days, looked at some of the routine things you look at with regard to whether you're going to mess up the bag system if you put it in the refrigerator. When you have good pliability, translucency, good label adherence, good ability for everything to be scanned, no ink smearing, no leaks, all other validation parameters passed.

We also looked at platelets with a few routine parameters: one to six days stored in the cold. Cold stored platelets stop swirling, which is not surprise to anyone knowing what happens to cold stored platelets in the cold. The platelet counts were lower than in

the cold stored platelets but not markedly so. And the pH was a little bit lower in the cold stored platelets but not so you could really know much of a difference.

We did TEG at two, three, and six, cold platelets versus room temperature platelets. And for the most part, they looked fairly identical or mirror images. On day six, you can see that the cold stored platelet TEG actually was, if anything, a little bit better. So, we felt that TEG parameters at the very least were just as good as the room temperature platelets and maybe showed a little bit of improvement or a little bit of better preservation over time.

So, on March 27, 2015, the FDA approved our request to store apheresis platelets at a refrigerated temperature without agitation for three days. And we needed to restrict the use of these cold stored platelets to the resuscitation of actively bleeding patients. So, then we went back to the AABB and told them that the FDA approved the use of the bag system to store platelets and so can we please get a variance from you? And they came back on October 8, 2015 and

said, “Your variance request is granted by the AABB. The approval is limited to one to six degrees stored platelet components with the following parameters.”

So, we were able to store without agitation for three days. The variance applied only to apheresis platelets collected using an automated blood collection system that we had, intended for use in actively bleeding trauma patients only, so not actively bleeding patients but actively bleeding trauma patients. We could store for three days. We could only use the resuscitation of actively bleeding patients, and we could not release them to the general transfusable inventory.

We also -- I may have passed over this letter. But the FDA also had not finished their guidance on bacterial prevention. So, we requested from the FDA that, because of the short storage time, that we not do bacterial detection. And the FDA said you did not have to do bacterial detection for three-day platelets.

So, our goal was to collect three Group A platelets a week and store in the emergency department

refrigerator. We started that in October 2015. A major challenge that we found was the product wastage. The three-day storage was a very tight window, and you have to quarantine for 12 to 18 hours until infectious disease testing is complete. So, the true availability of a three-day platelet is about two days. We also had problems with clot formation. These were plasma rich platelets that liked to clot in the refrigerator presumably because of the fibrinogen in the plasma interacting with the surface markers on the platelets and causing clots.

So, when we looked at October through August -- October 2015 through August 2016, we produced 119 cold stored platelets. Nine didn't get out of the transfusion laboratory because of suspected clots. We delivered 110 to our transfusion laboratory. So, we have a component laboratory and a transfusion laboratory. The transfusion laboratory is where we issue blood for transfusion. 110 got delivered to the transfusion laboratory. 21 or about 20 percent actually got transfused. 80 percent were discarded, 20

for clots, and 65 expired on the shelf. And the other reasons there were a couple of other reasons, including pneumatic tub system sending them who knows where.

So, the transfusion numbers now that we've compiled all of them, in the emergency department between October 2015 and July 2017, we transfused four units in 2015, 22 units in 2016, and five units in 2017. At the same time, the emergency department over the same time period transfused 152 room temperature platelets. Now, not all of those were for trauma patients, obviously. And we were restricted to use in trauma patients. But some of those were trauma patients, and some of our practitioners were choosing to use the room temperature platelets in lieu of the cold platelets that were in the refrigerator down in the trauma room. So, wastage continued to be extremely high.

So, we sort of circled the wagons and decided, well, maybe the best thing to do at this particular point in time is to move the cold platelets to the pre-hospital arena. That might improve our chances that

this would be a better utilization of the cold stored platelets. So, we moved the cold stored platelets exclusively to the air ambulance service on July 24, 2017, with the feeling that we could enhance our damage control resuscitation approach and improve the likelihood that they would be used.

So, what we did was this is what they carry out, and there's very limited storage and space on a helicopter. So, we had to validate, one, the storage configuration in order to make sure that this cooler maintained temperature. So, we did some validation studies and were able to put two red cells, a whole blood, one FFP in a row, one FFP on its side, and a flattened cold platelet on top. And that was able to be carried in our air ambulances.

One thing is, as Geir sort of pointed out, this is another situation -- is, if you're talking about pre-hospital platelet transfusion delivered by an air ambulance, a cold platelet, if you're going to use a platelet product that's a platelet product -- obviously, there's platelets in whole blood -- the only

option is a cold platelet. There's no way that we would have the room to carry and maintain, especially with our extremes of temperatures and other logistical issues of a room temperature platelet out on the air ambulances. So, this would be our only option. So, it was either a cold platelet or a no platelet for the air ambulances.

So, we decided, well, we're going to stick these platelets into an anaerobic environment, essentially, for a number of hours. So, we decided to do some studies, and we took a number of cold stored platelets. And we compare cold stored platelets up to three days in the refrigerator to a cold stored platelet that was also up to three days in the refrigerator, but during that time period we also stuffed them in the cooler for six hours to see if there was any difference in the parameters that we measured.

And what we found -- I'm not going to show the data here because I want to show some other data within the 25-minute period that I'm allowed. But we found no

statistically significant difference in platelet functionality per storage condition for the six hours that the platelets were stuffed in the cooler with regard to platelet count, aggregation, and accumulation of platelet-derived microvesicles. And platelets transported in a cooler for up to six hours cold stored do not function any less efficiently than those that we had stored flat in the refrigerator for three days.

So, we started to carry them on the air ambulances. And in 2017 through 2019, we transfused two units in 2017, 12 unites in 2018, and one in 2019 in the pre-hospital arena. And then we put the cold stored platelet program on hiatus on February 25, 2019 for a couple reasons. Mainly it was -- and this is good that our air ambulance folks are good stewards of the blood supply. They were worried about the attrition that we were getting with the number of platelets we were losing trying to maintain this cold stored platelet program. So, they said, as an alternative, “Can we switch over to carrying two group O negative low titer whole blood units on the air

ambulances rather than one group O negative low-titer whole blood unit and one group A cold stored apheresis platelet?" So, we made that switch after February 25. So now they're carrying two whole blood units on their ambulances. I'm sorry.

As part of our deal with the AABB, we had to, in our three-day variance, we had to do some outcome studies. So, we compiled -- we analyzed -- we tried to match as best we could 20 trauma patients that got cold platelets and 20 trauma patients that got room temperature platelets over a period of time when we were transfusing primarily in the trauma room. And what you find is that, for most of the parameters between the -- we tried to match these so that they were as well matched as possible. And you can see that the only differences that we saw in some of the parameters of the patients with regard to transfusions and coag test and other rebleeding and reactions, et cetera, et cetera, was that the cold platelet people got a statistically higher level of cold platelets than the warm platelet people and vice versa. And a couple

of the cold platelet folks also got whole blood as part of their resuscitation.

If I can get backwards here one more time, there was one other -- yeah. If you look at the characteristics of the age of the folks and the other parameters, you can see it's largely a blood trauma situation. The only difference between the two in these parameters is that the injury severity score was much higher in the cold platelet folks than the warm platelet folks over the study period. And if you look at -- that was statistically significant. If you look at the mortality results between the two, there was no difference in mortality and other parameters.

Now, this is 20 patients versus 20 patients retrospective analysis. So, the study was too small to draw any definitive conclusions. There were no adverse events, and cold stored platelets did not give any hints of being worse than room temperature platelets, even when used in a more severely injured group of patients who probably had a lower probability of overall survival with no difference in mortality. So,

what we see here with the three-day platelet is that, when we used them in our trauma population, that we really were seeing little or no difference. There were no thrombotic events for any of these patients and no transfusion reactions.

So, the final numbers before we put it on hiatus was we transfused 100 -- and then we broke this down because, in 2017, we went to all pathogen reduced cold stored platelets. But you can see that, overall, we transfused 46 units over that time period, and we discard 223. With a three-day shelf life plus restricted use in bleeding trauma patients only, and I just used this for back of napkins calculations, that at $600 per apheresis platelet that we threw away about $133,000, $134,000 worth of apheresis platelets that were cold stored.

So, a three-day cold stored platelet program for trauma, in my opinion, is not sustainable, especially in light of what we're also seeing. One of the issues is that we're seeing an upward drift of a total number of platelets we're transfusion for our

patients. So, we can't be throwing away a lot of cold stored platelets, which is another reason that we had to go away from them.

And what we found is that we have an external supplier and an internal supplier. As we had to mobilize more resources to collect apheresis platelets to meet demands, we also had to increase the number of platelets we purchased from our external supplier. And because we mobilized more people to collect platelets, we weren't collecting as many red cells. So, we ended up with increased red cell purchases externally relative to what we were collecting before. So, the trickledown effect of increased platelet use also helped -- and the impact on our donor center also influenced the fact that we needed to go away from cold stored platelets.

So, I went back to our Mayo Medical Transport folks just recently, and I asked, "You've got two whole blood units, basically a 21-day cold stored platelet in the whole blood unit. If we had the ability to have a longer cold stored platelet, would you use them?" And

the answer was very much a hearty yes from the Mayo Medical Transport folks. They would like to be able to mix and match based on what they're going out for for a pickup or treatment whether they want to use two whole blood units or carry one whole blood unit and a cold stored platelet or maybe even two cold stored platelets. They want to be able to mix and match before they go out. So, they said that, yes, if these were available in a longer storage period, they would embrace cold stored platelets.

But we cannot proceed with a plan until we can extend the shelf-life. So, the goal is, if we can, we thought is to try to pursue a 14-day cold stored pathogen reduced platelet. We felt that cold storage plus pathogen reduction would limit infectious disease transmission risk, including most profoundly bacteria, and the number and function of cold stored platelets we hope we were going to find would be an effective product for bleeding patients.

So, what we thought we should do, if we're going to jump back into this, is to look at some

parameters in the laboratory first, looking at pathogen reduced platelets and some functionality parameters. I don't know that there's a lot of data on pathogen reduced platelets and functionality parameters. So, if I can get this to go -- so what we did was we took ten platelets that were double collections, and we pathogen reduced them. And we put one half as -- these are plasma rich pathogen reduced products, stored them at room temperature for 14 days. And we did a pathogen reduced cold stored platelets, and we stored them without agitation for 14 days and did a number of assays.

One thing is that we looked at total platelet counts, and you can see, not surprisingly, that they paralleled each other for a period of time. And this is not intuitive, the red lines, which should be -- you'd think about warm -- is actually the cold platelets. And the blue lines are the warm platelets. So stand on your heads a little bit to be able to -- so if you look at the room temperature platelets, they maintain their platelet count more effectively than the

cold platelets. We weren't surprised by that.

When we looked at various platelet aggregation parameters -- and remember red is the cold platelets -- you can see that they parallel each other for a good period of time. But over time, there seemed to be a consistent pattern that platelet aggregation in the cold stored platelet was better maintained. And in some of the parameters, the room temperature platelet actually went to essentially no aggregation between 10 and 14 days. So even though there was a drop off with the cold platelet, as well as the room temperature platelet, the extent of the drop off was much less. And there was always some aggregation response.

When we looked at phosphatidylserine with annexin binding, what we found was early on that the PS levels were higher in the cold platelets, either without activation and with a variety of activators. Then things seemed to even out towards the end of the storage period for some of these parameters. Just for the sake of interest, now, the blue here is the cold platelets. What we did was, since room temperature

platelet I don't believe is actually ever going to be a 14 day room temperature platelet and the room temperature platelets that we're using right now are day five, what we did was we cut off -- so the red line is basically carrying over day five results all the way to the end while the blue line is all the way through 14 days. So, you can see that a 14-day cold stored platelet, which I guess is in the realm of possibility, has a much higher PS expression than a day five warm platelet.

When we looked at fibrinogen receptor of PAC-1 positive platelets in these, what we saw as, for the most part once again, higher fibrinogen receptor results for the cold platelets. There were some times when the warm platelet jumped up with a mixed agonist activation but then fell below again at 10 to 14 days. So, it looks like, as a fairly general theme, that the fibrinogen receptor in the platelets at cold pathogen reduced appears to be higher. And this is just another comparing day five room temperature platelet, which would be reasonable for when we would use the room

temperature platelet versus fibrinogen receptor basal expression without activation. And you can see that the basal expression is higher in the cold platelets at 14 days than at day five.

P-selectin positive platelets, you can see that, with warm platelets -- or with cold platelets, that they are higher early on with no activation. And then the line crosses, and some of the various patterns -- this is sort of a mixed bag of things. The mixed agonist activation shows at the later end that the p-selectin levels are higher. And this is basal expression of the surface p-selectin of a day zero through 14 platelet versus a day five room temperature platelet, which would be when we'd probably take them -- or we would take them off the shelf. So, the p-selectin is higher.

So, this is microparticles or microvesicles. And these are platelet specific microvesicles. And you can see that the platelet specific microvesicles that would have some procoagulant activity are much higher in the cold platelets than the room temperature

platelets with all of the different activators we used and also basal. Also, we looked at some other parameters, like how well was platelet count maintained, pH, and also whether we were getting any bacterial growth. You can see there was not too much to choose between. And this is our number ten pair, so ten R is our room temperature, ten C is our cold. And you can see that, for the most part, there's not that much to choose from the two, except that the room temperature at day 14 the pH was below what would be acceptable while it was maintained for the cold platelet. And neither one had any growth from bacterial culture, which we would expect.

So, to summarize, in 2013, we made a collaborative decision with the trauma service to pursue cold stored platelets. We got FDA approval in March of 2015, so about two years later, to use for three days in actively bleeding patients. Later on that year, the AABB approved us to use the product without agitation, without bacterial culture for actively bleeding trauma patients only. When the

program was active, we transfused 46 units. We discard 233. We started pathogen reduced cold stored platelets in February of 2017. Our clinical study showed that we needed to provide for our variance request -- showed that cold stored platelets appeared to be at least equivalent with no increase in adverse events during the three-day storage period.

Our goal is 14-day stored platelets. So initially, we've done laboratory studies. What we found was, in general, lower platelet counts over time, better preserved platelet aggregation in the pathogen reduced cold stored platelet, higher levels of procoagulant PS expressed on the platelet surface, higher levels of PAC-1 responsible for fibrinogen binding on the cold platelet surface, higher levels of p-selectin, which also serves some procoagulant functions, and higher levels of procoagulant microvesicles. We had better preserved pH and no bacterial growth. So that's where we are right now in our thought process and efforts as to whether we should continue down the line to pursue cold stored platelets.

We think that the information is reasonably positive at this point. So, I thank you for your attention.

DR. RICHARD KAUFMAN: Thank you, Dr. Stubbs. Our next talk will be by Dr. Donald Jenkins of the University of Texas San Antonio.

ROLE OF COLD STORED PLATELETS IN CLINICAL CARE IN THE GENERAL POPULATION

DR. DONALD JENKINS: Thank you for the opportunity to come and speaking with you today. This will be the least scientific talk you'll here all day, just a simple trauma surgeon. And I'm going to talk about a lot of the practical aspects of the patients we care for, their needs, with a focus on providing patients what they need when and where they need it. So, I have no disclosures but many people to acknowledge in terms of the role that they have played in the creation of this presentation overall.

So, we had noted back in the 2006 timeframe -- actually, I'm sorry, 2004, in Balad, Iraq, based upon thromboelastography that, despite the normal platelet

counts in many of our soldiers, as Geir had talked about in his cardiac patient population, the patients were bleeding. And the thromboelastography did reflect those changes in platelet function in that group. So shortly after that, we started, back home in San Antonio, a platelet first transfusion strategy in many of these patients because the starting hemoglobin in many of these patients was ten grams per deciliter, and red cells weren't necessary in the early going.

It was Rosemary Kozar and Shibani Pati that brought to light the potential as to why this may be the case. And it has to do with the glycocalyx of the endothelium being denuded and dysfunctional. It's a little challenging here with this remote control. But brought some science to why we were seeing what we were seeing and, I think, added some evidence to support our thought in providing a plasma and/or platelet first resuscitation.

We also had quite a bit of experience in the use of whole blood. And as a surrogate marker for cold stored platelets, it's the only thing that I have to go

on besides the small amount of data that Jim just showed you from our time in Mayo Clinic. So, I'm not going to bore you with the component therapy bit. I'm going to go off script substantially based upon some prior discussions that were held here already today.

So, this is what I wanted to speak about, especially when it deals with injured patients. The minority of our population lives in rural America. The majority of trauma related deaths occur in rural America. And there's something about that austere environment, the austere environment of the combat zone, the upper Midwest, the vast reaches of south Texas, and there's quite a bit of a problem in this country. In the civilian setting, there are about 30,000 people who die of injury that is potentially preventable each year. And the vast majority of those who die die related to hemorrhage. And this gets to the heart of the matter of providing patients what they need when and where they need it.

This is a great example of that in the upper Midwest where you see these three hubs. These are

three major Mayo Clinic hubs with these flight circles around there. They get you 30 minutes out and 30 minutes back, so you're an hour from the hospital. All of these other sites, some of them are clinics. But if you go out to Sleep Eye, Minnesota, where they've got a 16-bed hospital and the emergency department shuts down at ten at night and you have to ring the doorbell if you get sick, they don't have platelets. If you're on antiplatelet therapy and you're having a hemorrhagic stroke, you're hours from getting platelet transfusion. And I see that as a major problem. It's why we embarked on what we did. And it's interesting that the time-distance relationships that we see between those sites and what we see in the combat zone are eerily similar.

Now, I don't show this to show St. Mary's Hospital or that the Mayo Clinic has a helicopter. What I mean to show by this slide is that those are corn fields. A major metropolitan center, about 100,000 people, and there's cornfields ten minutes in any direction that you drive. So, people get injured

in those environments. They get injured in motor vehicle crashes. They get injured on the farm. They get injured falling out of a hay mound. And having the ability to provide those patients with the healthcare they need and the things that they need to live and giving that to them when and where they need it is all important.

This is a 22-county area in south Texas. There's about 4 million people that reside in this zone, half of them in that one county, half not in that county. Not every county has a hospital. That's 26,000 square miles. That's the size of the state of West Virginia. And I can tell you that there are, outside of that county, Bexar County where San Antonio sits, there's one hospital that has platelets in that zone on a regular recurring basis that are being used.

It brings us to a slightly different issue related to obstetrics we'll get to in a little bit. I'm sorry these slides got a little bit out of order, but we'll just go to the punchline here. There were 17,000 patients we evaluated in our trauma center over

a 32-month block of time. The mortality in that group sits at about 4 percent overall. About 4 percent of them required a transfusion. Of those who got emergency transfusion on arrival, the mortality rate was 40 percent. If they needed a massive transfusion, if you need your blood volume replaced on arrival to the trauma center, the death rate is 75 percent. That is not providing patients with what they need when and where they need it. So, we had to do something to change that, and South Texas Blood and Tissue helped us to make that changes.

These slides are like on auto advance. I have no control over them whatsoever at this point. So, we weren't terribly good at one to one to one resuscitation scheme. It's why we went to whole blood and a cold stored whole blood product at that. And it has to do with, if this next slide will come up -- ah, yes, helicopters. So, there are five helicopter EMS agencies with 18 ships spread across that 26,000 square mile land mass.

Now, we talked about component therapy to put

in those ships. I don't know how to do that with a ten-day cold stored plasma product and a 30-some day red cell product and a three to five-day platelet product. You tell me how you do the resupply and make available to our patients what they need when and where they need that. And it would be, I think, practically impossible to do that without something like a cold stored product.

This slide, a little busy, but let me just show you that these are the two trauma centers in San Antonio, the red stars. These are patients who got a massive transfusion on arrival to their trauma center, and they're colored coded by the number of patients that came from those ZIP Codes. When we talked about putting blood products in the hands of ground EMS units, we wanted to know where were the high spots, where were the danger spots that we needed to attend to. I draw your attention to the fact that the mortality in this group sits at about 65 percent, and the time from injury to arrival is less than 30 minutes. That's a problem.

So, we need to come up with transfusion triggers, training, and convince our pre-hospital providers that this was going to be a good thing. We've now transfused well over 1,000 units of whole blood in San Antonio, about half of that in a pre-hospital setting, about half of that in those trauma centers. If the slides will advance, there are some interesting things that we found.

Time to death has moved four hours to the right since instituting this program. And cold stored whole blood is the only way I can get cold stored platelets to my patients today. We now have cold stored whole blood in nine rural ground EMS agencies. There's over 100 units of whole blood sitting in various places across south Texas today, ready to resuscitate. It was Andre and Phil and their group that introduced us to this idea of cold stored platelets. We learned a lot at the THOR meeting about these little weirdos and how they work or don't work as the case may be and their reliance on monocytes to have their full function.

In lieu of looking at any more slides, I can't take it anymore with the slide advancing, I'll just talk to you about a couple of other things. So, if you look at the 100,000 troops that are deployed today across the combat zone, that includes all of North Africa and all of Southwest Asia, there are three locations where platelets can be obtained. They do try to push those forward to locations. And as you can imagine that waste is high. Maintaining the temperature in room temperature conditions and being able to monitor that is, as I think Jim had stated, nearly impossible to do.

When we look at our civilian patient population getting transfusion in a pre-hospital setting, depending upon who you talk to, the non-trauma patient represents 15 to 65 percent of those getting transfused, so uninjured patients. This includes obstetrics, GI bleed, dialysis, shunt ruptures, other forms of bleeding, you name it. When we get transfers into our trauma center from any of those outlying 20-some odd hospitals, a lot of times it's because they

have intracranial hemorrhage. And if they're on antiplatelet therapy, which anybody who's got health insurance and is over the age of 60 probably is on some form of antiplatelet therapy, the neurosurgeons want them to get platelet transfusions.

Obstetrics is its own special group of individuals. Peripartum hemorrhage is a real problem worldwide. The World Health Organization tells us a women dies of peripartum hemorrhage every four minutes. And transfusion strategies are lacking for those women.

We looked at this in our own institution. County hospital, 7,000 deliveries in two years, over 700 of those women needed emergency transfusion. Nearly 10 percent of them needed a massive transfusion. And it's a horrible problem. By statute in the state of Texas, to be the lowest level hospital that can schedule deliveries of babies, you have to have platelets on the shelf. And if you talk to Elizabeth Waltman from South Texas Blood and Tissue, those centers account for the highest waste of platelet products of any type of hospital out there, not to

mention the questionable safety with the sepsis risk in that patient population. So, having a cold stored product that would extend the shelf-life could be game changing.

And there are many hospitals in south Texas that have shut down their obstetric programs. Those moms have to come into town to deliver their baby, separated from their family and their support network because their hospital can't maintain platelets on the shelf. So, I think that there's a lot more to this in terms of the general population at risk who would potentially benefit from having a cold stored platelet product available to them.

We've used it. We've seen it work. We've used it in whole blood, and we store ours up to day 35. And it works just fine. It's a game changer, stops hemorrhage. In fact, the folks in -- Jason, I don't know if you're aware of this. Mark Aiser (sp) told me yesterday that Pittsburgh ground EMS is about to embark on a pre-hospital cold stored whole blood program. So that's fantastic. So, with that, I'm not going to use

up any more of your time. We'll save that for the question and answer session. Thank you very much.

QUESTIONS FOR THE SPEAKERS

DR. RICHARD KAUFMAN: Thank you. So, I'd like to ask if there are now any questions or comments from the Committee for the three speakers that we've just heard. Dr. Stramer?

DR. SUSAN STRAMER: Yes. My questions are for Dr. Stubbs. I had two questions. They may be simplistic. In the slide you had of the AABB variance granted, you had a sub-bullet that said they require 5151, the AABB standard for bacterial testing. So AABB allows you not to do bacterial testing for your cold platelet -- cold storage platelet program?

DR. JAMES STUBBS: Correct.

DR. SUSAN STRAMER: And then my second question is regarding the clotting and your wastage of about 80 percent of your cold stored platelets. Those

are in plasma, right?

DR. JAMES STUBBS: Correct.

DR. SUSAN STRAMER: So, what would happen if you had an additive solution?

DR. JAMES STUBBS: Well, we don't manufacture platelets in additive solution. And when we went to pathogen reduced, we have a system that won't allow us to pathogen reduce and have additive solution. So, we have plasma rich pathogen reduced product.

There is a couple things that happen. One is unexplainable, but it worked. One was we learned early on that, when we stored our cold store platelet in the refrigerator label up, like we store all of our other platelets, they clotted. We turned them label down. They stopped clotting for some reason. So, our number of clots went way down. I don't know why.

But when we went to pathogen reduced platelets, which are plasma rich, the clotting problem has not occurred. We don't get clots in our pathogen reduced cold platelets, and we had a significant number that we manufactured. So, for whatever reason, that

process also mitigates the clotting problem that we saw early on with our plasma rich platelets.

DR. SUSAN STRAMER: Thank you. It just adds to the number of variables to look at when you're looking at cold stored platelets.

DR. JASON STUBBS: Right.

DR. RICHARD KAUFMAN: Dr. Tanaka?

DR. KENICHI TANAKA: In relation to that question, I have not seen any data showing that cold stored whole blood generates clots while being stored. Do you see a difference when you store them at a cold whole blood versus cold platelet rich plasma?

DR. JASON STUBBS: Well, we did see it with apheresis platelets that were stored in the cold originally. We did see lots of clumps that we felt uncomfortable transfusing, so we took them out. Maybe it's harder with visual inspection or whatever, but we have not seen a similar problem with cold stored whole blood, which we store for 21 days at this point. So maybe it's a better acuity of visual inspection or whatever because you've got a yellow product versus a

red product. I'm not sure. But we haven't seen that with 21-day whole blood cold stored.

DR. RICHARD KAUFMAN: Dr. Kindzelski?

DR. ANDREI KINDZELSKI: A question to Dr. Jenkins. You had mentioned a use of the whole blood as the alternative for the cold stored platelets. Can you please say what kind of downside of using the whole blood is in your practice?

DR. DONALD JENKINS: So, it would be the patient population that doesn't need red cells. They need platelets. And there are plenty of places around the country that would love to adopt a whole blood program but do not have the wherewithal with their blood program to do so. If they had the availability of a cold stored platelet product, it would change the logistics dramatically. I could put platelets in many more of those hospitals that you see in the upper Midwest or in south Texas, making that product available for those who specifically need platelets.

DR. ANDREI KINDZELSKI: Thank you very much.

DR. RICHARD KAUFMAN: Maybe just to follow up

on that, Dr. Stubbs, you had mentioned that the air transport people at Mayo sometimes would like to have whole blood and sometimes they would like to have cold stored platelets. And I was just wondering if maybe you could elaborate a little further on what the difference in areas they were considering.

DR. JAMES STUBBS: Well, I think it would depend on if they were going out for someone who maybe had a specific problem with platelet function that's led to a bleeding problem, and intracranial hemorrhage or something due to an antiplatelet inhibitor or something like that. We do go out and retrieve those patients as well. And it would be probably preferable to travel and get a platelet component in them, as opposed to hanging a whole blood unit for those patients. So, I think they get good information a lot of times on what type of run they're going on and a little bit of advanced warning. So, they were hoping that they could mix and match ahead of time because of those parameters.

DR. RICHARD KAUFMAN: Thanks.

DR. DONALD JENKINS: Unfortunately, I grew too frustrated with the slide advancing business to show those slides. But there are three or four slides in that slide deck that you have in front of you that are the main teaching points in a policy that's used by the Mayo team. And it includes order of transfusion or product. In one case, what you'll see is that we made the conscious decision to give platelets first because of the shorter shelf-life and the increased waste. So instead of starting with a unit of whole blood, we would start with a unit of platelets in even that bleeding trauma patient. But it's wrapped up in what you have in front of you.

DR. RICHARD KAUFMAN: Thank you. Dr. Bryant?

DR. BARBARA BRYANT: I wanted to ask a question, Dr. Stubbs, about the -- I thought it was interesting. You commented that, if the bag was face down or face up depending on the label, you may see more clumps. Out of curiosity, what type of bag were you using? Because some are smooth on one side and rougher on the other. Does that related where you

stuck the label? I'm just kind of curious why the clumping -- how that varied.

DR. JAMES STUBBS: Well, we're using the Terumo system and the Trimas. So, the Trima/Terumo combination is what we're using, so that would be the bag systems that we're using because we're a Trima shop. I don't mean to advertise anything, but that's just the reality is that we collect our platelets on Trimas.

DR. BARBARA BRYANT: So, I'm not clear if those are the bags that have one smooth side one textured side. So that would be interesting to know.

DR. JAMES STUBBS: Yeah. I have no explanation. But one of my component lab techs just said, "Well, let's try this." So, we did, and the clumping just remarkably was -- we occasionally would still see it, but it went way down. It went way down. I don't know why.

DR. RICHARD KAUFMAN: Okay. Dr. Bennett?

DR. JOEL BENNETT: Spontaneously activated platelets in some of those bags, right? Were they

bound PAC-1 spontaneously?

DR. JAMES STUBBS: Right.

DR. JOEL BENNETT: What was the pH of those? Because 2b3a doesn't work very well at a pH of six and a half, for example.

DR. JAMES STUBBS: Well, these were higher than that. These were in the seven range. With the three-day platelets, we were right in the window of acceptability of pH, so they didn't drop way down in the three day. And that's all we have for clinical experience at this point is the three-day platelet. So yeah, the pHs were good. Maybe I should stay up here.

DR. RICHARD KAUFMAN: Dr. Jones?

LCDR JEFFERSON JONES: I have a couple of questions. First, can I just confirm you found no transfusion reactions?

DR. JAMES STUBBS: None.

LCDR JEFFERSON JONES: Okay. And the second, so your comparison for the PR platelets was room temperature PR platelets versus cold temperature PR platelets. Do you know of any data or have looked into

cold PR platelets versus cold non-PR platelets?

DR. JAMES STUBBS: Just in general? Out to 14 days that aren't pathogen reduced? Is that the question?

LCDR JEFFERSON JONES: Yeah. Or any studies that compare PR versus non-PR for cold storage platelets, any days.

DR. JAMES STUBBS: Oh, I'm not aware. I don't know if Andre is. Andre probably can answer that question for you.

COL ANDRE CAP: So, each of the services has their own BLA. Although we operate in a joint environment, they do things a little bit differently. So the Navy decided to make all their platelets pathogen reduced intercell platelets. So, in support of a variance filing request for them, we compared cold to -- cold non-PR to cold PR. And that work is I think being -- is submitted for publication. But anyway, it's going to end up in the FDA variance request. But outside 14 days, there was no really significant difference in in vitro parameters, and there was a

whole bunch of them, which we don't have time to go through now. But that'll be coming out very shortly.

DR. RICHARD KAUFMAN: Dr. Tanaka?

DR. KENICHI TANAKA: I have questions for Dr. Strandenes. I actually have two questions. One, when you reinfuse cold stored platelets, do you run it through the warmer, the temperature warmer?

DR. GEIR STRANDENES: No.

DR. KENICHI TANAKA: No? Okay. The second question --

DR. GEIR STRANDENES: But we run the cold stored whole blood through the warmer, so we run platelets through our warmer.

DR. KENICHI TANAKA: At room temperature, they just drip it in?

DR. GEIR STRANDENES: Yeah.

DR. KENICHI TANAKA: Okay. The second one, I see in your data the risto response on your aggregation data seems to be very good for a seven day. But it goes down in the 14-day cold stored platelets. So, did any of your clinicians see clinical response in the

field when you give seven-day cold stored platelets? Did they see any sort of better hemostatic response?

DR. GEIR STRANDENES: Yeah. I myself actually observed, if you want to have like a single observation. We have this huge -- that whole surgery, that was kind of the patient was actually -- the entire aortic arch from sentence to sentence with separated lung ventilation and extremely long ex-corp time and massively manifestation with the left lung. And we did ex-corp, and he was actually bleeding from the lungs. Immediately after we transfused on seven-day course of platelets, he just stopped bleeding. That is not evidence, but that was just an observation. Wow. What happened now? He stopped bleeding. So, the surgeons can see actually in the field. It doesn't show in the data. But I only think the data shows that there is single in here that shows that they work up until day 14. I'm not saying that that's the best product, but I would really love to have that.

DR. RICHARD KAUFMAN: Actually, I have a question for you as well, Dr. Strandenes. So, I think

there's definitely an appeal in using chest tub output in cardiac surgery patients to look at hemostatic efficacy as an endpoint. So, there was this recent NIH workshop, and there was definitely individuals there who had strong opinions about problems with chest tube output. One can be that sometimes it's blood that's in the chest tube, and sometimes it's serious drainage. Sometimes it's maybe normal saline or lactated ringers from the operative field, that sort of thing.

DR. GEIR STRANDENES: There's no ringers coming out of our chest tube. There's no way they can do that. So, we both prove our section free of anything before chest closure, so there should be very little blood in both plural spaces because normally they open both plural. So of course, yes, somebody would say that. But the reason for choosing chest tube output is we could actually use the bleeding during the ex-corp, but that doesn't really make sense because there is a lot of surgical bleeding there.

So, we suggested that, after that surgical hemorrhage control was over, that was when we should

start measuring blood lose. We could have measured hemoglobin in the plural act to see if there was any difference between them. But on average when you compare those two, I think the two groups that we compare that would be similar -- there's some explanation. So, it's not only blood that comes from the chest tube, but that's really after several hours that you will see that. So, I think the time period we measure what comes on the chest tubes -- most of that is actually just bleeding.

DR. RICHARD KAUFMAN: Okay. Thanks. That was helpful. Actually, sorry, Dr. Wagner, we cannot accept questions from the audience at this time.

DR. WAGNER: It's not a question. I just wanted to talk about that there was a publication in *Transfusion* in 2019 entitled "Impact of Cold Storage on Platelets Treated with Intercept Pathogen Inactivation."

DR. RICHARD KAUFMAN: Thank you. Dr. Stramer?

DR. SUSAN STRAMER: I also have a question for Dr. Strandenes. Sorry if I mangled your name. After

you present your pilots, what are the next steps in Norway?

DR. GEIR STRANDENES: Well, the next step is that we are seeking approval for using this product. We're going to use platelets until 14. And we have also really an ethical committee approval for extending it to 21. So, the next we're going to is a pilot trial on 20 patient receiving from 14 to 21 days cold stored. So, we plan to start using it.

DR. RICHARD KAUFMAN: Dr. Jones?

LCDR JEFFERSON JONES: Kind of as a follow up, do you know of any other countries or locations that are already approved or have widespread use?

DR. GEIR STRANDENES: Not in Europe as I know.

DR. RICHARD KAUFMAN: Are there any questions from those on the phone, Drs. DeVan, Ortel, or Morgan?

DR. CHARITY MORGAN: This is Dr. Morgan. I have a question for Dr. Stubbs. Regarding your data from the study of the cold stored pathogen reduced platelets up to 14 days, I noticed that a lot of the variables the cold stored platelets had higher

variances, more variability than the room temperature platelets. Do you have ideas about why that might be or what the sort of consequences of that would be?

DR. JAMES STUBBS: I'm not really sure exactly why there was a higher variance. We haven't really dug down to try to further explain that at this point.

DR. CHARITY MORGAN: Okay. Thank you.

DR. RICHARD KAUFMAN: Actually, I have several quick questions. I was wondering if you have modeled how many platelets would be transfused versus wasted if you had a ten day or 14 versus what you had, which was a three day?

DR. JAMES STUBBS: We haven't yet, but that's in the plans. With both whole blood and cold stored platelets, when -- right now, we're focused on the pre-hospital arena. And what we've done with whole blood, which is one of the reasons why that we went to 21 days from 14 days was basically logistical -- was we modeled out how many flights with a 14-day whole blood -- because we manufacture whole blood non-leukocyte reduced and stored it for 14 days. And after 14 days,

it wasn't used. It was discarded because we leukoreduce everything else.

So, we looked at the number of flights that went out where they did not have a whole blood available based on our collections and attrition rate and not having whole blood available 14 days and what it would do if we went to 21 days. And we found, at that point, that the great majority of flights for which they wanted to carry whole blood would be met by a 21-day product due to inventory management.

We're still throwing away a whole blood at 21 days. We're not watching it yet like Darrell's doing. But we're planning to do that same scenario-ing with a 14-day cold stored product as well. But we haven't done that yet. But that would be very, very helpful to find out, if we did this, how often would they be on the shelf in the air ambulances to be carried out. So yeah. We're thinking about doing that.

DR. RICHARD KAUFMAN: Thank you. Dr. Stramer?

DR. SUSAN STRAMER: Dr. Stubbs, don't go. So just two things responding to previous questions. Your

sample sizes were really small in the transfused cold stored. So, responding to the question, I think small sample size is going to lead to larger variability relative to large numbers when you compare to room temperature stored platelets. But my question is you just mentioned leukoreduction. So, these cold stored platelets were not leukoreduced?

DR. JAMES STUBBS: Oh, the cold stored platelets are because they're collected by apheresis. We developed a whole blood program kind of in parallel, and we looked at the leukocyte reduced whole blood product that was available versus the non-leukocyte reduced product that would also be platelet sparing. And we made an internal decision that we would go with the non-leukocyte reduced product because of some concerns regarding the functionality of the platelets that went through the leukocyte reduction process. So, our whole blood is non-leukocyte reduced. And we have it for 21 days. Our cold stored platelets are leukocyte reduced because they go through the apheresis process and there's a pathogen reduced leukoreduced

product, yes.

DR. SUSAN STRAMER: Thank you.

DR. JAMES STUBBS: Yup.

DR. RICHARD KAUFMAN: Dr. Baker?

DR. JUDITH BAKER: Thank you. My question is for Dr. Jenkins. I want to thank you for your presentation and all the speakers for their presentations. Access to care is a very important issue, and I was particularly struck by your comments on maternal health and the obstetric use. Has your group -- I know it looks like you're primarily working with military. I could be wrong. But is your group looking at use of cold storage platelets in the obstetric needs issues?

DR. DONALD JENKINS: So, we've just submitted a variance through South Texas Blood and Tissue for 14-day cold stored product. I'll be quite happy with a 21-day cold stored platelet product. And the reason I say that goes to some of the logistics, some of what Darrell had talked about earlier today about who is getting these platelet products is limited by access

and availability of the product to those individuals.

So, I work exclusively in the civilian setting now. We have a whole blood program for obstetrics that we started in July. It's going fantastic. And the way that we have handled things in terms of logistics and waste, because that's come up here repeatedly as well, is that when we started our prehospital cold stored whole blood program, waste of that whole blood was about 11 percent. It's less than one percent today because of the recycling program that we've put in place.

We'll let the pre-hospital folks have it for 14 days. If they don't use it during that timeframe, it comes to me at our trauma center, and we will use it 99 percent of the time during that remaining three weeks of lifespan. If I had a 21-day cold stored platelet product, we would do exactly the same thing. I'd put it out for ten days and bring it back for ten days. And I'll tell you I'm going to use it in our center, and it would be many centers in San Antonio that are doing cardiac surgery, spine surgery, that

would make very good use of -- transplant. We've got a couple of different transplant centers who would make very good use of that cold stored platelet product, and it wouldn't go to waste.

DR. JUDITH BAKER: Thank you. But just to clarify, are you familiar with any particular studies looking at the use of the cold stored platelets in the obstetric population?

DR. DONALD JENKINS: I am not.

DR. JUDITH BAKER: Thank you.

DR. RICHARD KAUFMAN: Okay. So if there are no further questions from the Committee, we'll break now for lunch. And we will reconvene at 1:15. Thanks very much.

[LUNCH]

DR. RICHARD KAUFMAN: All right. Welcome back, everyone. So, we will get started with this afternoon's session. I would like to introduce Dr.

Andre Cap, who is with the US Army Institute for Surgical Research.

US DOD COLD STORED PLATELET EXPERIENCE

COL. ANDREW CAP: All right. Thank you very much for the opportunity to speak with you all today. I'm going to try to navigate the clicker here.

DR. RICHARD KAUFMAN: And just as a comment, if you have any difficulty whatsoever with advancing the slides, we can have it advanced for you; you can just say, next.

COL. ANDREW CAP: Perfect. Will do. Thank you. I was asked by FDA to read the disclosure statement that I have there in the middle, which is that, as you can see, I'm an active duty officer in the US Army. My current assignment is studying cold-stored platelets as part of my official governmental duties.

So, everything I'm going to talk to you about, all the different products we evaluated and so forth,

is really stems from the need to be able to provide a hemostatic transfusion product to our troops downrange.

And I'd like to acknowledge all the people who contributed to this work and to our cold-stored platelet program; especially the Armed Services Blood Program and Joint Trauma System, and our colleagues in CENTCOM.

Just to review, you've seen this data from Dr. Triulzy. And basically, when we were first tasked with providing transfusion support in theatre, we did not have platelets. And we noticed -- in fact, we didn't have a lot of plasma. And mortality rates of patients resuscitated primarily with saline and red cells was like 60 percent.

And then we started getting more plasma and eventually platelets in there and got that down to a much more attractable number. As you can see here, the more platelets we gave in the first 24 hours, the greater the survival, both at 24 hours and at 30 days.

So, we think being able to provide platelets to bleeding patients, in this case combat trauma patients, is super-important.

We actually looked at the timing of that administration. And it turns out that if you gave platelets earlier in the resuscitation -- and mind you, this is all in-hospital or in-surgical facility data. Some of these places you would not a hospital; it's more like a tent with a couple of beds and a few surgeons, as Dr. Jenkins can attest to.

But if you give the platelets early, as in when they first got there, kind of a platelet-first strategy, more platelets in the first six hours, there was lower mortality as well. So, it's not just getting platelets to the patients, but getting them early when they need them, because they die fast as you saw.

And here's the problem. So, here's Afghanistan. And the sort of rings there are one-hour helicopter times from various surgical facilities around the country. The filled-in white dots are sort

of a measure of combat casualty density across the country.

You can see the middle of the country is full of mountains. Actually, the whole thing is full of mountains, which limits helicopter and ground transport. And so basically, the only place that we are able to bring a platelet collection team, due to things like status of forces agreements and limits on number of troops being deployed and so forth, was kind of where the big red arrow is pointing, which is Bagram Air Base.

And so, you're basically forced to collect platelets there, and then you have a five-day shelf life, at least at the beginning. And that made it very difficult to get the platelets all to these different surgical facilities.

And, you know, the enemy gets a vote on, you know, when you can transport things. Weather is a major problem in Afghanistan. It's also a bit of a problem in Iraq and other places. We have sandstorms and all that sort of thing.

So, the problem is the net result is that most of our forward surgical teams had no platelets. So only at the larger in-theatre facilities would we be able to have platelets, just because the five-day shelf life was too short.

And just to give you a sense of doing this, like here's Afghanistan layered over the United States. Imagine having one blood donor center collecting platelets for that territory; right. That's kind of the scale of the problem you have.

And, by the way, those FSTs are mobile, the troops are mobile, operations are fluid. I mean it makes this extremely hard to manage from a logistic standpoint.

Okay. So, we knew we needed another product. And you know, our -- one of our earlier speakers today from the FDA characterized cold-stored platelets as a novel product. I would argue that actually, it's not really a novel product, it's the oldest product in the platelet armamentarium.

And that's in a sense why we went to cold-stored platelets, because we thought, well, you know, there are novel platelet or other hemostatic products under development, but we need to be able to get something out there fast because we have people dying now. So, let's go to something that's kind of tried and true.

And we looked at this in a couple different dimensions, including safety, efficacy and then eventually clinical data to support this decision-making.

So first, safety, obviously refrigeration, you know, you would think reduces platelet growth -- I mean -- platelet growth. Bacterial growth in platelet units. And we've heard that that is the sort of number one problem with platelets.

And indeed, you know, we kind of made this claim and got a lot of pushback from people saying we've -- no, you haven't really proven that. So okay; we did some spiking studies to prove it, that refrigeration works.

And it turns out that as you can see on the left, there's no growth in the 4C-stored platelets. And we compare the platelets to platelet-poor plasma made from the same donor; and release aid and so forth which is less critical here.

But the point is that when we compared spiked plasma to spiked platelets, grown at room temperature, on the right you can see there's a 4-log increase in bacterial growth in the platelets, showing that the platelets are actually feeding the bacteria. And this is due to lactate production. And some bacterial really, like, lactate, like acinetobacter, staph epi, and staph aureus, for example, which is what you see here.

All right. So, in the interest of time we'll move on. But these are clinically-relevant pathogens that have been implicated in platelet contamination problems. Most recently, there's an outbreak of acinetobacter that was reported by the CDC and platelet units. So, you can see here that there are some real

advantages to putting them in the cold, from a safety standpoint.

This was also briefly mentioned in one of the earlier talks today. Because refrigerated platelets have sort of an activated phenotype, we were concerned about, you know, are they kind of always on; and will they stick to things they're not supposed to stick to, like healthy endothelium that makes nitric oxide, and prostacyclin and so forth.

So, we studied this in vitro in microfluidic studies. And what you can see is room-temperature platelets kind of going horizontally across the middle don’t stick very well to collagen-coated surfaces, period. So, when you put inhibitors on them like prostacyclin and nitric oxide, it doesn't really change anything because there's not much adhering.

Look at fresh platelets across the top. They clearly respond to the procyclidine and nitric oxide. And then on the bottom is 4C-stored platelets that also showed reduced adhesion and aggregation in response to

those physiologic inhibitors. So that was a good safety signal that gave us some comfort in that regard.

And then, just out of curiosity we looked at pharmacologic inhibitors of platelet function. And there too, we saw decreased aggregation responses in cold-stored platelets in response to pharmacologic antagonist.

So, the bottom line is that cold-stored platelets can be inhibited. Most of the conversation has been around the question of do they work? And so, the other question is do they work too well? And the point is that, you know what, they can respond to inhibitors. So hopefully, that's good.

And then actually we further characterized some of their intercellular responses to prostacyclin and nitric oxide and found that they were comparable to fresh platelets, so normal sort of signaling inside the platelet.

Now, what about functions? So, we talked a little bit about safety. So, we've done lots and lots of studies characterizing the function of cold-stored

platelets using a number of different assays. We've compared platelets made by the PRP method.

We've looked at Trima collected, Amicus collected, et cetera, et cetera, and stored in PAS, versus plasma. And I'm not going to show you all that data because we'd be here kind of all day.

But what we -- the one thing I did want to show you here that's important is, so yeah, we see the decrease in platelet count, like other people have shown you. And lactate does increase over time.

A little bit less than room temperature, but nevertheless, they are still metabolically active. And by the way, that means alive. Which is another key point, because again, one of our earlier speakers mentioned the concept of platelet viability.

And I think that it's important to remember that this concept has been sort of conflated -- recovery and survival has been conflated with viability. And viability, in most people's minds, means alive or dead. And these cold platelets are not dead.

They may express (inaudible) on the surface, but they are not undergoing apoptosis, they're not dead, they're metabolically active. Dr. Stolla showed you their mitochondrial function. They are most definitely alive and viable.

And you can see that in the clot retraction data here in the bottom corner. And you see, clot retraction is an assay I find kind of attractive because it integrates all the different functions of a platelet.

It has to be activatable, get its GB2E3A (phonetic) into an active confirmation. It has to bind fibrinogen. It has to aggregate, release, organize the clots into, you know, the fibrin bundles and so forth. So, it kind of shows you everything.

And you can see here that all the way up to day 21, cold-stored platelets retract clot. And this is clot weight on the Y-axis here. And so, the wetter a clot, the more water that's in it that hasn't been expressed out. Kind of like squeezing a sponge, the less clot contraction you have.

So, you can see that room-temperature-stored platelets, after about five days, start to lose their ability to contract a clot. And if you kill platelets, you have positive control, like treating them with Rotenone and 2DG to kill electron transport chain and glycolysis respectively. Therefore, making them go ATP, they do not retract clot either.

So dead platelets don't retract clot; live platelets retract clot. Cold-stored platelets are alive and kicking all the way out to 21 days without any question. Thrombin generation is preserved as you can see here as well, and clot strength as well.

Okay. And here's more data from riometry studies looking at clot strength; again, well-preserved in the cold-stored compared to room temperature.

Aggregation data, this is Todd Getz's work when he was part of our laboratory. And you can see here, aggregation to collagen, to TRAP and to epinephrine. Well-preserved all the way up to day 22 in the cold compared to room temperature.

And then dual platelet agonist, collagen and epi on top, ADP and epi on the bottom. Again, well-conserved in the cold compared to at room temperature over time.

So, all these data suggest to us that these platelets are alive and functional all the way up to three weeks of storage.

And here's some mitochondrial function data. You can see here, baseline respirometry on the left, and sort of activated oxidative burst on the right. And the room-temperature-stored platelets drop off over time, compared to much better preservation of mitochondrial respiration function. And this is actual respiration, oxygen consumption in an oximeter. So, clearly functional platelets.

And then here's some apoptosis data. Again, looking at mitochondrial depolarization in panel A, and then caspase activations. Loss of membrane integrity as measured by fluid and staining of actin over time going up in the room temperature compared to the cold. And then in Panel E the microparticle formation.

So again, live platelets not undergoing apoptosis, functional mitochondria and capable of contracting clot, aggregating and so forth.

So, as I mentioned, we've done a lot of in vitro work on cold-stored versus room-temperature platelets to include all these different assays on top.

And we've done some in vivo work, which I mentioned earlier in both intravital microscopy, as well as transfusing cold-stored green-florescent protein expressing platelets into non-green-florescent protein expressing rats that we could do immunohistochemistry; to find out whether in a coagulopathic trauma model the cold-stored platelets would contribute to human stasis, and they do. That work is all published. And I'd be happy to share it with you in detail if you like.

And other groups have looked at cold-stored platelet function as well and have either replicated the work I've mentioned or done similar work or related work, as you can see here. So, don't take my word for it; lots of people have looked at this.

And here's an example of some of that other work. This is work from Lacy Johnson in the Australian Red Cross, comparing in this case cold-stored to room temperature to cryo-preserved platelets, frozen in DMSO.

You can see the cryo-preserved platelets don't really aggregate; they do generate thrombin and contribute a little bit to clot strength. But the cold-stored platelets really contribute nicely to clot strength and maintain aggregation better than the room temperature out to three weeks.

By the way, these are buffy coat eradiated platelets. So, every permutation of a platelet product has been tested here, I think, at this point; in multiple hands and multiple continents and kind of sharing something similar.

And you saw Geir Strandenes' data, so I won't go into that much more. But just to say that here we have, for emphasis, more clinical data showing that at least out to 14 days, for sure, the product is active in hemostasis.

So, we didn't get all that data on day one when we started to transfuse cold-stored platelets in CENTCOM, but we gradually accumulated it over time. This work here from Dr. Strandenes was presented at ABB in 2018; we started our program in 2016.

So, we had some view of this before it was presented in 2017. And that's when we extended our shelf duration out to two weeks. And I'll show you that in just a second.

Here's some aggregation data, pre- and post-transfusion that Geir did not present. But again, showing in all these different patients improved aggregation function for the most part, along these different parameters post-transfusion episode, which also includes red cells and plasma.

But bottom line is more data is showing what I would call a good measure of viability, at least from a human stasis standpoint.

So, I told you the clinical problem we have. We started out with no platelets in-theatre, that was very bad. We started out with -- then we introduced

platelets in-theatre and we only had it at a few locations because that's all we could manage.

And that was great for the casualties who showed up to those locations. But unfortunately, you had all those other surgical teams all over Afghanistan and Iraq, and later Syria, which didn't necessarily have a platelet supply. So how are we going to fix that problem; so we turn to cold-stored platelets.

So, the first thing we did, we did a validation study in-theatre. This was done on platelets collected using the Haemonetics MCS 9000 system and store it in plasma. And we started storing them at Bagram Air Base in Afghanistan for a three-day shelf life. In 2016, we validated it out to the five days. And that's this document here.

And then after that program got started on a very limited basis, and people reported very little wastage -- actually, we did not have a clumping problem; we didn't have a big discard rate or anything like that. Perhaps because we had actually talked with

Dr. Stubbs and instructed everybody to store the platelets label-side-down.

But anyways, it worked out pretty well. And then we gradually expanded the program. And in June 2017, we extend it to 10 days. And then after the presentation of the cardiac surgery data from Norway, we extend it out to 14 days in February of this year.

So gradually over time, the percentage of platelets collected in-theatre increased. So overall, during this whole time period, from 2016 until now, we collected around 2,000 units. You would be shocked at our wastage rate, but that's just the way it is. You just never know when you're going to get casualties and when you're not, and so we need to have product on hand.

And unfortunately, I don't have a precise breakdown for you of how much of this was cold-stored and at what age they were used. And we're trying to get that data, but for this meeting, I was not able to get that data.

So, here are the patient characteristics of patients who received cold-stored platelets. And I want to start out by saying that this is not a clean clin- -- you know, comparison between cold-stored and room-temperature platelets. It's not a randomized trial by any means.

Of the 95 patients who received cold-stored platelets, 94 also received room-temperature platelets. So -- and most of these patients were pretty badly injured and got a lot of blood, and they kind of got the kitchen sink; right?

So, they either had cold platelets on hand, in which case they got the cold platelets, or they didn't, and they got room-temperature platelets.

But there are some other characteristics here that make these groups a little bit different. And these differences matter.

If you look at the cold-stored platelet group here you see it's more male, more likely to be other, as opposed to US Military or NATO. And I'll show you

on the next slide -- I'll just go ahead and advance to that -- that the mechanisms of injury were different.

So, the cold-stored group had much more -- much -- a higher number of patients who had injuries due to explosives of blast injuries or gunshot wounds, and statistically fewer than the group that got room-temperature in the nonexplosive category.

So, what does this tell us? So if you've been reading the news over the last -- well, since 2016 anyway -- you know that our footprint in both Iraq and Afghanistan is pretty light. And mostly what we are there to do is sort of as an advise and assist and sustain role.

Our troops are for the most part not engaged in active combat operations, except for our Special Forces Units. And we still take casualties, but it's not the same thing. The people who are taking the casualties are the Afghans. They had like 40,000 casualties last year. I mean think about that number.

So, what this means is that the cold-stored platelet group was basically mostly Afghans with combat

injuries, versus in the room-temperature group you had more things like car accidents, which also happen in-theatre and slightly more Americans than -- and NATO military.

So, this is a big deal, because this group is definitely more severely injured, the group that got the cold-stored platelets. That doesn't come out exactly in the ISS data. You can see it's approaching statistical significance.

But more multifactorial injury, more penetrating trauma, clearly, than the other groups. So there's a real difference at baseline between these groups.

Okay; moving on. So, how were they managed? Well, there was a lot more nonoperative management in the cold-stored platelet group. What does that suggest? I think there's just higher mortality in the cold-stored platelet groups; because these people are badly hurt, and some of them die before they can go to surgery is the answer.

Massive transfusions were similar, although again edging towards statistical significance there; more massive transfusion in the cold-stored group. Tranexamic acid use was similar. And basically, nobody was using Factor VII at this point in-theatre.

So, what about transfusions? Basically, pretty similar, although slightly fewer transfusions of platelets in the cold-stored group compared to the room-temperature group. But otherwise, plasma, red cells and cryo are pretty similar.

Crystalloids and colloids also pretty similar. Which by the way -- just pausing here for a moment. So, these are combat casualties, who are seriously injured, who have a reasonably higher mortality rate. And look at the total crystalloid use, 1.8 liters.

Fifteen, twenty years ago that would've been like 10 liters. So, things have changed quite a bit. And actually, total amount infused, we'll say, into these patients, is much lower as a result of that. So,

transfusing with blood is better -- if you're leaking blood.

Okay; outcomes. So, you can see here, there's no difference -- so the values in red are adjusted for ISS. And the black are the unadjusted variables. And you can see basically, there's no difference in outcomes between the two groups.

Venous thromboembolism, no difference, sepsis no difference, relatively uncommon outcomes. Sepsis, also relatively uncommon. Arterial thrombosis, no difference between the groups.

I'll just say here, this is actually pretty remarkable considering how many disease patients get tourniquets. You know, so there's a lot of arterial injury in these blast wounds and so forth. But nevertheless, thrombosis rate is low.

Dead and alive, similar at discharge as well. And especially adjusted for ISS. And so, remember that the cold-stored group is significantly more injured going into this than the room-temperature group.

So overall, we ended up with basically, equivalent outcomes, most patients getting about a unit of platelets. Sometimes, they got a little bit more than that. Everybody got room-temperature platelets pretty much. Some of the patients got cold-stored platelets, but when they were available.

To us what this says is, well, we got pretty much equivalent outcomes and we're able to push platelets out to more places because of the extended shelf life.

So, we feel that, you know, we've -- we got what we were hoping to get; right? We did a lot of background work looking at safety issues on the in vitro level, function issues on an in vitro level.

We got some pilot clinical data from our colleagues in Norway. And then we also depended a little bit on the historical data on cold-stored platelets.

And finally, all of that evidence allowed us to make the step to implement a cold-stored platelet program gradually, in a phased approach, three days, 10

days, 14 days, gathering pretty extensive data all along the way.

I'm emphasizing this so that you know that we were doing this very carefully in sort of rolling it out. And I think ultimately, in a manner that justifies it, with at least similar outcomes and with enormous benefit from a logistical standpoint. And I think hopefully in the future, better outcomes in the sense that all those patients who don't get any platelets, who have the higher mortality rate will now look like these patients.

Because remember, there's not a comparative group here of similarly injured patients who didn't get platelets; right? This is just platelets versus platelets.

So, we have the historical data, which I showed you right at the beginning where the mortality rate was basically double. And the patients who got no platelets versus -- the combat trauma patients who got no platelets, versus the patients who did get platelets.

All right. So, overall summary then. I think I'll skip over this in the interest of time. But basically, the cold-stored platelets were -- recipients were sicker, more likely to be non-US, because they're -- and more likely to be combat casualties, and overall, no difference in outcomes.

Limitations of this data. All right. Well, unfortunately, I'm not able to give you a breakdown of outcomes by age of platelets transfused. But please appreciate that we are starting with 95 total patients. And if we broke it down to this little group got three-day platelets, these guys got 10-day platelets, and these guys got 14-day platelets; and on top of that they got up to five-day-old room-temperature platelets as well, you're not going to be able to make any meaningful comparisons anyway. But these included patients who got platelets up to 14 days, and some as young as one to three days.

Obviously, this is a small sample size in a retrospective study, so we can't draw any super-firm conclusions from -- for all this. And we do have

limited follow up for the non-US patients who represented most of the combat casualties, as I've explained.

And it's a limited adjusted analysis. Like for example, I didn't show you any lab data, like the INRs and the lactates and so forth. First of all, because they were missing in about 75 percent of the patients.

And a lot of these Forward surgical facilities, there's no lab equipment, period. So there's no data. And that's just a limitation of what we are dealing with here. So, it's not what you would see in a great clinical trial, but this is not a clinical trial.

So, what are future directions for the DOD? Well, I think consistent with what you've heard from Dr. Stubbs and others today, and Dr. Strandenes, we would like to see a 21-day shelf life product. That would really, really help the military.

Why? You'll notice I told you that all of these platelets were collected in Afghanistan or Iraq,

or in some cases in Qatar and shipped into Iraq or Syria.

It takes about a week to collect a blood product in the United States, get it to a transshipment point, fly it to like Qatar, for example, which is another transshipment point, and get it from there to, we'll say, Bagram, or Bagdad, or whatever.

And then, you've got to depend on transport of opportunity. You know, there's not like a helicopter waiting for the platelet unit; right? They have other things to do. And so you got to get it to where it needs to go. And that's often several other days.

So even a 14-day product shipped from the US is still going to be a tough -- you have to have a very high operational tempo where you're shipping blood products at least twice a week for that to be workable.

21 days is what would be able to have a fully-tested product to be able to ship anywhere in the world. 14 days is tough.

We are super-thankful to our partners at the FDA for having granted us, in the Army, a variance for a 14-day storage. This is going to help us a lot.

And there are ways in which we can collect at places like Landstuhl and supply platelets to, for example, units in Africa, where the 14-day thing will be helpful, and also in the Western Pacific. I think that's going to be great when the Navy gets their variance program, and the Air Force as well.

And then we'd also like to incorporate pathogen reduction. I mentioned earlier today that the Navy uses exclusively pathogen-reduced platelets. And so, we have several different pathogen reduction technologies we're working with. And we'd like to be able to incorporate them into our platelet and whole blood programs.

Ultimately, all of this will serve the goal of an enhanced capacity to provide hemostatic resuscitation for our forward and save lives.

And I'll just make the point that 75 percent of the blood products transfused by the US Military

have gone to non-US casualties; many civilians and many host-nation, national, some combatants, some noncombatants. The point is, we're taking care of a lot of people over there, not just our own people.

So, one last kind of point for amusement. I just recertified in hematology. And I bought the American Society of Hematology Self-assessment Program review book for the Boards.

And I was looking through the transfusion medicine section and I couldn't believe it; but there it is right there, highlighted in red, cold-stored platelets made it into the ASH-SAP. So, I think there's demand for this on the civilian side as well. And I will leave you with that thought. Thanks.

DR. RICHARD KAUFMAN: Thank you, Dr. Cap. Our next speaker will be Dr. Phil Spinella from Washington University in St. Louis.

CHILLED PLATELET STUDY: CHIPS

BONUS: MICROFLUIDIC MODELS OF HEMOSTASIS

DR. PHILLIP SPINELLA: Hello, everyone. I want to thank the Committee for inviting me here to speak today.

I'm going to talk about our trial that we've developed and are submitting for funding and approval. It's called the CHIPS trial. CHIPS stands for Chilled Platelets Study.

And as a bonus for all of you, I'm also going to go through some of our microfluidic data. This morning, we talked a lot about methods of measuring platelets and other blood products for their hemostatic potential. And I thought it was important to share what we've been doing.

Next slide. For disclosures for the three co-PIs of the trial, Nicole Zantek, who's here, myself and Marie, these are our disclosures.

Next slide. So this morning, we talked about the challenges with in vitro assays of platelet function. And for the two main ones that are typically used, with aggregometry, whether it be light

transmission or impedance, it's really not a direct measure of function.

In the past it used to be called light transmission, the gold standard; I think it clearly is not. And especially when single agonist aggregation assays are used; it's not physiologic at all. Even when you do have multiple agonists, it's not physiologic. So, I think almost always, aggregometry data underrepresents true hemostatic capacity.

Conversely, with viscoelastic testing, with the agonists that are used at the concentrations that are needed, it winds up, I think, exaggerating hemostatic potential. You wind up getting an overrepresentation of hemostatic capacity.

And it clearly masks platelet inhibition. One company is trying to develop an assay to directly assess platelet inhibition. And it really has never been correlated in bleeding patients to see if it's accurate.

Regardless of those limitations, none of these tests, or any of the other ones presented this morning,

use biologic surfaces and shear forces, depending upon different flow rates within their assays. So, they're extremely non-physiologic. So, what they really mean is, very difficult to determine.

And since there is no real gold standard for platelet function, it's impossible to test these methods against a gold standard.

Next slide. So, we've incorporated microfluidic assays into our panel of tests that we're using at Wash U, when we assess the hemostatic potential of different blood products or agents.

And as you can see here -- does this pointer work -- blood flows from left to right through the small microfluidic chamber. There's an area of narrowing in the middle of the chamber that is either tissue factor or collagen-coated, in our lab. Other places use different agents as well. And then a clot forms at that area over time.

As blood flows through the chamber, it's weighed on a scale as it comes out. When the weight stops changing, or the rate of weights changing allows

us to also look at the rate of occlusion over time. And here you can see the florescence of cold platelets that were put through this stenotic model.

And since these stenotic models were basically meant to try to simulate the risk of thrombosis, this is one way to test cold platelets for their thrombotic potential.

Next slide. So here, you -- oh, go back. So here is just another video of a clot forming over time in the chamber. And over time, you see the occlusion index increasing over time, as the weight of the blood going through the chamber reduces over time. So we could measure the rate of the occlusion index occurring over time as well as the time to occlusion.

Next slide. So here, we compared warm- and cold-stored platelets. There were five donors in each of the groups that were compared. And you can see in the left-hand side that the occlusion index was really no different for a 21-day platelet compared to a two-day cold platelet.

And then we even compared the 21-day cold to a five-day warm platelet. Really, no functional difference in occlusion index or time to occlusion. So, this is, I think, valuable data showing that it's appropriate to consider platelets out to 21 days that are stored cold.

Next slide. But these are all in microfluidic models that are thrombotic, or stenotic that are meant to represent a concern for thrombosis.

So, when I hired a bioengineer from Georgia Tech, the first thing I asked her to do was, I said, we need to develop our own bleeding chamber. We need to be able to use microfluidics as a platform to assess the hemostatic potential of a blood product or agent in the context of bleeding.

So, what we've done is we've basically developed a puncture site within the microfluidic chamber, its tissue factor and collagen line at the injury site, so to speak. And blood flows into this large chamber and then, of course, it will clot over time.

Next slide. So here you can see two videos using the bleeding chamber. And this is with whole blood on the left. And you see the clot forming within less than five minutes, and no blood going through the simulated injury sites.

On the right though, we've not only developed dilutional coagulopathy models and platelet inhibition models, we've also developed a hyperfibrinolitic model. And by adding just enough tPA to cause 10 percent lysis on ROTEM, which is not a lot with the ROTEM assay, you don't see any clotting at all. So, we've developed physiologically -- or pathophysiologically-relevant models.

Next slide. Here, you'll see with diluted whole blood and the cryoprecipitate added to the diluted whole blood clot forming over time.

And we -- next slide -- compared -- this is just an example of how we can use this data -- compared to cryoprecipitate, out to 10 days stored at 2 to 6 degrees Celsius, and compared it to fibrinogen, which is the gray diamond at day zero.

And there was a shorter bleeding time for cryoprecipitate in this diluted whole blood model at low shear, compared to fibrinogen. So just an example of how this data could be used.

Next slide. So, what's really interesting about these microfluidic models, whether they be in a stenotic environment or a bleeding model, with florescent microscopy, we can quantify the constituents of the clot itself. So, in these experiments, we tagged platelets Factor XIII, (indiscernible 51:52), and fibrinogen. And we can quantify the amount of these proteins or cells in the clot. So, it's the way of getting at mechanism in addition to function. So, I think moving forward, this will be an important tool to use.

Next slide. But we feel it's important. And others have not done this, right, with any of the other hemostatic assays that are out there.

We want to correlate our in vitro results in this model with in vivo models of either thrombosis or bleeding; using intravital microscopy to see if the

occlusion time, clot morphology and even the clot contents correlate with the microfluidics, compared to puncture models in animal models, either venous or arterial.

Because as I said, we can alter shear our flow rates which affects shear in our microfluidic model. So, we feel we can simulate both.

So, if there is high correlation, eventually, this can be a bioinspired microfluidic assay. It has the potential to be used as a quality metric for hemostatic products, platelets and the rest of them.

Next slide. All right. So now, on to the talk about the trial. As we've talked about this morning, mortality is very high for patients with life-threatening bleeding. In adults, it ranges between 20 to 25 percent. In children, it's actually double that. This is from some published data from Rob Russel at UAB, and some unpublished data from a recent study we finished. So, the stakes are high.

Next slide. As some have said already today, there are 30,000 preventable deaths per year that are

due to traumatic bleeding. 30,000 per year; this is an estimate that was published out of the National Academy of Sciences report that was published a few years ago. Okay. So, this is a tremendous -- and this is only trauma; it doesn't count other etiologies of severe life-threatening bleeding.

As many have mentioned, the time to death is fast. So, we need to be able to respond quickly to reduce death from hemorrhage. We all recognize platelets are essential to stop bleeding.

What we haven't focused a lot on -- some have a little bit -- but platelets in general are not available at most nonmedical centers. Even most level 2, level 3 trauma centers, all the critical access hospitals that are out in the Midwest, where Don says you have to ring the bell to get someone to answer the door, these places don't have platelets.

And that's where the majority of these people who are bleeding to death -- or bleeding. So, if we could both increase the efficacy of platelets and also increase storage time, we could, I think, make a big

dent in that number of 30,000 preventable deaths per year.

Next slide. So, there's clearly -- you know, urgency here. And then when we look at the data -- I mean this is when it gets even worse. You look at the recent randomized controlled trials that have evaluated room-temperature platelets, compared to either not giving platelets or giving more or less. These two trials have not been discussed today, but they're the only two trials that have looked at platelets in isolation.

The PATCH trial was a randomized controlled trial of adults that were on dual platelet inhibitors, who had acute hemorrhagic strokes. 190 patients in this RCT. And they were randomized, either get platelets or to not get platelets.

The adults with intracranial bleeding, hemorrhagic stroke, had more death and more disability if they got platelets, room-temperature, with an odds ratio of 2. This was not expected. This can't be good.

Next slide. Then in children, neonates, in an RCT comparing high and low thresholds to transfuse platelets. The neonates that were randomized to have a higher transfusion threshold for platelets, therefore they got more room-temperature platelets, also had more death, more disability.

So, in the only two randomized controlled trials that have compared platelets to either nothing or less of room-temperature platelets, more death, more disability with intracranial -- in the clinical scenario of bleeding.

So not only is there urgency to get platelets out to people who need them, there's urgency in what our current practice is and what we are forced to use right now. We need something better, safer, that does not increase death or disability.

Next slide. So, when did this all happened? It all started back in 1969. I love to see the date, May 15th, that was four days before I was born. I like to think if I had been born four days earlier, I might have been able to influence this a little bit.

But I was born too late, and the cat was out of the bag May 15th. And from this paper that we all know, you know, Scott Murphy concluded that cold platelets should be abandoned for transfusion purposes. And that is basically, to a large degree, what has happened.

Next slide. But we've known since '73 -- and this is another RCT by Becker; showing that a cold platelet is more hemostatically active. Andre went through that ad nauseum. And there was improved bleeding time in this randomized controlled trial that included either adults on aspirin or adults that were thrombocytopenic.

Yes, there has been some negative trials around that time. But they had, as you said this morning, three patients in it. So, if I'm going to believe a study, I'm going to believe an RCT that has more than three patients in it.

Next slide. So, what's the rationale to do a randomized controlled trial, comparing cold to room-temperature platelets? I think at this point, we've

done all of the in vitro tests that we need to do. And no, no one is asking me my opinion, but I think we've done more than enough in vitro tests. Andre showed you the entire work the world has done in this area. And there's some in vivo evidence suggesting, or supporting, a hypothesis that cold-stored platelets may reduce bleeding compared to room-temperature.

Trials needed for licensing. It clearly would help implement the use of cold-stored platelets around the country; although you can see here today, there's a large interest. Then with the use of adaptive design, a large enough trial can evaluate the effect of different manufacturing methods in a trial; not in vitro tests, which we have a hard time assessing their value anyway.

And then we can also assess the effect of storage duration over time with cold-stored platelets. You know, how long should we store them for? We really don't know for sure.

Next slide. So, this hypothetical figure here on the right is just an example to show you that over

time with storage duration, cold platelets -- which by the way, Jim, I put in blue, because blue is cold; red is warm. Up in the Mayo Clinic, it's just so cold up there you just get things confused.

You can see early on, right, with storage rates, you can -- this is a hypothetical, it may or may not happen. But you could have a time at which they're superiority; a time at which afterwards superiority is lost, now you have noninferiority between your cold and warm platelets.

And at some point, the cold platelets might become noninferior. And it's real important for a trial to be able to determine both noninferiority as well as superiority because there may be some health systems that would only implement cold platelets if it was superior, right. If they had enough utilization and could deal with the waste that a lower storage duration would produce. I, of course, would want a superior cold platelet over something that's equivalent to a warm, if the data played out that way.

But there are other situations where you -- to have an adequate inventory, you need that longer storage duration, and you could tolerate or accept noninferiority. So, a trial really needs to be able to assess both.

Next slide. All right. So now, on to the chilled platelet study. This is our logo. Rick, we can make t-shirts with this and you can give it to your friends in Boston; that would be great.

Next slide. Inside joke between Rick and I, and a few others in the room. Hypothesis. We hypothesized that cold platelets would be noninferior, or potentially superior, to hemostatic efficacy, to standard room-temp platelets stored at 22 degrees when transfused to adult and pediatric patients requiring complex cardiac surgery who are actively bleeding.

Next slide. We have designed this trial to be a Phase 3, multicenter, randomized, double-blinded, adaptive, noninferiority, storage duration ranging trial in adult and pediatric patients undergoing

cardiac surgery. Where again, comparing cold to warm platelets.

Next slide. This trial now is intended to be used for licensure if appropriate. The DOD, who might fund this trial would themselves either apply for licensure, or industry related to the manufacturing methods may also apply for licensure.

Next slide. We want our trial to be generalizable, pragmatic, adequately powered, with minimal bias, clinically relevant outcomes, adaptive, have high compliance to procedures and, of course, ethical.

Next slide. So, as I've mentioned, this would be in complex cardiac surgery patients with active bleeding. And just as it was in the Norwegian pilot RCT, the decision or the indication to give platelets will be physician-directed. We will provide, recently published this year, Anesthesiology Society guidance on indications for platelet transfusion. But it will be physician decision.

We plan to include 1,000 patients, both children and adults with broad eligibility criteria, which I'll show on the next slide. We plan to use at least 15 sites. We could flex up to 20 if needed. And we could get this done with 1,000 patients in three years of patient enrollment, we feel easily.

We do plan to use multiple platelet collection platforms. It doesn't, in our minds, make sense to have a thousand-patient trial that's going to cost more than a few dollars and only -- study only Trima, only Amicus, only PAS, only PRT. We feel -- especially since the in vitro data does not show much difference in hemostatic efficacy between manufacturing methods, this is the right way to go.

When it comes to time to get the product into the cold and bacterial cultures, we are putting in the protocol or requesting that we don't do bacterial cultures on a cold-stored platelets. And the cold-stored platelets will need to get into the cold within eight hours from collection. This is the same standard

that is used for red cells right now, and we don't culture red cells. So, we felt it was reasonable.

And the blood suppliers, many of which the leadership is in the room, have all advised us that eight hours is probably the best they could do, based upon how they're collecting platelets. And we feel this is reasonable.

When it comes to pathogen-reduced platelets, though, that takes time to process it and eight hours is not possible. We are going to propose that a PRT-treated platelet gets into the cold within 24 hours of collection. And again, that's what the blood suppliers are telling me is possible, and the least amount of time at which is possible.

Next slide. Eligibility criteria. We're going to include, or proposing to include, children above 28 days of age and adults less than 85 years. Again, with complex cardiac surgery with plan bypass. And included in the analysis will be those that are transfused platelets either interop or within 24 hours postop.

Next slide. We're going to exclude those who received a platelet within 24 hours of surgery, if washed or volume reduced are ordered, if they have known anti-platelet antibody, if they're thrombocytopenic, known suspected pregnancy.

Next slide. If they were previously in the trial, if they object to blood, known IgA deficiency, congenital platelet disorder, bleeding disorder, or planned postoperative ECMO or VAD, which is pretty uncommon, but at times it is. And those patients would require significant amounts of platelets and it wouldn't be possible to get them only cold platelets, so they're excluded.

Next slide. So, I unfortunately left this bag in my bag, Andre. So, if you want to go into my leather brown bag and pull out the red blinding bag. We are using a blinding bag that is marketed actually for people who go out on month-long hikes in the wilderness. For real, people do this.

And they have -- this is for their IV bags. And it's temperature insensitive. Andre, would you

mind being my Vanna, Andre? Can you walk it around to the Committee? Yeah, hand it -- and yes. Thank you, sir.

With a cold platelet inside of it, you can't feel the temperature of it. So, this is a perfect blinding bag to use for the trial. Even the ISB sticker sticks on this outside really well. And like it won't come off; you'd have to pull it off. But it can be pulled off, so these bags can be reused.

The plan for the trial is to do a randomization with stratification by center, an allocation ratio of 2 to 1. And there you go.

Next slide. So, here's the fun stuff. Primary outcome. We spent a good two years discussing what we wanted the primary outcome for the trial to be. And we've settled on proposing a bleeding score that has both intraoperative and postoperative assessments of bleeding, which we feel is essential.

When we've looked at the RECESS trial, which was a trial of red cell age in complex cardiac surgery

patients, 80 percent of the platelets transfused in the RECESS trial was intraoperatively.

So, it's important for us to be able to assess bleeding intraoperatively when 80 percent of the platelets are being used intraoperatively. Chest tube output is a great outcome and it measures postoperative bleeding really well. But we're going to miss 80 percent of the platelets that are transfused and evaluating the efficacy.

So, Phil Greilich, who's on our steering committee, published this with Marie Steiner and others a few years ago. And in this 5-score bleeding score, that was validated in cardiac surgery patients, there's some subjectivity, as you could read the slide; and there's some objective criteria to the intraoperative grading for bleeding. And then postoperative, it's all about chest tube output and it's very subjective.

So, this would be measured for the first 24 hours after the start of the first platelet transfusion, which would likely be intraoperative. And the platelets can only -- the intervention will only be

for 24 hours after the start of the first platelet transfusion.

So, the outcome directly is overlapped with the intervention. And we've seen some other trials recently where that hasn't happened and has caused problems with interpreting the results.

The last thing I'll say about this, is that the highest grade of bleeding that occurs either intra or postop, will be the bleeding score assigned to the patient for their assignment group. So, if they have more bleeding postop than intra-op, a grade 3 bleed post and a grade 1 intra, they're going to be scored as a grade 3.

Next slide. Secondary outcomes. We will evaluate chest tube output -- or proposing; things could change. For a 24-hour chest tube output, as it says, a secondary outcome, transfusion totals in aggregate as well as each blood product will be assessed as a secondary outcome, as well as laboratory measures of hemostasis at 6 and 24 hours after the first platelet transfusion. We clearly will track

mortality as well as many, many safety outcomes. But clearly, we'll be tracking thrombotic events and transfusion related SAEs.

Next slide. Subgroup analyses. As you might imagine, we will evaluate patients according to their ABO group, gender, race/ethnicity, surgical complexity scores both for children and adults, where they're specific for those age groups. The age group of the patients themselves. We plan for now to study -- or to do subgroup analyses for less than 12 years of age, 12 to 65 years of age and then above 65. And then we'll do subgroup analyses according to the volume of platelets transfused.

Next slide. So now, when it comes to the adaptive and the innovative analytic aspect of the trial, which I think really makes this unique. And Berry Consultants, which, I guess, I would say is the premier adaptive trial group in the country, they're the ones that designed this for us.

We're going to start -- oh, these were my old -- interesting. All right; anyway. This slide is the old slide.

We're going to start with storage age for warm and cold platelets, both at seven days of age. Because warm platelets can be up to seven days of age under some circumstances. If after the first 200 patients, the interim analysis, there's at least noninferiority in the cold group. We're going to walk the cold group up now to 11 days. Okay? And then we're going to evaluate another 200 patients.

Now, with those 400 patients, there's at least noninferiority. We will then now walk it up to 16 days. And the same thing, interim analysis; if 16 is still noninferior to seven-day warm, now we'll go to 21. Now, with this adaptive design, you can -- if there's not enough data to determine noninferiority, you could continue to stay at that age group as well too, to collect more data.

So, we're allowing the data to inform us when we should increase the storage duration, and at what

point we should stop. And then, of course, if we don't meet a noninferior margin of one, and there's enough patients in that analysis, we could stop the study theoretically at the 16 age, or you could -- maybe 11; we don't know.

While there's been a tremendous amount of in vitro work been done so far, other than the one study done in Norway, where 14 days seemed to be similar seven-day warm, we really don't know how long we can go. And the adaptive design allows us to do that. And it actually -- with the number of patients that we are going to include, Berry Consultants tells us that they can tell us to the day, we lose superiority and to the day of storage duration that we lose noninferiority.

So, just because our time periods are seven, 11-day, 16-day, 21-day, a result could be -- at 12 days is when you lose superiority. And at 17 is when you lose noninferiority. I mean, it's extremely important for us clinically to be able to know that.

Test for heterogeneity. Clearly, if we're using multiple types of platelets collection platforms,

we need to be able to assess, is there an effect of one versus the other. We're going to use classic tests for heterogeneity, as well as Bayesian and hierarchical model analyses to do this.

Next slide. I go through a bunch of these. I said this already. Forward through all of these graphics, please. I'll let you know when to stop. Thanks; stop.

So clearly, informed consent will be done. Since we know when these surgeries are scheduled, we'll be able to get consent prior to surgery. And of course we'll have a DSMB.

Next slide. Now, we're going to use a RECESS Trial Network as the backbone of the clinical sites for the network. As I've mentioned, RECESS was a study in this same exact population. It was just studying red cells. Now, we're going to study platelets. So, we know the sites that were very good sites within RECESS; I think RECESS had close to 30 sites in it. We're going to include at least 15, maybe up to 20.

Many of the blood suppliers -- all the blood suppliers that supply the clinical sites that have expressed interest, have been engaged and some are even on our steering committee and provided input to the trial.

We have a highly experienced multidisciplinary team to lead the trial. For PIs, both Marie Steiner and I have led multiple, large RCTs. Nicole Zantek is a transfusion medicine expert that will assist us with those aspects of the trial, and has experience participating in trials.

The CCC at Wash U has led my trials. And I think they've been done well. U of Utah is going to be our DCC there, very well-established and experienced DCC, led by Mike Dean. They are the DCC for a few research networks, actually.

John VanBuren is going to lead the analyses for us. And then as I've said, the adaptive design by Berry Consultants. Roger Lewis, Kert Viele and Nick Berry.

Next slide. This is our steering committee and the Department of Defense contributors that have all participated in providing input to the trial. You can see here our steering committee is a good mixture of cardiac anesthesiologists, surgeons, hematologists, and transfusion medicine experts; as well as Andre Cap from the DOD and Kendra Lawrence's team from USAMMDA.

Next slide. These are the sites that have shown interest so far; and we honestly haven't really recruited many other sites outside of the RECESS network. All high-quality clinical trial sites.

Next slide. So, we've had time to survey them to get a sense of what type of products are they using. Because if we're going to use multiple manufacturing methods, we need to get a sense of what they're using.

And most sites, I've now learned, use two or three different types of platelets in their center. I wasn't aware of that. So, when we counted all of the platelets that they have in inventory at their centers, you see the most common platelet collection platform are Trima-Plasma, 72 percent of the sites us it.

But when you look at all of the other platforms, it ranges about a third of the sites use each of them in general. Even with PRT platelets, whether they're produced with Trima or the Amicus system. And if they use any type of PRT, 60 percent of the sites we plan to use -- well, could use -- are using PRT. So, we feel we can get a good balance of each of these platforms in the trial, because we could select or deselect them according to the mix that we want to have.

Next slide. I'm almost done. We have great blood supplier support. South Texas was the first to raise their hand many years ago when we started. But the Red Cross, New York Blood Center, Vitalent and Versiti have all been great partners.

I haven't listed any other ones because we haven't asked them yet. I'm pretty sure if we asked others they would contribute or support too.

Next slide. I want to acknowledge Kim and Susan in my lab. They're the ones that do all the microfluidic work.

Next slide. And I definitely want to thank my two partners in crime, Andre and Geir. Between the three of us, we've been plotting to develop this product and get it licensed for the past five to seven years, as well as with whole blood through the THOR network. So, I want to thank them for their support through all of this as well. Thank you.

Next slide. Funny cartoon.

QUESTIONS FOR THE SPEAKERS

DR. RICHARD KAUFMAN: All right. Thank you. So, at this time I'd like to ask if there are questions or comments from the committee on the presentations that we've seen from Drs. Cap and Spinella. Dr. Tanaka?

DR. KENICHI TANAKA: Great talk, Phil. I have a question to Dr. Spinella. So, in many different clinical practice you see a significant viability in transfusion practice. And some practice, probably,

they start with fresh frozen plasma, some place with the platelets.

So, you're going to have a mixture of data when you do this study. And how do you sort of analyze those data when multiple products are given at the same time?

DR. PHILLIP SPINELLA: Sure. I mean any bleeding trial is going to be handcuffed by variation in practice. Especially when they're severely bleeding because, you're right, they're getting all three blood products and practice is different.

With a 1,000-patient trial, with the randomization, we expect practice variation to be equal between the two groups. And we can do subgroup analyses that assess for the transfusion ratio or other specific practices. So, that's how we plan to deal with it. 1,000 patients is the first answer. Subgroup analyses is the second.

LCDR JEFFERSON JONES: For both the data that was presented on the Department of Defense side and for

the study, is cold-storage whole blood being excluded from use?

DR. PHILLIP SPINELLA: Yes, in the trial, cold whole blood -- if sites are using it for cardiac surgery, that site would be excluded.

COL. ANDREW CAP: So, I didn't present any cold-stored whole blood data. What you saw here was purely apheresis products made. And I neglected to mention our -- when I said that we started at the first site was just a three-day product using Haemonetics MCS 9000 stored in plasma; since then we have moved some Trimas into theatre, and we've collected both in plasma and in PAS. So that's a mix -- in Isoplate PAS.

So that's a mix of, probably at this point, mostly Trima-collected products, about half and half plasma versus PAS, and a little bit of the Haemonetics data. But there's no cold whole blood data in this; that’s a separate topic. Yeah.

DR. RICHARD KAUFMAN: I have a question for Dr. Spinella. So, one of the things that was helpful in the RECESS trial was that the sites used a trust

score to try to figure out which patients were more likely to bleed.

So, it's a 0 to 8 score with things like preop hemoglobin and other factors. And so, if your trust score was 3 or higher, it meant you had at least a 60 percent chance of getting blood.

DR. PHILLIP SPINELLA: Right.

DR. RICHARD KAUFMAN: So, I wanted to see if -- was that included?

DR. PHILLIP SPINELLA: Well, there's not an analogous score to predict platelet use in either adults or children. But we did go through the RECESS trial data to see what could be used to predict who was going to get platelets that require a complex cardiac surgery. And actually, 40 percent of the complex cardiac surgery patients are getting platelets. And honestly, we feel comfortable with a 40 percent rate of patients getting transfused if consented.

We know, and we're going to fund the trial in a way to cover the time for coordinates to consent, and then those patients are not transfused

intraoperatively. So, we're happy with not using any score because a 40 percent rate of transfusion, for those that are consented, is more than enough for us.

DR. RICHARD KAUFMAN: Thanks. Dr. Cap, any thought about randomizing bases to getting cold- or room-temp platelets?

COL. ANDREW CAP: So -- you know, we did not -- this wasn't a study, right; this was just a sort of practical implementation to allow us to try to push platelets -- you know, further a field to where they could do the most good early on in bleeding patients.

And we don't really have a -- I don't know if we could do that without some kind of IRB approval. And so, we sort of just treated this as a change of practice. I mean you could think of it as a natural experiment in terms of the patients who did or did not get exposure to the cold platelets, based on where they were.

DR. PHILLIP SPINELLA: I's against the regs. You're not allowed to do a randomized controlled trial

in soldiers. The concern for coercion doesn't allow it. It's not in the regs. It's a no-go.

DR. RICHARD KAUFMAN: Good to know.

COL. ANDREW CAP: Well, that's certainly true. But even if we wanted to just sort of -- I mean we did not randomize, and we had no plans to randomize; let's put it that way.

DR. RICHARD KAUFMAN: I guess getting back to Ken's -- sorry, Dr. Tanaka's question. Was any thought given to maybe-- not make a really complicated transfusion algorithm, but even for red cells, which will be an important secondary outcome in your study. Any thought given to trying to standardize --

DR. PHILLIP SPINELLA: There was definitely thought, right; but then when it comes to practicality. And getting cardiac surgeons in one institution to agree to a transfusion algorithm would be quite difficult. Getting 15 centers to get cardiac surgeons -- oh, and by the way anesthesiologists -- to agree with an algorithm just was a bridge too far.

So, we definitely thought it would be optimal in a perfect world; but we decided it was not reasonable.

DR. RICHARD KAUFMAN: Dr. Bryant?

DR. BARBARA BRYANT: The primary outcome being the bleeding score. I've worked with several cardiothoracic surgeons who have been involved in developing these bleeding scores.

And one of the things they always talk about is that when they get a group of cardiothoracic surgeons in a room, and they all let them take the test, 75 percent of them fail. And then they have to put them through the training and show them the videos, and then they let them take the test again and then they pass. Will there be that type of process place?

DR. PHILLIP SPINELLA: Oh, definitely. Yes. Very -- what's the word, rigorous training of the anesthesiologists and the coordinators at the sites. They'll be in the OR from the beginning of the trial.

And honestly, if you look at that score, most of the intraoperative scores are related to the amount of packing that occurs, which is objective.

DR. BARBARA BRYANT: Right.

DR. PHILLIP SPINELLA: It's either no bleeding, mild oozing and then the amount of packing, or leaving the chest open. So, even cardiac surgeons should be able to get that right the first time.

DR. BARBARA BRYANT: Right.

DR. PHILLIP SPINELLA: No offense to any cardiac surgeons, especially if you're on the BPAC Committee, by the way. Clearly joking. All right.

DR. RICHARD KAUFMAN: All right. Are there any questions from our colleagues on the phone, Drs. DeVan, Ortel, or Morgan?

DR. CHARITY MORGAN: This is Charity Morgan. I have a question for Dr. Spinella about the study designs for the CHIPS study. I understand that you may not be the person that came up with the design, so please just let me know if you have to ask somebody to answer this question.

But I was looking at -- so the overall design. It talks about how you're looking at each sort of level, the maximal storage time, cold-storage time. And so, people might be getting blood -- say the maximum level you're looking at is 10 days, someone might get platelets that's been stored for six days or eight days, but anything up to 10 days.

And it talks about trying to figure out the relationship between how long the product's been stored and what the bleeding score will be. And I noticed you mentioned a kind of a linear relationship between those. Did you guys consider looking at maybe more complex relationships? Just from looking at the data earlier in the day, it seemed like a lot of hemodynamic parameters don't move linearly as the storage time increases.

DR. PHILLIP SPINELLA: I guess if -- are you asking me, is the statistical analysis going to include nonlinear assessments of the data?

DR. CHARITY MORGAN: Yeah. I guess would you consider doing that? Yes.

DR. PHILLIP SPINELLA: Yes. The answer's yes.

DR. CHARITY MORGAN: Okay. Thank you.

DR. RICHARD KAUFMAN: One other question that I have about the study, which I think is a really -- I think it's a really interesting design. You talked about how there really isn't a good sort of surrogate marker for the need for platelets or for -- there's not a gold standard.

But I'm wondering if maybe it would be possible to get some samples during this study and maybe even batch them, freeze them and look for a potential useful marker, even after. Because if the study worked well, you'd be able to have, in essence, a gold -- a clinical gold standard.

DR. PHILLIP SPINELLA: I didn't go into a ton of detail. The laboratory assessment will be pre- and post-transfusion. There will be pretransfusion labs done.

They will be clinically performed labs. The places that do -- we'll do TEGs, so there will be a

subset. And we don't have the potential funding to do a repository.

But if people want to help find some funding to do that, it's possible. We're going to be collecting blood. We just couldn't fit that into the budget. But yes, that would be a great ancillary project to do; I agree.

DR. RICHARD KAUFMAN: Yeah. And even with TEGs. So, even if you were not using the information at the time to make a transfusion decision; being if you had data, and then you could see did any TEG parameter --

DR. PHILLIP SPINELLA: Yeah --

DR. RICHARD KAUFMAN: -- did any other tests match the parameters.

DR. PHILLIP SPINELLA: I guess the problem with that though, as I'm starting to think about it, is that the -- whatever, you know, Kaufman factor is used to assess for bleeding, we've already decided who gets transfused and who doesn't.

It would be better to try to figure out who bleeds enough that might need a platelet transfusion. And you'd have to design -- it would be a different study to try to determine what can predict who needs a transfusion.

You don't want to have a predictor of physician behavior, which is what this would be in this trial

DR. RICHARD KAUFMAN: All right. Well, thanks a lot. So, we're going to take a break now, until 2:40. To 2:45; so, we'll take a 10-minute break. Thank you.

[BREAK]

OPEN PUBLIC HEARING

DR. RICHARD KAUFMAN: All right; so, we'll go ahead and get started. We're now going to move to the open public hearing part of the meeting. I will read the required text.

Welcome to the open public hearing session. Please state your name and your affiliation relevant to this meeting. Both Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meetings, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, as you begin, to state if you have any financial interests relevant to this meeting such as a financial relationship with any company or group that may be affected by the topic of this meeting.

If you do not have any such interests, also, FDA encourages you to state that for the record. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking, and you may still give your comments.

Our first speaker will be Dr. Mike Fitzpatrick, PhD, President and Director of R&D Cellphire, Inc.

DR. MICHAEL FITZPATRICK: Good afternoon. Before I start, you should have copies of the statement and I'll just paraphrase some of it for time sake.

It's a pleasure to be here. Thank you for the opportunity to speak. As a past member of the Committee, I'm aware of things you have to address, and the gravity and the difficulties in addressing them, and the advice to give to the Agency.

The company I'm with, Cellphire, is not developing a cold-stored platelet. We are developing a lyophilized freeze-dried platelet product that, when it's rehydrated, bears similarities to an activated cold-stored platelet or an activated thaw to frozen platelet.

We progressed through a number of nonclinical animal studies demonstrating safety. And to acknowledge a question earlier from the group, those studies have included studies with preexisting deep

vein thrombosis and preexisting arterial thrombosis, to see if the freeze-dried platelets exacerbate those conditions.

And with the help of the Agency, we have developed those models and been successful in showing safety. We've demonstrated biological activity in the mouse, rabbit, dog and nonhuman primate, completed an exploratory IND in normal health subjects, and just completed one in bleeding thrombocytopenic patients.

In addition, we have a lyophilized canine platelet that is commercially available in 32 states, Canada, Singapore and Hong Kong; and completed a 92-animal study that compares our product to DMSO cryopreserved canine platelets. And we demonstrated superiority at one-hour post-infusion and non-inferiority at 24 hours post-infusion; and those data are not published yet but will be soon.

So, I just give you that background to let you know that there are other products that are activated platelets besides cold-stored platelets, including DMSO cryopreserved platelets and the freeze-dried platelet.

During the past year while we've been conducting the thrombocytopenic bleeding study, we've been in discussions with the agency on the follow-on Phase II clinical trials. One continuing in bleeding thrombocytopenic patients; the other in open thoracoabdominal aortic aneurysm, which is pretty complex cardiac surgery.

We convened a couple panels of experts in hematology, oncology and surgery. And we have Dr. John Holcomb and Dr. Terry Gernsheimer, former members of this committee, as our primary consultants. We presented to the agency endpoints concerning time to hemostasis.

And while Dr. Spinella presented to you a scoring system, if in the Greilich paper, based on our interpretation, that resulted in a dichotomous decision. And if the score was less than two, the patient had lower morbidity and mortality and less hemorrhage. Greater than three, higher morbidity, mortality, and greater hemorrhage.

We think our time to hemostasis proposal to

the agency is also dichotomous and is based on a larger study in the proper study of 480 patients versus the Greilich study of 43.

So, why do I bring this up? I bring it up because -- and we'll just skip to the end here, because I know you can read the discussion later. I bring it up in that we would ask that the committee and the agency entertain the fact that time to hemostasis, and determining hemostatic activity of an activated platelet, is not an easy thing to do.

In our discussions with the agency, we came to the conclusion that doing an exploratory Phase II study in both patient populations, in order to look at statistical and clinical relevance, was the appropriate way to move ahead because of the difficulties in being able to show primary and secondary endpoints and efficacy with these products. And we would ask that you keep an open mind, that you entertain multiple solutions and multiple types of trials as we move forward.

Because characterization, and as we have seen

in the huge amount of laboratory data that's available on platelets, we still don't have a good predicter of clinical correlation. And the ultimate goal is patient outcome. Not days of storage, but patient outcome. How can we improve patient outcomes?

And how can we take one of the most significant things that we heard from Dr. Jenkins and from Dr. Spinella, which is, there are 30 thousand deaths occurring annually that could be prevented. And we saw from Dr. Jenkins, in his whole blood study, that they reduced mortality from 75 percent to 37 percent using whole blood, of which platelets and plasma are a component. And if we look at the PROPPR study we see that platelets and plasma can reduce mortality, and the two together reduce mortality more than one alone.

So, what I'm asking is that you keep an open mind; that we allow products like ours to continue to move forward in Phase II trials. And that we discover what are the appropriate endpoints, and how to measure them, so that we can have pivotal Phase III trials and bring these products to the patient; so that we can

have an impact on a patient-centered study and decrease mortality and improve our ability to treat hemorrhage in this country. Thank you.

DR. RICHARD KAUFMAN: All right. Thank you. So, our next speaker will be Mr. Michael Parejko, President of America's Blood Centers.

MR. MICHAEL PAREJKO: Good afternoon, everybody. America's Blood Centers, ABC, is North America's largest network of FDA-licensed, independent, non-profit community-based blood centers. Our members collect, process, distribute over half of the U.S. blood supply. And we thank the FDA and BPAC for the opportunity to present our member's views on cold-stored platelets.

The use of cold-stored platelets presents challenges as well as opportunities. The most significant challenge appears to be related to the required 3-day expiration. The most significant opportunity lies in extending the expiration date to make widespread use of cold-stored platelets more feasible. In order to gain more information on this

important topic, ABC conducted a survey of our members to gage the interest level in cold-stored platelets.

A total of 40 of the 46 ABC members participated in this survey, representing nearly 6.9 million collections. Currently, no member, centers are manufacturing cold-stored platelets, citing the 3-day expiration as the greatest challenge.

43 percent of the participating centers are actively planning to manufacture or distribute cold-stored platelets. 41 percent indicate that either have or are in process of seeking a variance to the use of cold-stored platelets. The majority, 65 percent, intend to seek for expiration of 14 days.

The current plans for 76 percent of the respondents include providing cold-stored platelets to trauma hospitals. Additionally, 71 percent of the respondents indicate that cold-stored platelets would serve geographical distant and rural hospitals, and another 53 percent are interested in providing them for labor and delivery. We, therefore, urge the committee and the FDA to seek data that would support the use of

cold-stored platelets in these and other settings and not limiting it to trauma.

A concerned express by our members is the time it takes to get a variance approved by the FDA to allow the use of 14 days cold-stored platelets in other scenarios besides trauma. Many members will not begin the discussions of using cold-stored platelets with their hospitals or clinician customers until the data is available on the feasibility of such an approach.

We urge the committee and the FDA to think broadly in their considerations of cold-stored platelets and seek data that would support expeditious decision making by the agency once the data is available.

I've got a couple minutes left, and I want to beat on the drum that has been talked about. Dr. Spinella mentioned it; others have mentioned it. The 30 thousand deaths that happen each year that are preventable. Doing some quick math, that's 82 a day.

That's nearly 3 and a half an hour. We've been here about 7 hours. Since we've had this

discussion, 24 deaths have happened that could be preventable. I think that, when we look at big numbers, we forget about the small sometimes. So, in the period of time that we've been here, 24 or 25 deaths could have been prevented. Thank you.

DR. RICHARD KAUFMAN: Thank you. Our next speaker is Dr. Beth Shaz. She's the president of AABB and will be making a joint statement representing AABB, American Red Cross and ABC.

DR. BETH SHAZ: Thank you. I'm Beth Shaz. I work at the New York Blood Center, and I'm also the AABB President. And I am speaking today on behalf of AABB, America Blood Center, and the American Red Cross. We appreciate the opportunity to present this statement in support of FDA's stated interest in engaging stakeholders to explore the scientific consideration for cold-stored platelets intended for transfusion and the indications for clinical use.

We appreciate FDA's recent approval of the alternate procedures submitted by the Armed Services Blood Program, which permits the storage of this

innovative product at 1 to 6 C for up to 14 days without agitation for use in treating actively bleeding patients without the need to perform bacteria risk control strategies.

We believe cold-stored platelets may have an important role in the treatment of actively bleeding patients in civilian populations. The availability of cold-stored platelets could significantly improve patient care by expanding transfusion options for actively bleeding patients and positively impacting the availability of this challenging product through the extended expiration date of up to 14 days, while decreasing patient risk for bacterial contamination through cold storage.

As FDA engages stakeholders, blood collectors also have many questions that must be answered. We are interested in the collection and product management requirements that would support the logistics for the collection of these products, including storage and transport temperatures as well as timeliness necessary to manufacture and label these cold-stored products.

We are interested in the data that will be presented, the collection devices, product types, including the potential use of pathogen reduction technology.

We are pleased that FDA is pursuing new information and enjoyed hearing the evidence and the Blood Product Advisory's recommendation that will ultimately inform FDA's decision on the safety and efficacy of this innovative product in the civilian clinical setting. Thank you for the opportunity to offer these comments on behalf of our members.

DR. RICHARD KAUFMAN: Thank you. I'd like to welcome our next speaker, Dr. Jose Cancelas, who's a professor of pediatrics at Hoxworth Blood Center at the University of Cincinnati. And he will be giving a brief presentation.

DR. JOSE CANCELAS: Thank you very much. I want to thank the FDA and the organizers at BPAC for inviting us to give this talk. I wanted to make some point about the in vitro and in vivo preclinical data that came from our lab. And they'll bring probably a new perspective on some of the things that have not

been discussed probably today.

So, first of all, I want to thank all my co-authors and the members of our team, especially Dr. Hegde and Dr. Zheng, who are here in the audience. These are my conflicts of interest. I'm just to tell you I'm a public employee of the state of Ohio, so I'm poor.

Anyway, so, one of the things that, this morning, probably was not significantly emphasized is all the work done by Karin Hoffmeister and Thomas Stossel, John Hartwig. And even, you know, Scott Murphy, during 14 years, trying to define mechanisms, how these cells -- how really the cold storage lesion happens.

Today, we know that it's a complex process. But what we know very well is that this, in the end, results in a clearance of platelets by the liver on the macrophages. This complex typically associates several things. So, on one side, desialylation of the platelets, glycoprotein 1b. On the other side, apoptosis signals. On the other side, shear distress

by glycoprotein 1b induced. So, we know that there are some drugs that have been shown in several pool occasions, that the inhibitors can ameliorate the cold induced storage lesion but do not fully prevent it.

So, the question number one is, what's the molecular basis of the platelet lesion induced by refrigeration today? After 50 years, we don't know yet this answer. So, we try to identify this, and we make a hypothesis, a crazy hypothesis, about maybe the same cold receptor. In fact, there are many putative cold receptors that could be really signaled in, you know, inside the platelet that could be responsible for the phenotype.

So, we call these cold receptors that could be activated, a group of proteins called RhoA-GTPs that could be controlling cytoskeletal filaments that they, in the end, control one of the hallmarks of the cold storage lesion called the glycoprotein 1b cluster, defined by Karen Hoffmeister.

So, we did this in the mouse because this is an evolutionary concept mechanism as demonstrated by

many people. And what we found is that you need just 15 minutes of the storage in the cold below 16 degrees for mouse platelets to already have activation of this RhoA-GTP. And then you do, being as a genetic model, you knock out the target -- in this case, RhoA -- and the platelets become cold insensitive. They can circulate the same way as a room temperature platelet.

So, for us, this was telling us that this was a molecular target that could be intervened. So, the question is, does RhoA inhibition prevent platelet storage lesion of cold-storage platelets? And the answer is, yes. We take human platelets, in this case, Acrodose pools. And we use pools because they solidify everything from person to person and we know that that's true.

So, this is very good, this FDA-approved product, Acrodose and PRP pooled platelets with continuous agitation of 1 to 6 degrees. This is case Day 7. As you can see that -- we can see that when you look at the vehicle contour of RhoA activated, we use a small molecule called G04, we can prevent the

activation of RhoA.

So, we use a humanized animal model. So, these are human platelets transfused in a single transfusion into NSG mice that have been irradiated sub-lethally. And so, they have some thrombocytopenia and they have also received a macrophage depleting agent, Clodronate, to really look at the liver mediated clearance of the platelets. And you can see the same.

Meanwhile, you have, in red, the cold control. You can see that the cold G04 or cold G04 with a wash, they survive the same as room temperature vehicle-controlled platelets. So, you say, well, is this true for macrophage? And the answer in macrophage is the same. You do a culture of macrophage similar to MMA. But for platelets, you have the control.

And very interesting -- when you have different time for -- well, Day 1 for cold, there is no big difference. Day 3, Day 7, Day 10, Day 14, you will still see a linear response regarding a storage time, regarding phagocytosis by macrophage of the platelets that is prevented by G04.

So, that question is, okay, they circulate, but are these platelets clotting? And the answer is, we used an aspirinated mouse model, in this case, it's a mouse. And what we did, this here -- it's a Basal model -- has around 50 seconds of timed for bleeding time.

Then, when you transfuse no platelets in the mouse after aspirin, it gets to around 150 seconds. You transfuse room temperature platelets; the mouse corrects the bleeding time at 24 hours post-transfusion -- this is done at 24 hours post-transfusion. And you can see a very good correction, similar to the Basal control.

When used cold platelets at 24 hours post-transfusion, there is no correction because the platelets have been cleared already in the mouse. But when you use G04, because the platelets are surviving, you can see a very good correction of bleeding time. So, that tells you that, in the mouse model at least, 24 hours post-transfusion, you are able to maintain bleeding hemostatic activity of these platelets.

So, we say, okay, but these are mice. So, who cares? So, we went to monkeys. Monkeys are non-human primates, in this case, our Rhesus monkeys, and we did two crossover trials. One, it was for biotinylated platelets. And I agree with Dr. Stolla, it's very hard to do it right. You label the studies with cold platelets, so we decided to do biotinylated platelets in the monkey.

And we did a crossover trial, Phase I, Phase II, between cold wash and cold washed G04, where the monkeys were randomized to get one first or the other one later. And we used some monkeys just barely with nothing else -- just aspirinated -- to check bleeding times.

So, what we found is that when you look at platelet survival and each monkey is compared with itself, it's a better study. And you can see in general that you have a significant improvement in the platelet survival, around 50 percent.

Meanwhile, in -- there was only one monkey where we saw nothing finish between the control and the

test. And presently, that monkey's the only one that didn't correct the bleeding time more in the test versus the control. Meanwhile, the other five monkeys were able to have a better bleeding control in five of the monkey's versus -- the test versus the control.

So, what's the mechanism? I mentioned before, glycoprotein 1b, and this is what we noticed. It used these cold platelets, you have -- you know, glycoprotein 1b gets completely prevented by this drug, G04 -- G04 in normal conditions -- and wash.

And when you look at also other markets, that tells you about what happens with the glycoprotein 1b. What we've noticed is that glycoprotein 1b, normally, when it's in cold platelets, gets clustered. Not only, but doses endocytose through a marker we've defined called vacuolar protein sorting 33b. And this is prevented by G04. So, you can mess with that and we can use colocalization coefficients.

So, in conclusion -- make it fast -- we noticed refrigeration of platelets in outside-in signaling, that activates RhoA. And RhoA is able to

prevent a membrane lipid bilayer homeostasis. I didn't show you all the data we have on microparticles and everything else, but this is able to completely prevent that. Non-endocytic and galactosyl/fucosyl-transferase location, normal glycoprotein 1b and, in the end, platelet survival and function.

So, when used reversable G04, that can be reversed either by washing or in vivo by just dilution within the plasma of the subjects. So, we don't think we need the washing, so you can completely prevent the problem.

So, why should I care? Our current platelet storage methods are unsatisfactory. Extended storage of cold platelets in current solutions may result in suboptimal products. Large Phase I/II trials like Dr. Spinella's will help answer this question. G04 platelets may circumvent the time-dependent loss of function of cold platelets and current restrictions for cold platelet indications.

Remember, 70 percent of our platelets are not used for trauma. They're used for human patients, for

the prophylaxis or low-grade bleeding, bleeding Grade 1 or 2. So, this is a big problem. We are talking -- all the talks today have been for 30 percent of the patients, not for the other 70 percent.

Understanding of molecular mechanisms is to be the basis for the development of rationalized approaches to “universalize” cold platelet storage for both bleeding therapy and prophylaxis. And I think that this could be the basis of a one platelet inventory for therapeutic and prophylactic platelet transfusions. Thank you.

DR. RICHARD KAUFMAN: Thank you, Dr. Cancelas. Our next speaker is Ms. Elizabeth Waltman, Chief Operating Officer of the South Texas Blood and Tissue Center.

MS. ELIZABETH WALTMAN: Hello, everyone. My name is Elizabeth Waltman. I am the Chief Operating Officer at South Texas Blood and Tissue Center. And I'm delighted to be here today to share a blood center’s perspective on cold-stored platelets and why it is important to us.

Working together with the University Hospital in San Antonio as well as UT Health, the Institute of Surgical Research, Southwest Regional Advisory Council, and multiple EMS providers, in South Texas, we've developed and implemented the largest civilian network of pre-hospital low-titer O whole blood for resuscitation. Non-leukoreduced low-titer O whole blood is an all-in-one pre-hospital tool, in part, because it contains cold-stored platelets.

Next slide. All right. We had multiple challenges at the blood center, the first one is time and distance. All blood centers provide an essential public health care service; for without access to blood products, patients' lives will be in peril.

I represent a regional blood center spanning 48 counties. The map on the left shows our service area in which we provide whole blood, blood components, and transfusion services for 100 hospitals, 3 Level 1 trauma centers, and over 60 EMS pre-hospital service providers.

Texas is a big state, and the distance from

the blood center to the hospital can be substantial. In fact, one of our Level 1 trauma centers is an excess of almost 400 miles away from the blood center with no direct air delivery. Because of the obstacles of time and distance, many hospitals demand platelet inventories well above their average usage. According to the American Hospital Directory, Texas has 366 hospitals, the most of any state in the U.S.

That said, there are 35 Texas counties with no physician, 147 counties with no OBGYN. That means 1.8 million women are in Texas without access to an OBGYN for care. That's like saying the entire city of Phoenix does not have OB access for women.

The map on the right shows the scarcity of critical access hospitals and other rural hospitals. The time to emergency/trauma services can be quite long. Therefore, the appropriate blood products must be available either pre-hospital or in hospital when and where the patient needs it.

The Texas Administrative Code, Title 25, Part 1, states that hospitals with maternal designation of

Level 1 must have appropriate blood bank services available on a 24-hour basis, as well as written guidelines for care for massive hemorrhage and transfusion of pregnant or postpartum patients. Level 2 hospitals and higher must have platelets as well. Next slide.

Our next challenge is the increase in usage. According to the NIH, blood transfusions are among the most common medical procedures in the U.S. Healthcare is the largest employer in the U.S. Today, blood centers are challenged to keep enough platelets on the shelf to address the increase in demand due to the growing and aging populations, the incidence of cancer, and trauma.

In 2009, the American Society of Clinical Oncology projected that cancer diagnosis through 2030 would increase, by 45 percent, from 2010. Curetoday.com estimated that 14 percent of all blood collected in the U.S. goes to cancer patients, and the majority of those transfusions are platelets.

According to the Gun Violence Archives, to

date, in 2019 alone, there have been 374 confirmed mass shootings with 420 fatalities and 1500 injured. If blood centers are to provide enough platelets and other blood products for these patients, as well as for rural and remote trauma and maternal hemorrhage resuscitation, we have to look to ways to expand availability and reduce outdating of platelets. Next slide.

Our third challenge is the short shelf life. Most blood centers provide room temp platelets to hospitals in the form of single donor platelets, random donor platelets, and pooled platelets, which have a shelf life of five days. If you do additional testing, you can move it to seven. Generally, the testing and transportation to the hospital can take two to two and a half days.

That means, in the hospital, the shelf life is two and a half to three days on average. The FDA has granted a variance for 3-day cold-stored platelets. If these platelets were produced in a blood center after infectious disease testing and transportation, the

platelets would have a hospital shelf life of about one and a half days.

In addition to time and distance, short shelf life contributes to the high level of expirations. The AABB estimates that the national platelet expiration rate is about 12 percent for blood centers and 22 percent in hospitals. In rural hospitals, the return rate is very high and most of those platelets expire.

Our fourth challenge is the diminishing donor pool. The process to give platelets is long and not very comfortable. Fewer and fewer people want to spend as much as two hours in a blood center donating platelets. Over the past 17 years, the average age of platelet donors has increased and the number of annual donations per donor has decreased. In addition, this year, the number of paid plasma collection sites has exceeded the number of volunteer blood donor sites in the U.S. We believe this is having an impact on the availability of blood for our hospital. Next slide.

Challenge number 5, bacterial testing. Room temp platelets provide a favorable environment for

bacterial growth, which could harm the recipient. Recently, the FDA published bacterial risk guidance to the industry to address potential bacterial contamination of blood products. Based on the data provided by the AABB's National Blood Collection and Utilization report of 2017, approximately 77.5 million blood products were transfused in the U.S. between 2013 and 2017. During that same timeframe, 23 deaths associated with contamination were reported to the FDA.

In order to comply with its guidance and continue to provide the same amount of platelets, my blood center will need to recruit an additional 2,500 platelet donors, purchase additional capital equipment, additional supplies and people at an estimated cost of $1.3 million per year to implement. To provide additional platelets to maternal access hospitals will require more donors, more cost. Blood centers cannot shoulder the costs to implement this guidance. And the cost will be passed along to the hospitals, the patients, and the insurance providers. Next slide.

So, what's the solution? We believe that the

solution, in part, is cold-stored platelets, because they are refrigerated and there is a significant decrease in risk to the patient due to bacterial contamination. They're activated to address active bleeding, trauma, and maternal hemorrhage resuscitation. The 14-day dating will reduce expirations and improve availability. And because additional sampling is not required for bacterial testing, platelet split rates will not be affected.

They will prevent an increase in the cost burden to the healthcare system and patients. And no agitation will be required; therefore, they can be transferred or transported with red blood cells or low-titer O whole blood and transfused pre-hospital. It is our hope that BPAC will recommend to the FDA your support of a variance of 14 days for cold-stored platelets within U.S. blood centers. Thank you.

DR. RICHARD KAUFMAN: Thank you. Our next speaker is Dr. Richard Benjamin, the Chief Medical Officer for Cerus Corporation.

DR. RICHARD BENJAMIN: Good afternoon. I

thank the committee for an opportunity to speak. My conflict of interest, I am the chief medical officer and a stockholder in Cerus Corporation, a manufacturer of pathogen reduction technologies. The INTERCEPT pathogen reduction system is the only FDA-approved system for platelets in the U.S. It's indicated to reduce the risk of transfusion-transmitted infection, including sepsis, and as an alternative to gamma irradiation for the prevention of GVHD.

Currently, those platelets need to be stored at room temperature for up to five days in the U.S. And in many countries in Europe, storage can be up to seven days. The INTERCEPT technology today can replace irradiation for GVHD, and it also can replace testing for CMV, for Zika, and Babesia microti.

The FDA Final Guidance states that platelets that have been treated by an FDA-approved pathogen reduction device, according to the instructions for use, need no further measures to control the risk of bacterial contamination of platelets. So, we can replace bacterial culture.

Worldwide, over 6 million pathogen inactivated INTERCEPT-treated products have been transfused. And in the coming year, over a quarter million platelets will be transfused in the U.S. that have been treated with our technology. One of the things we've learned is that, even with clinical trials, you have to transfuse many hundreds of thousands of a blood product to really understand its efficacy and its safety.

For example, in France, Switzerland, and Belgium, who now have universally implemented INTERCEPT platelets, there have been no definite cases of sepsis or fatalities related to bacterial contamination with over 770,000 platelets transfused. And those are statistically lower than those periods when parts of the countries were not using pathogen reduction in the prior period for Switzerland when they weren't doing any culture testing.

So, what about INTERCEPT-treated platelets with cold storage? We heard a little bit of data from Jim Stubbs from the work he's done. Cerus has not actually performed any in-house experiments with cold

storage, but they are to publish things in the literature I should mention.

One was an abstract at the AABB from Dr. Cap's group that, I think, he mentioned in his talk. And the second is the paper in transfusion that was recently published from Belgium, Six et al. And essentially, they say the same thing, that they show that INTERCEPT cold-stored platelets are slightly different to conventional cold-stored platelets, but in a way that makes them potentially more procoagulant. They are potentially better hemostatic agents than conventional coastal platelets. And I can go through the data quickly.

Both collagen-stimulated aggregation and TRAP-stimulated integrin activation was decreased slightly. Coagulation started faster. Fiber information rate under flow conditions was increased. And importantly, peak thrombin generation in static conditions was increased compared to conventional cold-stored platelets or for room temperature INTERCEPT platelets. This activity was robust out to 21 days.

So, we conclude that cold storage of INTERCEPT platelets are more procoagulant and are potentially better hemostatic agents than conventional or room temperature platelets. So, the next question is, do you really need pathogen reduction on a cold-stored platelet? What we do know is that platelets are contaminated at the time of collection, and we've spent many years debating the interventions necessary for room temperature platelets. And now we do have a final guidance that will protect patients.

What we don't know is the clinical significance of bacterial contamination in cold-stored platelets. We simply do not know. To say that we can draw on the experience with cold storage of red cells means we're not producing data of the safety of cold storage of red cells. I think it is not a good approach to this problem.

The only data that I know of, of cold-storage platelets, is that referred to by Dr. Cap from his lab, Ketter et al. They did evaluate a small number of strains where they put 1,000 CFU per mL of various

strains into platelets and kept them cold. And they showed, as in the figures on the right, that with gram negatives and gram positives, the concentrations remain stable. The red arrows on the right point to the straight lines where the bacteria -- they were still viable, but they did not grow. They didn't test outside of five days, so we don't know what happened after five days in these platelets.

What we do know is that there is no known safe level of bacteria in a blood product. The FDA cannot tell us you can have 10 bugs in a bag. They do not say that. A contaminated product is a contaminated product. Whether there are enough bacteria to cause severe sepsis or not belies the fact that we don't know whether low levels of bacteria would colonize lines or cause other sort of infections in patients. We simply do not. We've never really adequately looked at that.

So, what about the story about red cells? Are red cells really that safe? Again, we haven't focused on bacterial sepsis with red cells because we assume they're safe. So, I would say that the hemovigilance

data around red cells and sepsis is very suspect. We do know that bacteria can grow robustly in red cells at 4 degrees.

And part of the ISBT TTID Working Party Subgroup for Bacteria, over the last 10 years, the subgroup has worked with an international group to establish international reference strains. And the WHO have blessed 14 strains that are checked by the Paul Ehrlich Institute for warm platelet use for testing. And the subgroup is currently working on a red cell panel. Some of that work was recently published in the ISBT Science Series.

As a start, the subgroups submitted from around the world bacteria that were involved in red cell adverse reactions. And the Paul Ehrlich institute in Germany took those strains -- there were 32 strains -- and they inoculated them at very low levels into three red cell products each. So, the inoculation was 10 to 25 CFU per bag. So, that's the physiological inoculation with these strains. What they found, they then stored them for 42 days and sampled regularly at 1

to 6 degrees.

They found that 17 of the strains died by Day 42. They weren't viable. They found two that remained absolutely static -- they were bacteria static -- seven that grew in one or two of the three bags and not in all of them, and they found six strains that grew robustly. Growth invariably was detected by Day 7.

So, now, if we look on the righthand side, we can see Pseudomonas fluorescens. By Day 5, it starts being visible. Remember, the national concentration was about 0.01 CFU per mol. Undetectable, really. By Day 5, that strain was coming up. And by Day 14, the strain was at 10 to the 8th CFU per mol, enough to kill you. A very similar data was seen in Serratia liquefaciens, which started coming up around Day 7 and got to, by Day 14, very high levels, as did the Yersinia entercolitica -- two different strains. And Serratia marcescens and Listeria monocytogenes were slightly slower.

I point out that the two strains of Yersinia and Listeria don't need to cause sepsis. Those are

chronic infections. Yersiniosis and listeriosis are chronic infections. Sepsis isn't what you're looking for. If you get listeriosis, it's a chronic disease. It's not just an acute infection. So, I would posit that we do need to worry about bacteria in cold-stored platelets, especially if you want to go past five days of storage.

So, what are your options? Well, bacterial detection methods are not sensitive in those five days because the concentrations are too low. And detection or culture won't work. Pathogen inactivation really is the optimum FDA-approved technology for preventing infection and sepsis with cold-stored platelets.

So, moving on, cold-stored platelets are going to break many paradigms, right? We can only use them for treating bleeding and not for preventing bleeding. We're going to store them in the cold. The CFR allows three days of storage today. We don't know really what the optimum is, but I believe the data that says that they probably are good out to 21 days. We don't actually know the dose. The CFR talks about whole

blood cold-stored platelets. And the dose is independent on how many whole blood units you actually pool.

So, actually, it's not determined what the dose is. There's no requirement to have 3 times 10 to the 11th platelets in a whole blood pool, and there's no really knowing what the optimum therapeutic dose is. So, we need to work that out. Bacterial safety, I've just mentioned. There is no safe level of bacteria in platelets. And we need to be circumspect about bacterial safety.

The other thing we need to worry about is leukocytes. At 4 degrees, lymphocytes will survive very nicely and could cause GVHD. So, do you need to irradiate these products? What about emerging infections? If I'm sitting in Bagram Air Force Base in Afghanistan and collecting my platelets, I'm very concerned about emerging infections.

Recovery and survival -- well, we know that recovery and survival is probably not a good way of measuring these products. The recovery -- remember

those platelets you see circulating is the platelet not involved in hemostasis. It's doing nothing. The ones that are stopping bleeding are the ones that have gone out of circulation and are at the site of bleeding.

We need to ask what happens to those platelets on transfusion. And finally, hemostasis is the way we should actually be assessing these products, not by recovery and survival. INTERCEPT pathogen inactivated platelets will litigate the bacterial safety that GVHD and the emerging infection issues and are possibly more effective.

My last slide, just to summarize, they may be safer, they may be more effective, they are possibly different. They solve the problems of collection in austere environments for emerging infections. They solve the problems with GVHD. They are the only bacterial safety system that you can use.

Finally, clinical trials -- if we're going to do these in civilian populations with unproven technologies, they need to demonstrate and not assume bacterial safety. We have to do something about

bacteria in these products. With that said, Cerus is highly supportive of this program, would like to see a good clinical trial done, and would like to see 14-day cold-stored platelets approved by the FDA as soon as possible. However, if they are more than five days old, they need to be INTERCEPT treated. Thank you.

DR. RICHARD KAUFMAN: Thank you. Is there anyone else from the public that would like to come up and make a statement? Is Dr. Jason Perry here?

DR. JASON PERRY: I don't have anything to add. I concur with what has been said.

DR. RICHARD KAUFMAN: Fair enough.

DR. JASON PERRY: We need cold-stored platelets.

DR. RICHARD KAUFMAN: Okay. Are there any other clarifying questions from the committee? All right. Hearing none, so that will conclude the open public hearing. So, we will now move to the open committee discussion. Oh, yeah, sorry. Anyone on the phone? Dr. DeVan, Dr. Ortel, or Dr. Morgan, any questions?

DR. CHARITY MORGAN: This is Charity Morgan. I don't have any questions.

DR. THOMAS ORTEL: This is Tom Ortel. I don't have any questions either.

OPEN COMMITTEE DISCUSSION/QUESTIONS FOR THE COMMITTEE

DR. RICHARD KAUFMAN: Okay. So, I think we'll move on then to the committee discussion. Yeah. So, I'm going to start just by reiterating the questions to the committee that were presented at the beginning.

We were asked to please comment on the available data on cold-stored platelets, including discussion of knowledge gaps and potential need for preclinical or clinical studies with respect to the following: A) length of storage beyond three days; B) indications for use such as treatment of active bleeding; C) differences in collection platforms and storage media; and D) pathogen reduction.

And the second question, please comment on the design of any additional studies needed to evaluate the

safety and hemostatic efficacy of cold-stored platelets to support their widespread use in the United States.

So, I'll say, I think it's been a really interesting session today. These are really exciting and complicated issues. Just to sort of kick off the discussion, I was really struck by the presentation made at the beginning showing kind of that pyramid representing the FDA's current framework for evaluating platelet products.

So, if you recall, there's basically a set of in vitro assays that are done kind of forming the foundation of the pyramid, and then in vivo radiolabeling studies that are done. And then, at the top, for products that are different enough from things that have already been approved, hemostatic efficacy in vivo is what's looked at.

For conventional room temperature stored platelets, the gold standard has really been at the top of that pyramid looking at thrombocytopenic patients and looking at their rates of Grade 2 or higher bleeding. And as Darrell Triulzi illustrated earlier,

most of the bleeds that are seen are Grade 2, so not terribly significant clinically -- by definition, not requiring a red cell transfusion. It's not possible to power studies. It's not possible to make them large enough to power them for the endpoints that we really care about, which are Grade 3 bleedings requiring transfusion, or Grade 4 bleeding requiring -- life-threatening bleeds.

With cold-stored platelets, it really seems that a very different framework is needed. So, I think that, as we've seen over and over, the middle of the pyramid -- sort of looking at recovery and survival -- in many ways, does not make sense for these products. We accept that it will be lower. So, then, you're really faced with the challenge of, how do we assess hemostatic efficacy in vivo?

So, anyway, let me stop there and open it up to the committee for any thoughts or comments. And we can kind of go around. Dr. Bryant, why don't we start with you?

DR. BARBARA BRYANT: I think the presentations

have been very good today and have brought up several issues that we need to address and think about how to approach the need for studies that will look at bleeding as an endpoint, I think, are very much needed. I think some of the background work has been done that shows that the platelets and markers that we see, the activation, these type of things that we've known about and now have been proven, have been very helpful.

But now we need to see what this looks like in a population of patients that maybe aren't the healthiest patients in the world. The cardiac studies, I think, is a real good place to start. People that have atherosclerotic heart disease, maybe even people that have other issues. So, we need to make sure that there's no harm in these activated platelets.

I feel that there needs to also be studies looking at the pathogen inactivated platelets as well, because that's very important in what we do as well.

I think how we go about doing this and how we set these studies in place will be very important as it sets the stage as we move forward. I believe that

there is definitely a need for cold-stored platelets, extending the expiration date out, if we can prove the efficacy and safety of these products.

DR. RICHARD KAUFMAN: Thanks. Dr. DeMaria?

DR. ALFRED DEMARIA: Well, I come to cold platelets on a steep learning curve. And part of me, after hearing this and reading the materials before the meeting, made me wonder why we're not doing 14 to 21-day cold platelets already. And understanding -- it seems, to me that three days sort of rendered the whole question moot in terms of utility.

And that -- part of me thinks that this should go faster, and part of me thinks that the clinical trials are really necessary to determine safety and efficacy. So, I think that it's something that should move as quickly as possible.

DR. RICHARD KAUFMAN: All right. Thank you. Dr. Stapleton?

DR. JACK STAPLETON: Well, like Dr. DeMaria, I come into this with a steep learning curve. But I think the data are pretty convincing that there's a lot

of experience with Day 7 and even out to 14 in some instances. And I think that the approach, outlined by Dr. Spinella, of doing a stepwise approach into this makes a lot of sense to me. So, I think that's a great plan.

One question I -- and I'm not sure I caught it completely. But the data showing the -- I think it was salmonella and listeria growing in blood. I believe those were blood red cells. And those were intracellular pathogens. And so, I think that a careful analysis of actual platelet units for replication at 4 degrees with bacteria is important to conduct as well.

But most bacteria don't grow at 4 degrees, or they don't grow very well. So, I think an analysis of that would be an important component of taking this forward. I agree with Dr. DeMaria and Dr. Bryant that this should proceed quickly.

DR. RICHARD KAUFMAN: Thanks. Dr. Baker?

DR. JUDITH BAKER: Thank you. I agree with all of my panelists here and thank all the speakers for

their fine presentations. I was struck by the access issues. And what I would add to the encouragement are the studies as suggested that would look into different populations such as women, Europe's -- women of reproductive ages. I was heartened to hear about the study that will be looking at the pediatric population, because these are indeed trauma cases that occur every day, everywhere.

Without diminishing the absolute need for the military population and their needs, but the other populations that were mentioned by our military speakers that are not necessarily soldiers but are civilians everywhere that are also not elderly, not facing the severe cardiac problems that were mentioned in some of the trials.

So, I would encourage studies that would look at this broader array of patient populations. Thank you.

DR. RICHARD KAUFMAN: Thanks. Dr. Perez?

DR. ELENA PEREZ: I would just echo what's been said so far. And I think we saw some very

encouraging preliminary data that's definitely underscoring the need to go beyond the three days that's already in place. And I think the active bleeding population is a good starting place to then go from there to broaden to other populations.

One of the things I was wondering about was standardization of the collection platforms and the media, and what are the differences in how different collections take place and how they're brought to temperature, and other variables that might impact the efficacy, if it would or if it wouldn't?

I'm not very familiar with the pathogen reduction techniques, but I would want to identify where does the contamination take place and what kind of steps we could do to prevent that. But clearly, it seems like we're on a path towards moving forward with this, and I think it's definitely something needed. So, I'm in support of it.

DR. RICHARD KAUFMAN: Thanks. Dr. Jones?

LCDR JEFFERSON JONES: I completely agree with the public health's kind of implications that there is

a sense of urgency. If there is something available to prevent -- I can't imagine all 30 thousand can be prevented even if platelets were available. But even if a portion of those could be, that that sense of urgency needs to be in place but balanced with -- when talking about PRT platelets, it was nice to have all of that European surveillance data available when making decisions.

And it appears, for cold storage platelets, we don't have anything close to that level of both safety and efficacy data. So, that does give me hesitancy related to that. For the differences in collection platforms and storage media, I think they talked about -- I mean, in some of the reading materials we had, I did see some statistical differences in different platelet-additive solutions and collection platforms.

I guess it wasn't quite clear to me, I guess, if the assumption is none of those are clinically significant and that's why, in a study setting, it can just kind of all be grouped together. But if it is the case that those may be statistically significant, that

could kind of -- if we kind of group it all together, then it might interfere with future findings if there are some that are much more effective than others.

And then the last point I'd make on D pathogen reduction, for room storage platelets, there have been a lot of cost analyses that take into account the kind of bacterial contamination cost associated with it. If there is comfort enough to not require any sort of bacterial testing of cold storage platelets, then that would be a different calculation. But I would echo that, theoretically, it doesn't seem that there is a large risk of bacterial contamination, but we really just don't have the data.

And because the urgency is there, it would be ideal to have continued surveillance for contamination, either through cultures or at least through close monitoring for patient associated sepsis symptoms.

DR. RICHARD KAUFMAN: All right. Thank you. Dr. Shapiro?

DR. AMY SHAPIRO: I think it's a very difficult topic. And I would favor taking a more

pragmatic approach in order to save lives. So, I would take a two-pronged approach.

I would proceed with the studies that people have planned; but I would also determine areas of greatest need in the country and create a fast track for allowing longer cold storage platelets to be available, with very robust data collection systems to report data for their use in all of these systems.

I just don't think it's reasonable to conduct controlled trials while we continue to allow people to die for lack of products that could be made available to them to save their lives. There may be risks associated with that including bacterial infection.

I'm impressed by the data from France, Switzerland, and Belgium. I would encourage that some of these areas that could apply for fast-track use -- pathogen reduction as well -- and look at outcome of patients and report any infections in the populations served.

In terms of the collection platforms in the storage media, I found some of the data to be

interesting and somewhat contradictory between different reports. I would think best practice for each system ought to be made available for each area using each system.

For example, which way to store the platelets, label up or down? And information about expected results for the decrease in counts that could be observed. And again, to report that as robustly as possible while studies proceed in populations that are more controlled and at less risk of mortality, in the meantime, due to access to other products, like cardiovascular patients.

DR. RICHARD KAUFMAN: Thank you. Dr. Kindzelski?

DR. ANDREI KINDZELSKI: Yes, I will not disagree with my colleagues; meaning I will agree with my colleagues. And I think we all heard the importance of the subject that we gathered here today to listen about. Especially, it is important in the consideration of the need of the product in remote rural areas, in small hospitals and OB/GYN conditions.

I feel that substantial data exists to consider the potential to explore extension of storage beyond 3 days, and specifically to 14 days. I think it is important to talk a little bit more about the indication. And personally, I feel that it should be used for treatment, not necessarily prophylaxis but treatment in a very general meaning of that word. All type of acute bleeding, including trauma as well as maternal hemorrhages.

And regarding the clinical trial and trying to do the trial that will describe all patient populations, I think it is impossible to that. Well, we don't have time to do a clinical trial in different patient populations.

If it will be a clinical trial, it should be a very well-controlled clinical trial in the best selected patient population to show the efficacy and safety of the product. And regarding the pathogen reduction, I think it's always a good idea.

DR. RICHARD KAUFMAN: Dr. Bennett?

DR. JOEL BENNETT: So, as a hematologist, I'm

well aware of the problems of platelet availability and platelet storage. So, I would be very enthusiastic about a way to increase the availability of platelets. The ability to store them for 14 days would be, I think, a real boon to clinical hematology, certainly to me, although I do use outdated platelets -- no, I (inaudible) so that could be a problem.

So, on the other hand, I'm also a physician-scientist whose studied platelets and platelet function for a number of years. And I'm well aware of the inability of in vitro studies to predict the hemostatic function in vivo. On the other hand, I was really impressed with the studies that demonstrated that cold-stored platelets are more active than warm-stored platelets or room temperature, which is sort of surprising to me.

So, I think this needs to be considered in the implications of that. I think the fact that if -- at least on some units, you could see platelet aggregates as things are stored. I think this is something that needs to be studied and considered. You certainly

wouldn't want to be infusing platelet aggregates into people, even acutely bleeding people. So, I think there's more basic science that needs to be done.

DR. RICHARD KAUFMAN: Thanks. Dr. Tanaka.

DR. KENICHI TANAKA: I have been using room temperature 5-day old platelets for about 20 years, and I never felt those products worked quite well in post-cardiac surgery patients. So, it is a welcome sort of a challenge to improve pre-clinical practice.

I think the data presented today really showed efficacy, at least in vitro and some in vivo, for 5 to 7-day cold-stored platelets. But after 7 to 10 days, based on the restore reaction, I think product also kind of start to go down in terms of function.

And it's still better than room temperature stored platelets. But when we try to prove the point, I think it's good to have the best functioning products that is probably 5 to 7-day old cold-stored platelets. I think we should first test those and then move onto additional -- as Phil designed the study, I think that's good approach.

And I think in terms of indication, treatment, or on-demand uses, of course, I think it's the best option. And there are certain populations in whom you do not want to have a prolonged elevation of the platelet counts. And even in cardiac surgery, after two or three days, platelet count usually start to go up. And it's almost over the baseline after four or five days. So, I think we are aiming for transient hemostasis. So, you know that to achieve that, I think we should have the best functioning platelet product.

I think that also applies to intracranial hemorrhage, maybe cirrhotic patient who had a bleeding episode because prolonged elevation of the platelet count can cause venous thrombosis and other thrombotic complications. And that has been shown in a cirrhotic patient with platelet-elevating interventions.

DR. RICHARD KAUFMAN: Thank you. Dr. Stramer.

DR. SUSAN STRAMER: Yes, thank you. I represent industry. And during the entire day, the entire session and the open public hearing was presented by industry. So, you heard a wide variety of

comments supporting the clinical need for hemostasis. Access is important. This is all preventable mortality, as has been presented. At least for me, the in vitro and in vivo studies that were presented have a great deal of limitations. I think they were very small in sample size, and it was difficult, at least for me, to understand what their clinical relevance was.

I think, perhaps, they're important to do, but again they have limitations. I would like to comment that bugs will grow in platelets at 4 degrees, especially as we store them over long periods of time. So, we shouldn't assume that we won't see septic transfusion reactions from these products. And if we consider that the rate is not important enough to introduce the mitigation as we have for red cells, that's one thing, but bugs will grow in these products.

Another thing regarding pathogen inactivation, is we've been on a road now with PI availability to eliminate doing testing for certain agents like Zika or Babesia or bacteria if we have PI.

Regarding logistics, you heard from Dr. Shaz in the AABB statements, that logistics have to be worked out. Over the next 18 months, blood centers will be very involved in implementing bacterial mitigation strategies as required by FDA guidance.

I'd also like to comment on Dr. Spinella's data. Although a thousand patients sounds like a large number, if I understand the data, or the presentation correctly, that will be split in a conventional arm and a test arm. It will also be split between additive solutions and PI, and time will also be another variable. So, within each cell or each component of the study, ends will be small.

And as we are challenged with all of these studies with small end, it's impossible to prove superiority. I mean, we can prove non-inferiority, but that will just be no significant difference. So, I just say, with all of these studies, we need to be cautious of small numbers.

DR. RICHARD KAUFMAN: All right. Thank you. And I think it's a good point about the different types

of products being combined into one study. And there's good and bad to it. It's not as pure. On the other hand, the matrix is so large that it would be impractical to test every combination, this or that additive solution, this or that percentage for so many days and so on. I think one of the things that Dr. Spinella did a good job explaining, frankly, was the tension between answering scientific questions and impracticality.

And I do think that they chose the right patient population for a study of hemostatic efficacy. That is, I think, cardiac surgery is the right place to do it. Many of these patients get platelets; and many of these patients need platelets because of what we know to be a lot of different effects, for example, that cardiopulmonary bypass has on platelet hemostatic function. And finally, there is a way -- albeit, with limitations, it's standard to measure chest tube output. So, there is a way to look at that.

I do wonder if maybe some adjustments could -- even in a subset of patients -- be looked at. That is,

as Dr. Strandenes mentioned earlier, you could, for example, measure the hemoglobin or hematocrit in the chest tube output to make sure you're looking at blood. You could also, for that matter, normalize for the patient's hematocrit at the time. That is, if you are bleeding the same amount but your own hematocrit is lower, you're bleeding more by definition.

So, there may be some ways to potentially validate that you're looking at what you think you're looking at. But overall, I think it's a good study to do. One other patient population that might be interesting to look at, as Dr. Tanaka indicated, would be the patients all on anti-platelet medications who have head bleeds. So, their one advantage is that you have a really nice way to quantify the size of the bleed by radiology.

And for that matter, as was pointed out by Dr. Spinella, in the two RCTs where the effect of platelet transfusion on head bleeds has been looked at, platelets have not been shown to be beneficial. So, it's very natural, I think, for us to want to have a

way to reverse anti-platelet agents. And maybe that would be another place to look. That is, in a neurosurgery population. Now, if you made a change in the radiographic findings, but didn't affect meaningful patient outcomes, neurologic outcomes, then you'd say that it didn't matter.

One other comment that I wanted to make is that I think there really is a lot of room to improve platelets. Darrell Triulzi mentioned at the beginning in the PLADO study that 70 percent of the patients in each of the arms of the PLADO study -- the low, medium, and high arms -- had Grade 2 or higher bleeding, mostly Grade 2. That was getting the standard of care. In some cases, double the standard of care and they were still bleeding quite frequently.

We know that room temperature stored platelets work. The best data for that come from a couple of studies where patients were actually randomized to get platelets for prophylaxis, or not get platelets for prophylaxis in the setting of therapy-related thrombocytopenia. So, they would only transfuse those

platelets if they bled. In the German study, there were actually two deaths in the arm that was not getting prophylactic platelets.

But nevertheless, I think the products that we're getting really could be quite a bit better. And I am encouraged -- even though it's really preliminary, really small numbers, it was encouraging to see at least a signal in the data from the Norwegian study. So, anyway, I definitely think it merits serious follow-up. So I don't know. Any other thoughts? Dr. DeMaria.

DR. ALFRED DEMARIA: Can I ask a question based on Dr. Shapiro's issue around pragmatic information? Considering the position of industry, the consensus of this panel, and usage around access where I don't think anybody would argue that you're better off with cold-stored platelets than no platelets if it's a life and death situation. And considering that cold-stored platelets are now allowable within very constrained parameters, what would be the potential for using regulatory variance to encourage or to allow for

sort of pragmatic trials?

It would hopefully not detract from the randomized controlled trials. But is there a potential that FDA could be more liberal in terms of variances for those platelet suppliers who wish to incorporate cold-stored platelets in their inventory?

DR. RICHARD KAUFMAN: I think it's an interesting question. I certainly cannot speak for the FDA on that matter. I think that there's quite little experience at this point with using these things, at least in the civilian world. And for that matter, in the military experience, it's also, in the grand scheme of things, relatively limited.

I think that is a really good first step, getting some experience with this adaptive study and having a few hundred patients, at least, getting these things and having some comfort with the safety if nothing else.

My guess is they're probably fine. But I think it'll be really important to look for safety signals, unwanted clots, basically, from getting these

more activated cells. And my hope would be that, after getting some experience with one big initial study, then maybe others could follow in a more expedited sort of way. Sorry. Dr. Jones.

LCDR JEFFERSON JONES: I mean, I know that whole blood is not the topic to be discussed here. But given the public comments and the consensus on the need for action on preventing deaths, it seems that whole blood has a role to play here as well; particularly as there appears to be an increase in need of platelets and a decrease in potentially the number of available donors. But it seems that that should be taken into account as well.

DR. RICHARD KAUFMAN: Thank you. Let me ask if -- Dr. Morgan, any comments that you would like to make?

DR. CHARITY MORGAN: Yeah. I wanted to sort of echo what someone said earlier about the preliminary data that we've seen today. It was very encouraging, although it did have, in most cases, small sample sizes. But what I was struck by was the high

variability and the heterogeneity that we saw in some of the properties of the cold-stored products. I think what that indicates, to me, is that it's going to be difficult going forward to tease out the relationship between storage time and the performance of these products.

The last studies we saw were simpler and easier to interpret, but how they translate to the clinical setting is not entirely clear. And in contrast, Dr. Spinella presented a pretty complex design for a clinical trial. And maybe that level of complexity is needed to address some of those issues they're going to see in the clinical setting. But I do worry about, with such a complicated design, how interpretable those results are going to be.

So, I just think there's a lot of work to be done. I think it's going to be a much more complicated issue than we're expecting to see.

DR. RICHARD KAUFMAN: Thanks. I mean, I think the hope will be, for that study, that randomization and a reasonable sample size will take care of a lot of

underlying problems. But I think your concerns are appropriate.

One other thing that is well known to people in transfusion medicine but is maybe not as obvious to those from other fields, is that there really is an incredible variation from platelet unit to platelet unit, even just based on the donor and for that matter, the recipient.

The standard for judging the recovery and survival of a conventional platelet is actually done with orthologous volunteers. A fresh platelet gets drawn and labeled with one label, and then a platelet is treated or stored, and then whatever the test is or whatever the difference is and then labeled with a different radio label. And then the studies are actually done as dual radiolabeling experiments, in part to account for this variability that you see if you take one person's platelet and put it into someone else.

You got a little bit of sense of that from Dr. Cancelas' experiment as well where individuals were

sort of their own controls. Those were monkeys, but the same principle, I think, applies. So, yeah, it's a very complicated business. Dr. Ortel, do you have any comments you would like to make?

DR. THOMAS ORTEL: Yeah. I found, actually, all the presentations from the discussion to be very interesting. This was also a steep learning curve for me as well. I do like the idea of looking at the indications for use. And the FDA could approach this with a stratified approach where, clearly, some of these areas -- such as for the military, such as the remote rural areas in the U.S. -- there's a greater need for a product that you can get there.

So, providing some access or increased length of storage in these kinds of areas makes sense. Whereas, for other areas, such as prophylaxis to prevent bleeding as Dr. Triulzi described, actually is probably something that could be studied separately.

I mean, I like the clinical trial that was presented. But recognizing the length of time that it takes to get these types of trials done, the number of

years it took to get RECESS done, we're not going to -- it's going to take a while to get that data available for people. So, I think that prioritizing certain areas where the need is greatest and moving forward with those makes sense.

One of the other things that I would say that, what this also highlighted is just the limitations on the diagnostic studies that we've got, that we can use to assess a response to the administration of these kind of products.

I do think that what we do need, as Dr. Bennett said, more basic research as well as translational research in this area; just to better understand the differences in unique properties of platelets that are prepared by these two different ways. Even the different patient populations might benefit differently through the different approaches.

DR. RICHARD KAUFMAN: Thank you. I mean, I think, with respect to your last point, not to belabor this, but there are a huge number of in vitro assays that can be done. And a few can reasonably well

predict whether platelets will or won't circulate. But we don't really have a way of saying, okay, well, if we give this unit of platelets, it'll definitely stop the bleeding.

It would be a lot simpler and easier if we had a really great surrogate marker. If you could fix that in vitro, you would know you had something. So, without that, I just wonder if it would be useful, as some clinical studies are being done, to collect some correlative data using different assays that might have some value; and then see if there's correlation, at least, with solid clinical outcomes, such as decrease in bleeding.

DR. THOMAS ORTEL: I would agree with that completely. I think taking advantage of ongoing clinical studies to look at translational opportunities is critical as we move these forward.

DR. RICHARD KAUFMAN: And lastly, Dr. DeVan? Are you on the line? All right. I'll take that as a no. Dr. Stramer?

DR. SUSAN STRAMER: I just have two more quick

comments. Back to Dr. Spinella's trial, although it may be complicated and a long time to execute the study, what we will learn about cold-stored platelets, we will also gather more data on conventional room-stored platelets. So, I mean, no one mentioned the benefits also that we lack a lot of data on the platelets we use today. So, it'll be a good head-to-head comparison.

And then, as many had mentioned, that I just wanted to reiterate, that even if we do clinical trials that are complicated and take long periods of time, that shouldn't preclude additional variances from being granted by FDA, if they have merit, so we can move along a double-pronged track to gather more data in different venues.

DR. RICHARD KAUFMAN: Thanks. I think that's a good point. Dr. Bryant, you had previously made a comment to me about the label up versus label down. Would you like to --

DR. BARBARA BRYANT: In the reading, with the Terumo system, there's a comment that the bag was made

with one side smooth and one side textured. And I thought that was odd. Whereas the other system, it was, I think, PVC and it was smooth on both sides.

So, I was kind of curious, you know, when the comment was made that they saw more aggregation, if they had it one way or the other, label up and down. You tend to always put the label on the bag the right way -- the same way every time. So, I kind of wondered if that had something to do with how the bag was positioned. If the textured side was down, did you see more aggregates as opposed to if you flipped it over? So, that may be something real simple to take a look at. And maybe it was looked at. I don't know.

I've also been racking my brain; I've been in blood banking, not necessarily as a physician but as a medical technologist for over 40 years now. When I first started blood banking, we had platelets in the refrigerator, and we were moving to that new-fangled way of keeping them at room temperature. And I've been thinking today, I remember all the labels being up. But it was kind of interesting.

And I don't remember the difference in a blood bag once we made the transition; but that was back in the '70s and, I don't know, it's been a while ago. But I think there was some value in how we approached things then, and we've learned a lot over the years, of course. And I think these studies, taking a look at them and seeing; we've got so many new technologies out.

Also, in one of the studies that we read, they talked about the crisscrossing of whether you use INTERCEPT or InterSol, and which bags you used and what instrument you collected with. And we don't really know how much variation there is with all of that. We assume that there is and that you'd do each study each way, but there may be ways to do them where that may not be as important as we might think it is. But I think there's a lot to learn in some of these studies that we can do.

DR. RICHARD KAUFMAN: Thanks. Dr. Shapiro.

DR. AMY SHAPIRO: Well, I just want to note that Dr. Cap's -- or was it Colonel Cap's -- study was

the only one that mentioned the clot retraction and strength. And actually, it's an old test.

And I think it has tremendous value, actually, and maybe better than just platelet aggregation with specific agonists, which is fought with difficulties, including handling, how long it takes to get to the lab, how long they settle, and how the test is done. So, I think that's a really good test.

DR. RICHARD KAUFMAN: Thanks. I was wondering if maybe you or Dr. Bennett, or Dr. Tanaka, could perhaps comment on -- of the in vitro tests, are there other ones that you particularly think might be valuable in this setting?

DR. JOEL BENNETT: So, it looks like von Willebrand's factor binding, the 1b could be important. Ren Hao Li and his friends at Emory have been studying von Willebrand's factor binding, the 1b, and they have a peptide and an antibody that, I think, in animal studies improves platelet survival or recovery. So, that would be something to look at.

With regard to clot contraction -- actually,

we sort of studied that in a way in that, if you stimulate platelets they activate calpain and calpain perturbs the platelets out of skeleton. And it looks like lot of things inside the platelet get cleaved after they get stored. We had an ash abstract looking at Kinlen (phonetic), for example.

So, things happen when platelets sit around for a while, even in the cold, that may not necessarily be good for them, that need to get looked at.

DR. RICHARD KAUFMAN: Well, thanks. And then, of course things get more complicated too. We've mainly been talking about platelets collected as they normally are and then stored in the refrigerator. As one of the speakers brought up, there's also, frankly, other potential products -- lyophilized frozen platelets, DMSO-stored platelets that are frozen.

There are actually artificial platelets that some groups have tried to develop; so you can take lipid micelles and put in functions to bind to, for example, von Willebrand's disease -- von Willebrand factor. And how you evaluate those is going to vary,

simply by their -- really, by their nature.

Ultimately, for me, what really matters is how well are they working in people? So, it may be great if we could ultimately define kind of an in vivo gold standard -- maybe heart surgery. But otherwise, how to look at them, I think, is going to be very, very different depending on exactly how they're made.

DR. JOEL BENNETT: No, you're right. I mean, a lot of animal models don't necessarily mimic what happens in people. So, all these laser injury models in mice and that kind of business, I don't know how well they correlate with what actually happens when you transfuse something. I mean, is lacerating a liver in a rat the same as giving platelets to somebody who's bleeding from cardiac surgery? I don't know. So, I think that's another variable.

DR. KENICHI TANAKA: I personally use a TEG/ROTEM type approach, at least during the surgery for cardiac patients. And what it does is usually we can exclude low fibrinogen; because if you have low fibrinogen, even if you have a platelet adhesion

aggregation, you may not eventually make a clot. So, hemostasis doesn't get achieved.

So, I think it's a multi-model approach. And sometimes I feel that focusing on a single intervention is very difficult, because a lot of times we have to give multiple agent. And then the risk associated with multiple agents -- for example the INTERCEPT platelet may be more procoagulant. Then we have to modify other products, you know, what we are currently giving.

So, those are unknown questions, and it's very difficult to monitor. And I do think you have to combine multiple monitors to look at the different aspects of a hemostasis. So, you know, the adhesion type flow chambers and then fibrinogen assays probably have to be combined to look at the real hemostasis. I don't think there's a single device that would show us hemostasis in any patient.

DR. AMY SHAPIRO: I think the problem with the testing is the setting. So, in trauma, it's an uncontrolled setting. So, you can look at a product and you can test a product, but there's tremendous

dilutional effect in the rate of bleeding and what else you're putting in there.

And the ability to do that testing in a field or when you're picking a patient up, as compared to cardiovascular surgery where it's fairly controlled; you know the hemoglobin, the patient's heparinized, they're going on a pump and you're using a known modality to look at specific parameters that you can correct in that setting. So, I don't think there is one test, based upon the setting, for the individual.

DR. RICHARD KAUFMAN: Dr. Bryant.

DR. BARBARA BRYANT: I just want to add something to what Dr. Tanaka said. We don't really have a lot of experience giving activated platelets in the operating room. And with these cold-stored platelets that are activated, we may find ourselves practicing medicine a little bit differently. You know, you may not need the two units as you're coming off the pump. If you have a problem, maybe one would just do fine and you'd be done.

So, I think there's a lot going to be learned

as we do the clinical studies.

DR. RICHARD KAUFMAN: Dr. Verdun.

DR. NICOLE VERDUN: I want to thank the committee for all of their thoughtful comments. I just wanted to add an additional comment that I would love for everyone to comment on -- or not everyone, but for some of you to comment on.

But I think that one of the questions that FDA is considering is, what is the data needed to be comfortable with having cold-stored platelets in every hospital in the United States, right? So, I mean, we talked a little bit today about benefit and risk in certain populations where you have remote access issues, where you have military that need the product.

But what is the data that's needed that you would be comfortable having cold-stored platelets in the middle of a hospital in Chicago or New York? And do we have that data, or do you see some of the things that were presented today that could give you that data? So, just a little bit more discussion on that would be actually helpful. Thanks.

DR. RICHARD KAUFMAN: Well, let me ask our hematologists. So, not to put anyone on the spot, but we've talked a fair amount about the challenges of assessing hemostatic efficacy. But I think I would like to circle back and talk a little bit about safety.

So, one of the issues is that you often don't see adverse events unless you're really looking for them. So, in the proposed study or in other studies, what would you like to see to be comfortable that you weren't causing unwanted venous or arterial thrombi by giving cold platelets?

DR. JOEL BENNETT: Well, so -- thanks. Well, I mean, you can assess things in people, for example. You can measure -- well, people bleeding, it's a problem, I guess, D-dimers and those kinds of things. But I guess there are ways to look at coagulation -- well, once you get things stabilized, coagulation activation. One could do ultrasounds of people's legs if that were a concern.

That's sort of a hard question. With regard to things that I would be concerned about, as far as

using cold-stored platelets, I think it would be important to figure out the right way to make them. And that might get around some of the questions about activated platelets.

So, I would like to see that if somebody were making platelets that we're going to move for 14 days in Texas, doing it the same way as they were making them in Philadelphia, for example. And I'd sort of like to know the right way to do it, you know? You know, if 20 percent of the platelets all had aggregates in it, that would sort of bother me.

So, I think that's important. With regard to clinical outcomes, you know, I guess being a doctor is important, and you can look for things that cause possible problems.

DR. RICHARD KAUFMAN: Thanks. Dr. Kindzelski.

DR. ANDREI KINDZELSKI: Coming back to the question from FDA, I think nothing prevents --

MS. CHRISTINA VERT: Can you speak up please?

DR. ANDREI KINDZELSKI: Sorry. Coming back to the question from FDA, I don't think that, currently,

there is anything preventing having a hospital in Chicago or New York to have cold-stored platelets. It's the problem for the middle of nowhere in Texas to have cold-stored platelets.

With three days cure and three days storage, they can be available in big centers. But those are small hospitals that are suffering, I think, in this point of time.

DR. AMY SHAPIRO: I think if, in the middle of Chicago, if there are trauma patients with acute hemorrhage, you could extend the length of cold-storage platelets at this point in time based upon the data to make it available. As long as they're used for the appropriate indication, and as long as data is reported about any adverse events that you would want to collect related to that.

Just when you're talking about testing, it did bring up to mind, there are some places where they're looking at thrombin generation assays that can be done on the surface with a prick; and it goes through microfluidic, and it's done in real time, and it's very

fast.

So, things like that, when they become available, could be very useful. It's years away.

LCDR JEFFERSON JONES: I think I'd just like to agree that less than a black or white, is it ready now or not, that it'd be much more comfortable that it could be started anytime, conditional on reporting adverse events.

Dr. Spinella presented secondary outcomes of thrombonic events and transfusion-associated serious adverse events which, I think, is a good model for -- if there's a way for those that are on the earlier end, a kind of cautious approach that those that are earlier to adopt, that there would be a reporting system in place could be a way that would be more comfortable.

DR. KENICHI TANAKA: I think major confounder in the massive transfusion or patients who get platelets, I think it's the red cells. Because when you look at the cardiac surgery, probably those who get platelets, 60 to 80 percent of the patients all get red cells. And then there's probably two or three units.

Then, in addition to those, they get platelets.

So, it's very hard to look at the side effects or thrombotic potentials related to platelet intervention because those patients tend to get incubated for several days after surgery. And by itself, a DVT risk is much higher. You actually need a lot of data to dissect all of these details. So, I think that's a challenge.

DR. RICHARD KAUFMAN: Dr. Perez.

DR. ELENA PEREZ: So, coming from a non-hematologist with no blood bank experience, I'm just wondering if, because of everyone's initial nervousness about maybe spreading the time beyond 3 days, what protocols are in place or what qualities about the product -- is there a safety checklist before a product is released that it should meet and maybe give some guidance to people out in the field about when is a product right to be released from the blood bank and used as a cold-stored platelet?

I don't know if my question makes sense. Kind of like a safety checklist. Like if there's aggregates

present, or if there's this many platelets in the product before it's released to be used.

DR. RICHARD KAUFMAN: Yeah. I mean, I think maybe that's something, I don't know, maybe James Stubbs could comment on. I think that if a platelet had a bunch of big aggregates in it, none of my blood bank techs would want to issue it, for sure.

DR. ELENA PEREZ: Or are there other --

DR. RICHARD KAUFMAN: Yeah, are there other sort of QC measures that could be used? Well, one of the challenges is that a lot of the things that can be used for room temp platelets really doesn't seem to change that much with platelets.

I don't know that pH, for example, is going to be all that valuable for cold-stored platelets. Maybe at an extreme end, 21 days, 28 days, something like that, but -- so, yeah, I'm not sure. It sounds like the ones that get discarded now are frankly ones where just big aggregates are formed visually.

DR. THOMAS ORTEL: Richard?

DR. RICHARD KAUFMAN: Yeah?

DR. THOMAS ORTEL: This is Tom. I'm just curious, I'm not a blood banker. But I'm curious, the concept of cold-stored platelets isn't going to create a new source of platelets. So, we still have the donor issue. And I'm assuming that within any institution, if they started preparing "don't" cold-stored platelets, they would have fewer room temperature stored platelets.

So, this would be something that, at different institutions, they would have to decide if they really needed to have a reservoir or a pool of platelets that were being cold-stored. How would you approach this at your place?

DR. RICHARD KAUFMAN: Yeah, it's a great question. I was always under the impression that 80 percent of our platelets were going for prophylaxis. That may be true at our institution; we support a large cancer center.

But it does look like for the country, at least, based on the data that Dr. Triulzi presented, that something like half go for prophylaxis and half go

for therapeutic use, that is, for bleeding. I guess you'd have to look at it at your own place and try to figure out, well, how big is our trauma service, or how big is our CT surgery service? And how often would we expect to be using cold versus room temp?

Because you're right. If we were to do it tomorrow -- let's say that it were allowed that you could keep platelets at either room temperature or in the cold for, let's say, five days. If we did that with our inventory and just split it in half, it would definitely be problematic in that we certainly wouldn't have enough platelets at room temperature to be able to supply our, at least, 25 a day that are going for the hematology oncology patients.

So, I think it would have to be sort of figured out on a hospital-to-hospital basis. And certainly, at the beginning, it would be particularly difficult because there'd be a lot of education for the clinicians; and you want to not tie up a big part of your inventory and then have them not be used. Dr. DeMaria.

DR. ALFRED DEMARIA: I think another aspect of that would be discard of product. I was just looking at the Massachusetts data, and about 30 percent of the platelets in small hospitals are discarded, about 25 percent in the medium-sized hospitals. It goes down to 7 percent in the big hospitals. And if cold-stored platelets could help the medium and small-sized hospitals to reduce wastage, then it would help with the donor pool.

DR. RICHARD KAUFMAN: Yeah, I think, potentially. It all would depend on where they're going. The bigger hospitals, particularly the ones supporting cancer centers, have relatively low discard rates, even with the 5-day platelet. For the country, though, I don't know the exact numbers. I think it's, I don't know, 10 or 15 percent, maybe more of all platelets get discarded currently just from that data.

DR. ALFRED DEMARIA: They're much higher than that in rural --

DR. RICHARD KAUFMAN: Much, much higher if you're -- yeah, to the point where, frankly, some of

the community hospitals that don't issue a lot of platelets, they just don't even have them. They have to get them from Red Cross or that sort of thing. And it creates some really uncomfortable situations, as you can imagine, with an occasional trauma patient that comes in.

Well, let me ask the group. How would people feel about switching from Day 3 to Day 5 cold-stored platelets today, based on the data that we currently have? I wouldn't say that's my top number, but I would say that that's -- most places are using 5-day platelets. You can use seven with some extra bacterial testing, but five is sort of the current standard.

Five is already an incredibly difficult shelf life, because it's effectively a 3-day shelf life. And so, it's already incredibly hard for donor centers and for hospitals to supply patients with platelets just for anything, even just for prophylaxis. But yeah.

DR. AMY SHAPIRO: But if you're talking about active bleeding, not prophylaxis, why not consider 14 days?

DR. RICHARD KAUFMAN: Well, I think that you could. The question is -- and this is always really tough -- how far do you want to go without solid clinical studies? Which I think will be coming. But I think it's a difficult question, when do you make a clinical or policy change when the data are really limited?

DR. AMY SHAPIRO: But if you talked about this from a pragmatic standpoint, if you have 5-day storage to get it out to a remote area, and to have it available for trauma and acute bleeding, you've got a day and a half where it's there. You know? You're going to waste the product. So, I think, to really get it to these areas, you have to think about 14 days.

DR. RICHARD KAUFMAN: So, that can be the question too. It's already been done for the military. It's been done. It's happening.

DR. AMY SHAPIRO: Um-hm. Norway, they're going to 21.

DR. RICHARD KAUFMAN: All right. Dr. Bennett.

DR. JOEL BENNETT: At our current state of

knowledge, using 14 days stored platelets in the cold?

DR. RICHARD KAUFMAN: It's a great question.

DR. JOEL BENNETT: I'm not sure our people would -- they'd do the same thing, I think, you could say. And maybe not yet.

DR. RICHARD KAUFMAN: I think if I were dealing with the sorts of issues that Dr. Cap has described in far forward regions, with those sorts of constraints, sure. In my hospital today, in Boston, I'd probably want to be a little more conservative and wait for some more data.

DR. KENICHI TANAKA: Yeah, I agree. I would use five to seven days as a cutoff at this point. But I would consider extending it to 14 with the future study results. But I agree with you. In the rural, difficult to reach area, maybe it's a consideration. And maybe that's also variance, you know?

DR. RICHARD KAUFMAN: Dr. Stramer?

DR. SUSAN STRAMER: Yeah, it could be a variance. That's what I mentioned today. And if platelets don't move interstate, within the state, the

hospital can do what they want. So, they could already extend.

I mean, I think the question really is, what are the QC parameters to release a cold-stored platelet? I think that's what Dr. Verdun was asking; what parameters would we use to make sure the platelet was safe and efficacious? If that's what I'm understanding.

DR. NICOLE VERDUN: More of what I was asking was, what kind of studies would be needed to support widespread cold-stored platelet use across the United States for storage up to what has been discussed today, up to 14 days? And there was even one presentation where -- a discussion of up to 21 days. But that was my question.

DR. JOEL BENNETT: So since -- for me, anyway -- since in vitro studies aren't going to help you, I think you need clinical trials. Right? You know, you can't throw some platelets in an aggregometer and say these are going to work when you give them to somebody.

So, I think you need -- if you can make what

you think is a safe preparation, that seems to have active platelets in it, if you give it to people and it works just fine then I would feel okay. Right?

DR. RICHARD KAUFMAN: Dr. Tanaka, and then --

DR. KENICHI TANAKA: A good design might be a pragmatic stepped wedge design, so you can turn one hospital into a cold-stored platelet center. And then, each month, you can increase a number of hospitals.

Then you can do before and after data analysis; so, you can do it for, you know, Texas, somewhere in a rural place. And you can get bunch of rural places, you can use that cold-stored platelets. Look at the clinical outcomes in OB or intracranial bleeding, for example.

DR. JACK STAPLETON: I would agree. I think, from a pragmatic standpoint, how much data do we have on warm platelets? And we have 3-day storage that were acceptable now. So, the question is, can we expand the access and monitor for safety, it seems to me.

DR. RICHARD KAUFMAN: Dr. Jones?

LCDR JEFFERSON JONES: I agree that possibly a

phased approach where particularly those hospitals -- it might be difficult to get sufficient numbers -- the hospitals that are greatest need now, that if it's between no platelets and 14-day cold-stored platelets, that that could be a potential first. Get the highest priority at hospitals on a sort of variance.

And sorry if I -- the regulation part of that might be incorrect. But if those were a variance to get those highest priority hospitals first with a surveillance of those areas could -- pragmatically, to try and save lives as soon as possible.

DR. RICHARD KAUFMAN: Dr. Bryant?

DR. BARBARA BRYANT: I think pretty much it's been covered. But when you asked the question about five days, if we went out to five days, you'd only gain two days on the cold platelets. Because right now, we're okayed at three.

So, you'd go out to five. That doesn't really help solve any problem, because I already have 5-day platelets -- actually, 7-day platelets -- at all my locations, even the ones that are far away from us.

So, that doesn't really help us there. Moving it out to the 14 days to give us time to use those platelets decreases the wastage.

There are issues about dual inventory. And even though some of my far-reaching hospitals that may be 60 miles away, that I would love to put a cold platelet out there, they do have patients that show up for prophylactic transfusions. So, am I going to have to keep a 7-day platelet out there and a cold platelet?

But those are things we'll all work out as we work through this. But I think, to get to the 14-day platelet, I think there needs to be some studies, just to show safety between, let's say, that 5-day mark on up to the 14-day mark for the cold platelet.

DR. RICHARD KAUFMAN: All right. Dr. Eder.

DR. ANNE EDER: We just want to clarify one point. That as Mayo did, you do still need a variance to do this when you're doing it in the state. So, while we would consider variances, it's not correct to say that you can do whatever you want when you distribute the platelets.

DR. AMY SHAPIRO: I think what I was suggesting was developing a method for a fast-track variance for areas of great need, because it appears that the variance process takes quite a bit of time. Is that incorrect? It's incorrect?

DR. ANNE EDER: So, the regulations don't have a timeline for variances, but we try to approve them within a reasonable amount of time. Some variances are very complicated, especially if they're the first ones submitted, and then they take longer.

So, we try to consider them within a reasonable amount of time, usually within less than 12 months. So, with these variances, that's why we're -- I'm sorry.

DR. AMY SHAPIRO: Well, I think, when you're talking about people dying in remote areas, and dying from hemorrhage, 12 months is a long time.

DR. ANNE EDER: What I was trying to say was this conversation has helped a lot and will help expedite variances. There isn't a need to have a fast-track variance. We can approve variances within a

reasonable amount of time.

DR. RICHARD KAUFMAN: All right. Dr. Jones.

LCDR JEFFERSON JONES: Do we have any idea what the expected timeline -- sorry if I missed this -- of the proposed study, the last presentation of the day? Are we talking about three to five years before data is known?

DR. RICHARD KAUFMAN: I don't think we know. Dr. Triulzi's nodding his head. I think that it's still at a relatively early stage. Let's say five years.

LCDR JEFFERSON JONES: Yeah. I mean, it seems something to take into account. I think part of me says we at least want to wait for that data before doing any widespread intervention. But -- right? We do have, it appears, an urgent need that, perhaps, before that data is known, doing this kind of -- particularly for high-need areas, making these variances easy; perhaps based on ones that have already been passed, and getting some sort of protocol available to those to make it easier to file and get

them approved quickly.

DR. RICHARD KAUFMAN: Yeah. I think that may be a reasonable path forward. That is a compromise between wanting to have some solid data versus addressing a more urgent need, as has been done with the military. So, I think that that seems logical.

All right. If there are no further comments, I think I would like to bring this meeting to a close. I really want to thank the speakers today. It was a really interesting session. And I also would like to very much thank the committee members for their thoughts about this incredibly complicated issue. So, thanks very much.

[MEETING ADJOURNED]