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Center for Biologics Evaluation and Research (CBER)
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OPEN PUBLIC MEETING

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

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CALL TO ORDER AND INTRODUCTION OF COMMITTEE

DR. KAUFMAN: My name is Richard Kaufman. I'm the Chair of BPAC. I'd like to welcome members of the committee as well as participants that we'll be hearing from today, members of the public, as well as the audience that may be joining by webcast.

Just to start out, I would like to have the members of the committee introduce themselves. Can you please provide your name, institutional affiliation, as well as your expertise? We'll start with Dr. Schreiber.

DR. SCHREIBER: Martin Schreiber, Oregon Health & Science University, General Surgeon with an interest in novel blood product research.

DR. BLOCH: Hi. Evan Bloch, the Associate Director of Transfusion Medicine at Johns Hopkins. And my interest is transfusion-transmitted infections.

DR. STAPLETON: Jack Stapleton, Infectious Disease Professor at University of Iowa. I'm Director of the University Viral HIV Clinic, and my laboratory

does HIV flavivirus co-infection work.

DR. DEMARIA: Al DeMaria. I'm a Medical and Laboratory Consultant at the Massachusetts Department of Public Health in the Bureau of Infectious Disease and Laboratory Sciences, and formally State Epidemiologist for Massachusetts and Medical Director of that bureau.

DR. BRYANT: I'm Barbara Bryant from the University of Texas Medical Branch in Galveston, Texas. My interest is transfusion medicine. I'm a Transfusion Medicine Medical Director.

MR. TEMPLIN: Hi, I'm Christopher Templin. I'm the patient rep, personally in Birdsboro, Pennsylvania.

DR. HOLLINGER: Blaine Hollinger. Baylor College of Medicine in Houston. Professor of Medicine in molecular virology and epidemiology, and interest in bloodborne pathogens.

DR. DEVAN: Hi, Michael DeVan. I'm the Medical Director for transfusion services at Walter Reed National Military Medical Center.

DR. SHAPIRO: I'm Amy Shapiro. I'm the Medical Director of the Indiana Hemophilia and Thrombosis Center. My interest is hemostasis and thrombosis and benign hematology.

DR. ORTEL: Tom Ortel, Chief of Hematology at Duke. My interest is hemostasis and thrombosis.

DR. LEWIS: Roger Lewis. I'm the Chair of Emergency Medicine at Harbor-UCLA Medical Center in Los Angeles. My interest is in biostatistics clinical trial design.

DR. BASAVARAJU: Sridhar Basavaraju, Director of the CDC Office of Blood, Organ, and Other Tissue Safety.

DR. KAUFMAN: And I'm Rick Kaufman. I'm the Medical Director for the Blood Bank at the Brigham and Women's Hospital. My interest is in transfusion medicine.

I'd like to also introduce two individuals on the phone. Dr. Stramer, are you there?

DR. STRAMER: Yes, I am. I'm Susan Stramer. I'm the Vice President of Scientific Affairs at the

American Red Cross. My interests are infectious diseases and testing.

DR. KAUFMAN: And Dr. Chitlur?

DR. ATREYA: We'll introduce her when she comes.

DR. KAUFMAN: That's fine. So, at this time, I'd like to ask Dr. Atreya to please read the conflict of interest statement.

CONFLICT OF INTEREST STATEMENT

DR. ATREYA: Good morning. This is Prabha Atreya, Designated Federal Officer for the advisory committee. The Committee Management Specialists for this meeting are Ms. Joanne Lipkind and Natalie Mitchell. The Committee Management Officer for this is Marie Keller (phonetic), who assisted in the Conflict of Interest screening and also making travel and/or meeting arrangements. On behalf of FDA and Center for Biologics Evaluation Research and the Blood Products Advisory Committee, we would like to welcome you all. Dr. Judith Baker is the Consumer Rep and she will be here shortly.

The press or media person are here, that's Megan McSeveney. She's in the back. Also, Paul Richards in the audience if you have any media questions. I also would like to remind everyone to please check your pagers and cell phones. Please make sure they are either turned off or in silent mode. Also when you make comments, please first state your name and speak up so that your comments are accurately recorded for transcription, and for the benefit of the FDA staff here in the room, and members of the public and those listening via webcast.

Now, I'll proceed to read the Conflict of Interest Statement. The Food and Drug Administration is convening today, March 21st, 2019 for the 120th Meeting of the Blood Products Advisory Committee, under the authority of the Federal Advisory Committee Act of 1972. Dr. Richard Kaufman is serving as the Chair of the meeting for Topic III.

Today, on March 21, 2019, for Topic III, in open session, the committee will discuss blood donation policies regarding men who have sex with men, MSM. The

committee will hear an update on donor deferral policies and donor HIV Risk Questionnaire study. Also, an overview of the Transfusion-Transmitted Infections Monitoring System. In addition, the committee will hear presentations and discuss pathogen reduction of platelet donations as an augmented procedure. The topic is determined to be a Particular Matter of General Applicability.

Presenters and speakers will provide data on various products or strategies that serve only as examples for the committee to have a scientific discussion while considering various classes or products or strategies related to the topic.

This meeting is not being convened to recommend any action against or approval of any specific product or strategy, or to make specific recommendations that may potentially impact any specific party, entity, or individual in a unique way.

Similarly, this meeting will not involve approval or disapproval of labeling requirements, post marketing requirements, or related issues regarding the

legal status of any specific products and any discussion of individual products will only serve as an example of the product class.

With the exception of industry representatives, all participants of the committee around the table are appointed as Special Government Employees, or as regular government employees from other agencies. Hence, they are subjected to federal Conflict of Interest laws and regulations.

The following information on the status of this advisory committee's compliance with the Federal Ethics and Conflicts 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. This Conflict of Interest statement will be available for public viewing at the registration table.

Related to discussions at this meeting, all members and SGE consultants of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their 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, grants, CRADAs, teaching, speaking, writing, patents, royalties, and primary employment.

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 interest conflicts when it is determined that the agency's need for the particular individual's service as a subject matter expert outweighs the concern related to his or her potential conflict of interest. However, based on today's agenda and all financial interests disclosed by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code 208.

Dr. Sue Stramer is currently serving as the industry representative to this committee for Topic III. She's Vice President of Scientific Affairs at the

American Red Cross. Industry representatives act on behalf of all related industry, and bring general industry perspective to the committee. They are not appointed as special government employees and are non-voting members of the committee. Hence, industry representatives are not screened, and do not participate in the closing sessions, and do not have voting privileges.

Dr. Judith Baker is serving as the consumer representative for this committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting-members of the committee, and hence, do have voting privileges. They do participate in the closed sessions if they are held.

Mr. Christopher Templin is serving as the Temporary Patient Representative for Topic III of this meeting. He’s serving as a member on the board of the Directors of The Committee of Ten thousand. Patient representatives are appointed as special government

employees and hence are screened and cleared prior to their participation. They are voting-members of the committee and hence do have voting privileges. They do participate in the closed session if they are held.

Dr. Blaine Hollinger serves the committee as a temporary voting member for all topics of the meeting, including today's topic. He's the Director of Eugene B. Casey Hepatitis Research Center, Baylor College of Medicine. And he brings his vast expertise in bloodborne infectious diseases for the benefit of the committee.

With regard to external speakers, Dr. John Brooks is employed by the CDC, and serves as one of the speakers for this meeting under Topic III. Dr. Brooks is a regular government employee and has been screened and cleared prior to his participation.

At this meeting, there may be other regulated industry speakers or other outside organization speakers making presentations. These participants may have financial interest associated with their employer and with other regulated firms. FDA asks, in the

interest of fairness, that they address any current or previous financial involvement with any firms whose product they may wish to comment upon. These individuals were not screened by the FDA for conflict of interest.

FDA encourages all of the participants to advise the committee of any financial relationships that they may have with any firms, its products, or if known, the direct competitors.

We would like to remind the members and consultants and other participants, that if the discussions involve any of the products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from such involvement, and the disclosure will be noted for the record.

This concludes the reading of the Conflict of Interest statement for the public record. At this time, I would like to hand over the meeting to Dr. Kaufman. Thank you.

DR. KAUFMAN: All right. Well, thanks again. Again, I would like to thank the committee members for participating. I think this should be an interesting discussion today. Really, it's a meeting about trying to strike an appropriate balance between considerations of patient safety and considerations of social justice. So, we'll be thinking about ways that it may be possible to maintain the current level of safety of the blood supply while potentially increasing access to blood donation.

The Topic III is blood donation policies regarding men who have sex with men, or MSM. For this morning, it's Topic III A, an update on donor deferral policies and donor HIV Risk Questionnaire study. Our first speaker is Dr. Anne Eder from FDA, who will be talking about blood donation policies regarding MSM.

INTRODUCTION TO THE TOPIC

DR. EDER: Thank you. Good morning. My name is Anne Eder. I'm the Acting Deputy Director for the Office of Blood Research and Review at CBER. As Dr. Kaufman said, our topic for today is blood donation

policies regarding men who have sex with men, which I'll abbreviate as MSM.

In the morning, you'll hear an update on donor deferral policies and a proposal for an HIV Risk Questionnaire study. In the afternoon, you'll hear a proposal for an alternative procedure to donor deferral with the use of pathogen reduction and platelet donations from MSM. I'm going to give a brief history, provide background on the MSM deferral policies. I'll introduce the topics and then the speakers and set up the questions for discussion. There are no voting questions today. We're asking the committee to discuss around the topics that we introduce.

FDA is responsible for protecting the safety of the blood supply, which depends on the implementation of donor screening measures based on the available evidence. The AIDS crisis in the 1980s and the recognition that HIV could be transmitted through blood transfusion or plasma derivatives had profound effects on the US blood system.

This slide takes liberty to condense 20 years

of history onto one slide, so forgive me. But in 1982, the first cases of AIDS from blood transfusion and plasma derivatives were recognized. Although most cases of AIDS occurred in MSM and other risk factors, the recognition of this association with risk factors led FDA to make recommendations early in the ‘80s for donor education about signs and symptoms of AIDS and asking MSM and other at-risk donors not to donate, excluding them from donation.

The identification of the virus, first as HTLV-III, and now, of course, HIV, led up to the first donor screening test for HIV. The antibody test was licensed in 1985. But by the time this test was implemented, thousands of transfusion recipients and people with hemophilia would die from AIDS. In 1992, FDA issued the 1992 Memorandum, which made recommendations for blood donation and direct questioning and indefinite deferral of men who have ever had sex with another man, even once, since 1977, or the MSM Indefinite Deferral Policy, which is abbreviated on the slides.

The 1990s would see improvements in technology. In the subsequent generations of HIV, serological tests became increasingly more sensitive. The most sensitive test, nucleic acid testing, was introduced in 2000. Fast forward to present day, an MSM are still a risk group. About 1.1 million people are living with HIV. An estimated 38,700 were infected in 2017. This number has been relatively stable since about 2012. While MSM comprise about 7 percent of the US male population, MSM accounts for over 60 percent of new infections overall, and over 80 percent of infections in men, as you can see on this pie chart.

You'll hear much more today about HIV epidemiology in the session this morning. You'll also hear more about FDA regulation of the blood supply, which is summarized on this slide, which depends on multiple layers of protections. First, donor education. Blood centers must provide explanation about readily identifiable risk factors, closely associated with exposure to relevant transfusion-transmitted infections, or RTTIs. Today, we're talking

about HIV.

They must screen donors with donor history questions and defer those with behaviors associated with RTTIs. Donations are tested. Blood centers must keep donor deferral records so as not to recruit donors who are ineligible, and have procedure for quarantine, recall, and lookback on unsuitable components. Evidence that donor education and donor screening are effective, or at least indirect evidence that donor screening is effective, is shown on this slide.

This slide shows HIV and hepatitis rates in blood donors versus the general population -- the rate per 100 thousand for hepatitis B, hepatitis C, and HIV, which we're focusing on today. The rate in the general population, shown in gray, among all donations in red, and among repeat donations in yellow. So, you can see, for HIV, the selection pressure removes about 90 percent of the risk upfront before screening. If the education and screening had no effect, the rates would be more similar in the general population compared to blood donors.

So why is this important? Why do we still ask questions when we have sensitive tests? The screening tests are extremely sensitive, but they are still not perfect. If a donor population has a higher incidence and prevalence of HIV, there will be a greater chance that more donations will be in the window period and potentially infectious. And this slide provides a schematic illustration of that window period and transfusion risk. The window period is that interval of time after infection. This slide shows the concentration in blood of the different tests and the time after infection.

In the window period, the tests are negative, but the virus can still be transmitted through blood. The antibody test has a window period of about 3 weeks. The p24 antigen test, when it was introduced, shortened that window period. But it was soon replaced with nucleic acid testing, which is more sensitive.

Depending on which test is used and whether testing is performed in mini pools or individual donations, the window period today has decreased to 7

to 10 days. But still, even if the virus is undetected, blood transfusion can still transmit HIV to patients.

Since NAT was introduced in 2000, FDA has had public meetings, workshops, and advisory committees to revisit the deferral. This slide highlights key meetings and their outcomes.

In June of 2012, an HHS Advisory Committee on Blood Transfusion and Tissue Safety concluded that the indefinite deferral policy was suboptimal but recommended further study to inform a possible change of the indefinite deferral policy. In September 2010, the HHS Blood, Organ, Tissue Safety, or BOTS working group, proposed to design three research studies and an operational assessment of quarantine release errors, which I'll show on the next slide.

In November 2014, the results of these studies were presented to the committee, which considered alternative deferral policies such as eliminating the deferral policy altogether, recommending shorter time-based deferrals, or individual risk-based assessment,

or pretesting. The committee voted 16 to 2 in support of a policy change from the indefinite deferral policy, to the 12-month deferral policy, and emphasized the importance of having a system for monitoring transfusion-transmissible infections in blood donors.

The supporting evidence for that decision is shown on the next two slides. In a study of participants' understanding of the pre-donation history questionnaire, volunteers were recruited from the community -- and MSM were preferentially recruited -- to evaluate how donors answered the questions. And donors -- sorry, to understand how the participants in the study understood the question. The studies showed that people understand the questions, but they answered the questions through the filter of, is my blood safe? There was no difference in MSM and non-MSM patterns of response.

The Retrovirus Epidemiology Donor Study, or REDS-II, the study of risk factors for retrovirus and hepatitis virus infections, looked at about 196 HIV-positive blood donors and evaluated for their risk

factors. So, these were donors who were found to be infected with HIV. MSM had a 60-fold increased risk and was a leading independent risk factor for HIV infection among blood donors. Having multiple sexual partners, in contrast, was a 2.3-fold increased risk.

The REDS-III Blood Donation Rules Opinion Study, or BloodDROPS, was a confidential survey of current blood donors -- so these are current blood donors, men who are donating blood -- and found out about 2.6 percent of male donors who are currently donating report MSM. About half of those who were noncompliant indicated, under the indefinite deferral policy, that they would adhere to an MSM-12 policy.

An operational assessment of quarantine release errors was also considered. Quarantine release errors is the erroneous release, or the mistaken release, of an unsuitable component before testing is completed or other criteria are met and unsuitable components are distributed. With today's computer systems and blood systems, the risk of a quarantine release error related to a test result is very low.

Finally, the Australian Red Cross was the first blood center to report their experience in changing from a 5-year deferral to a 1-year MSM deferral. They reported their experience before and after the change, reporting on 5-year time periods and over 4 million donations in each, before and after the change. They saw no difference in the rate of HIV-positive donations. They also performed a confidential survey and found a very low rate of MSM undisclosed risk of about 0.2 percent.

So, in 2015, FDA released final guidance that moved -- that changed MSM from an indefinite deferral to a 12-month deferral. This aligned it with other deferrals for possible sexual exposure to HIV. The other risk groups, or the other indefinite deferrals, did not change. The other 12-month deferrals in this guidance document did not change. Today, we're focusing on the MSM and MSM-related deferrals. FDA is committed to ongoing evaluation of the MSM 12-month deferral policy and potentially advancing the policy based on the available scientific evidence.

To this end, in July 2016, a public docket requested comments and supporting scientific evidence regarding potential blood donor deferral policies and asked for comments on alternatives to time-based deferrals and the feasibility of individual risk assessment strategies. The responses were mixed, but a notable cross-section of hospitals, plasma users, blood centers, and advocacy groups commented at that time that data were not yet available to consider a further change of the MSM 12-month deferral policy.

In this morning's session, you're going to hear about what other countries do with respect to MSM deferral policies, and the countries that use time-based deferral or shorter time-based deferral than the US uses, countries that use risk-based or individual risk assessments, and countries that use alternative measures, such as quarantine and retest.

This morning, you're also going to hear an update of the Transfusion-Transmissible Infections Monitoring System, or TTIMS. TTIMS was launched in 2015. It's sponsored by FDA, NHLBI, and HHS. The

collaboration comprises more than 60 percent of the US blood supply, with the American Red Cross, Vitalant, the New York Blood Center, and OneBlood. TTIMS collects and analyzes data on the incidence and prevalence of HIV, hepatitis B, hepatitis C, among blood donors, and collects demographic variables, behavioral risk factors, and biorepository samples from seropositive donors.

This morning, you're also going to hear about an HIV risk factor questionnaire, which is a research study to assess MSM risk-based questions as an alternative to minimize HIV risk, at least as effectively as the current deferral policy. This is an FDA-sponsored research study developed through collaboration with the Blood Equality Working Group with representatives from advocacy organizations, community health centers, blood collectors, and public health agencies.

The speakers and topics for this morning are Dr. Mindy Goldman, who will discuss global developments in MSM deferral; Dr. John Brooks, who will discuss the

epidemiology of HIV in the US; Dr. Alan Williams, with FDA and the Office of Biostatistics and Epidemiology, who will give an update on the Transfusion-Transmissible Infections Monitoring System; and Dr. Barbee Whitaker, with FDA in the Office of Blood -- Biostatistics and Epidemiology, who will present the HIV risk factor, or HRQ, study.

Again, we're not asking you to vote today, but we're asking you to discuss or comment on what has been learned from implementing other MSM policies internationally, such as risk-based deferral methods or quarantine and retest for plasma, and how this information can be used to inform the current US MSM deferral policy. We're also asking you to comment on questions proposed for the study in the HIV Risk Questionnaire and whether there are any additions or modifications to this study in order to best identify behavioral risk questions to predict the rest of HIV transmission in the MSM population.

So, with that, I conclude.

DR. KAUFMAN: Thank you, Dr. Eder. I would

like to introduce to our next speaker, Dr. Mindy Goldman from Canadian Blood Services.

Actually, before Dr. Goldman gets started, I wanted to note that Dr. Meera Chitlur is now available on the phone. Dr. Chitlur, would you please introduce yourself?

DR. CHITLUR: Hi. This is Meera Chitlur. I'm a Pediatric Hematologist from Children's Hospital of Michigan and Wayne State University in Detroit. Thank you for having me here today.

DR. KAUFMAN: Thank you.

DR. GOLDMAN: Okay, well, I'd like to thank the FDA for inviting me to speak. Rich, did you want to say something else before I get going?

DR. KAUFMAN: Yes. We have one other member of the committee that I would like to ask for introduction. Dr. Judith Baker?

DR. BAKER: Thank you. Apologies. Judith Baker with the Center for Inherited Blood Disorders in Orange, California and UCLA -- Pediatric Hematology at UCLA. My background is public health. I work

extensively with the US Hemophilia Treatment Center Network and sickle cell disease as well.

DR. KAUFMAN: Thank you. Dr. Goldman, please.

REVIEW OF GLOBAL DEVELOPMENTS IN MSM DEFERRAL POLICIES

DR. GOLDMAN: Okay. Around the world in 20 minutes, here we go. I don't have any conflicts of interest, but I do have a very definite perspective on this in that I've been involved in formulating and evaluating and thinking about this issue for a long time from the perspective of a medical director of a large blood service in Canada.

As you might expect, when you look internationally, there's no general consensus on criteria for MSM. There are various factors that do influence policy, and these include: what is the actual epidemiology of HIV in that country, which can be, of course, quite different from in the US; donor screening methods; regulatory requirements; government decrees; risk analysis and modeling studies; and finally, last but definitely not least,

the history of response to threats in the past, which Dr. Eder outlined for the US before. There are basically a couple of main approaches.

The first one, which we're all very familiar, is the time-based deferral. So, any MSM in a given time period will lead to a deferral for a given time after last MSM. It's very straight forward. The second group is so-called risk activities based, sometimes called "gender neutral" policies. These policies consider certain sexual behaviors to be high-risk, regardless of whether the partner is the same sex or the opposite sex, in that, usually, there is a given timeframe for that activity and there will be a deferral for a given time after that risk factor. So, that might be a new partner, let's say, or more than one partner.

Then, finally, more recently, there's a few countries that have looked at alternative criteria in combination with other safety measures. And the main one will be plasma quarantine and retest. So, as always, with any donor criteria, the problem boils down

to how to analyze results. This is always a difficult question. Disease transmission is, thankfully, extremely rare, so that is not the outcome that we're looking at. There's a bunch of kind of surrogates that we use to tell us if what we're doing is safe or not safe.

Usually, we look at HIV rates in our donors, incidence rates in repeat donors, anonymous surveys to try and assess compliance with the criteria, and all these factors go into risk modeling studies. The results are going to depend on many factors in addition to the actual criteria themselves. We all know that because our criteria have become more liberal in the last few years, but our HIV rates in our donors are much lower than they were, let's say, 25 years ago. So, clearly, something that had nothing to do with the blood suppliers has happened there. So, there's a lot of factors in the outside world that influence what we're going to see in our donors.

Obviously, HIV incidence and prevalence in the general population, public health messaging so people

know that they're at risk; they should get tested. And then, if they are tested, how easy is it to go get tested? Then, when you know you're tested, you should know that you shouldn't come in to donate blood. So, all of those things are really not related to what our criteria are at the blood center.

At the center, there's different methods of administration of the questionnaire. And then, of course, you're still relying on a human being, the donor, to understand what you're asking and to comply and see the question and answer it the way you would like them to answer it. So, if we look at each of the types of screening, we're starting with time-based deferrals. As Dr. Eder mentioned, from the 1980s until about 2000, many countries had a permanent deferral for MSM "ever, or even once since 1977." Australia was the first country, in 2000, to move to a 12-month deferral. Since about 2011, many countries have moved to shorter deferral periods which range from 3 to 12 months.

Why was this done? Some of the countries did risk modeling that suggested that there would really be

absence of a significant risk increment if they did move to a shorter deferral period. Of course, all the testing has improved tremendously. And, in terms of the 3-months deferral in the UK, the UK has an independent advisory committee on the Safety of Blood, Tissues, and Organs, called SaBTO, which, a few years ago, had recommended changing from an indefinite to a 12-month deferral, and then, more recently recommended moving from a 12-month to a 3-month deferral.

As I understand the report, it was mainly based on the virus that had the longest window period for them, which was hepatitis B, nucleic acid testing being done in mini pools, and they arrived at their 3 months by taking about double the window period with that test and adding in a few days of pre-infectious period, and deciding that that was about 3 months.

So, if we look at where we are in 2019 with these time-based deferrals, we have England, Scotland, and Wales with this 3-month deferral. That was instituted in late 2017. We have the Ministry of Health in Denmark announcing that they will go to a 4-

month deferral. I believe that's actually going to happen this summer. And then, we have a large number of countries that are at a 12-month deferral, including Canada, Australia, New Zealand, and a whole host of European countries in addition to the US, obviously.

So, what have the results been? Well, the change to a 12-month deferral in countries that have done a careful analysis -- and quite a few actually have -- was not accompanied by an increase in HIV rates in the donors or an increase in NAT-only positive donors, which would be, actually, the donors of most concern because, likely, very recently infected. In these modeling studies that were done in several countries, there was an expected increase in the number of HIV-positive donors and that didn't happen.

So, in this review by March Ermere (phonetic), one of the leading modelers, he suggests that actually, probably those studies, which of course are filled with a bunch of estimates, likely were overly conservative. Because what they predicted didn't actually happen. Post-implementation compliance studies, these anonymous

surveys of donors, were done in several countries and really did not show any change in non-compliance or, if anything, a slight improvement, because people who had more remote MSM and had been non-compliant with earlier criteria, are now actually compliant because you have a shorter deferral period.

We're awaiting publication of UK results with the 3-month deferral. They did present some results at their British Transfusion Medicine Meeting and have told us verbally that their HIV rates have not changed in their donors since they've moved to the 3-month deferral. I think there will be probably some abstracts of ISBT and ABB from the UK.

What are the strengths and weaknesses of this approach? Well, we know it well. It's simple and it's similar to the other types of questions that we ask donors, so that's a good thing. It's standardized. For us, standardization is close to godliness. And the changes have enlarged our overall donor pool. So, there's some people who used to be deferred who can now donate, and that's always a good thing because we're

always short on donors.

What are the negatives here? They, too, I think, are pretty obvious. Well, at some point, you're going to be stuck. Right? Because you're going to be kind of a bit at the limits of your window period, plus a little bit of extra. So, you're not going to be able to shorten the deferral with this approach. Then, another major limitation is that you're still deferring all sexually active MSM, including those who are in a stable monogamous relationship from donating. So, from a justice perspective, or what is the actual lowest risk population of MSM, they are still being deferred using this type of approach.

Now, we're going to move over and look at risk activities-based criteria, looking at Italy and Spain. So, here, as I mentioned, donors are asked about sexual partner. It does not matter if this person is of the same sex or of the opposite sex, and they're deferred for what is considered a high-risk sexual behavior. So, that might include a list of things including having a new partner, having more than one partner, or

having so-called casual partners. In other words, you and your partner are not in a mutually exclusive relationship.

The time period of interest, where you're asking about all these things, could be 4 months in Italy or 12 months in Spain. I just wanted to say that, although we don't have these types of questions in the US or Canada for all donors, in some countries with just trends, they do have some of these broad criteria about a new partner for all donors, in addition to some specific MSM partner deferrals.

There are quite a few other differences between Italy and Spain and what we're doing in North America. They are using physicians to screen the donors with the ability to ask additional questions and have, probably, more refined individual risk assessments than we would ever have in our highly regulated manufacturing environment in Canada or the US. There's no national uniform questionnaire, so there's less standardization and more variability between blood centers. So, you end up a little bit

with trying to compare apples with oranges, rather than really just looking at the differences in criteria.

The results are harder to evaluate on a national level. There has been a study published from Catalonia in Spain, which is where Barcelona is, showing a high HIV rate in the donors, 7.7 out of 100 thousand which is quite high. 61 percent of the positivies there were in repeat donors, which is quite unusual. 10 of the 214 positive donors, or 4.7 percent, were NAT-only positives. So, likely, infected very recently in the weeks prior to donation. 89 percent of positive donors and 90 percent of these NAT-only positives were male donors, with a lot of them having MSM as a risk factor.

When you look at European data that have been published, the HIV rates in donors in Spain and Italy are quite a bit higher than other Western European countries. This is not an exhaustive slide; it's just a few studies from the few countries, just looking at HIV rates per 100 thousand NAT-only rates, and then kind of the ratio of positives in first-time versus

repeat donors. As Dr. Eder showed you, usually most of the positives are these prevalent infections in our first-time donors. And there's very few positives in repeat donors. So, at the top, you see Catalonia, then you see an Italian study, a US REDS-II study, CBS, and England.

So, you can see the HIV rate per 100 thousand and how much higher it is in Catalonia and Italy compared to the US and compared to Canadian Blood Services and England, which are really extremely low. NAT-only rate -- again, you can see how high it is in Catalonia. It's not available in the Italian study. It's quite low in the US, and yield of NAT is approximately zero for Canadian Blood Services and for England, for many, many years. Then, you can look at the ratio first-time to repeat donors.

So, you can see, for most countries, it's quite high. In other words, most of the positives are first-time. Like, for that REDS-II study, it's 5.9 times higher in first-time versus repeat donors. Interestingly, given that Catalonia and Italy have the

same approach, you can see how there's something different happening in those places because, in Catalonia, it's 1.2. In other words, a lot of the HIV-positives are repeat donors. But somehow, Italy, supposedly using the same approach, most of the HIV-positives are first-time donors. So, there's clearly other things other than just the criteria themselves that come into play here.

What are the strengths and weaknesses of this approach? Well, for MSM individuals, there's an attempt at a greater categorization of high or low-risk donors. So, an increase in specificity where they're not all thrown into the same high-risk boat. It removes the question and deferral specifically for MSM, so it's reducing perceived stigma and prejudice against gay men. On the negative side, it's a more complex approach and more interpretation is possible for each of those questions. There's a higher residual risk using the data from Spain and Italy. And if you feed those numbers into a modeling study, you will come up with a higher risk than what we have with our approach.

As applied in a gender-neutral way, it would substantially increase deferral of currently donating TD marker negative donors. So, if everyone's going to be deferred for having a new partner or more than one partner, we're going to be deferring a lot of donors that are currently happily donating with negative TD markers. So, it would decrease specificity overall and, therefore, may have a negative impact on the adequacy of supply.

What about alternative criteria and other safety measures? Additional measures that reduce infectious risk, such as quarantine and retest of donors, may permit adoption of alternative criteria. So, in Israel, there is a program now that is enrolling MSM. Where there is no deferral, people donate whole blood. The plasma is quarantined, and it will be released for transfusion once the donor returns at least 4 months later. Obviously, when they return, they'll be retested. The red cells and platelets will be discarded from that donation. That would never fly where we are. We would not be able to discard two-

thirds of the donation. But anyway, that's what they're doing.

In France, all donors are asked about if they've had more than one sexual partner in the last 4 months, so that's part of their general criteria. They are now allowing MSM who meet that criterion to donate plasma. So, if they have not had more than one sexual partner in the last 4 months, the plasma will be quarantined, and the donor has to return and be retested at least 2 months later. Then, the plasma will be issued for transfusion. So, you could, obviously, also combine this approach with pathogen reduction technology, which is a future topic later today, or with source plasma donation.

Strengths and weaknesses of this -- well, maybe the additional steps may compensate for any possible risk increase. We love belt and suspenders and parachuting in the blood sector. You're adding a few things there, so maybe you could give something up. You would get a lot of useful data about eligibility of MSM donors for all our other 65 questions that we ask,

information about TD markers, and compliance.

That will help you with developing further policy changes, maybe for whole blood donation or other types of donation. It would increase eligibility for MSM, although additional processing requirements, such as quarantine, mean that you're still going to be asking an MSM question. Right? Because you're still going to be treating and processing the blood from those individuals differently than other donors.

What about weaknesses? Well, it's going to increase your operational complexity and cost. Just think of that freezer for that quarantine stuff, and then the IT controls for when it comes out of quarantine. All that may lead to increased errors. Quarantine and retest is limited to plasma donation. You can't do that for components that have a short shelf life. And if you have sub-optimal performance of your pathogen reduction technology, you may have an increased risk because you're relying on that to compensate for more liberal criteria in the donors.

So, just wanted to mention a little bit about

what we're doing in Canada. So, both Canadian Blood Services and Héma-Québec, which are the two blood suppliers in Canada, changed from an indefinite deferral to 5-year deferral in 2013, and then to a 12-month deferral in 2016, after risk modeling and very extensive stakeholder consultations with both patient groups and advocacy groups.

There's been no change in our very, very low TD marker rates or in our compliance. And we've done serial anonymous donor surveys. Both organizations have the submission in, now under review, at our regulator Health Canada to change to a 3-month deferral. Many research projects are underway as part of a federally funded research program. You can go to our website to read a lot more about those.

In summary, there's no international consensus on MSM policy. There was a trend towards shorter time-based deferrals, with no adverse safety impact to date. Risk behavior-based strategies have shown high HIV rates in donors, although this may be influenced by factors other than the criteria themselves. Quarantine

and retest of pathogen reduction steps may mitigate for possible risk increments associated with alternative screening approaches.

Thank you very much for your attention.

DR. KAUFMAN: Thank you, Dr. Goldman. I'd like to introduce our next speaker, Dr. John Brooks from CDC.

EPIDEMIOLOGY OF HIV IN THE UNITED STATES

DR. BROOKS: Good morning. I've been asked to join you all this morning to review the epidemiology of HIV in the US in 2019. I work for the Division of HIV/AIDS Prevention at CDC, and I'm the Senior Medical Advisor there presently. I have no relevant financial conflicts of interest to disclose or others. So, let's get started.

I just want to open this by showing you what tremendous progress we've made controlling HIV in the United States. Some of you may recall that it peaked in the late 1980s, early 1990s. And it was with the advent of HIV testing and the first drug that was approved that we began to see new infections declining.

With the current -- with ongoing improvements in antiretroviral therapy, numbers of infections continue to decline. In the most recent period, from 2009 to 2015, we've seen continued declines with the advent of PrEP. I'll review some of the reasons why this is the case later on.

But, first, I just wanted to also highlight that we have seen, as a result of these declines, really enormous strides in reductions in death among people who have been diagnosed with HIV infection, as well as increases in the length of life of persons after HIV diagnosis. Deaths have declined by 20 times and length of life has increased by at least 17 years over the period we've been doing surveillance.

As a result of that, HIV is no longer a leading cause of death as it was in the early 1990s among people of the highest risk -- young people, age 25 to 44. As I mentioned before, this is due predominately to the advent of effective antiretroviral therapy. So, today, among the six leading causes of death, HIV is no longer among them in this group. Let

me come back now and look more closely at this more recent period and talk about the HIV epidemiology as we know it today. I'm going to start from the right side of this figure, and the most recent data we have are for the year 2016.

First is shown, on the -- on your right side, excuse me. Not the left side. On the right side are HIV diagnoses. And as Dr. Eder mentioned earlier, that's 38,739 were diagnosed in 2016. That's the actual number of infections which had a positive test. But I'll note that the average person has been living with HIV for 3 years before they're diagnosed. That's 7 years for people who are African American or black in this country. Using a CD4 depletion model, where we take the CD4 cell count at the time of diagnoses and then work backwards to estimate the likely date on which the infection occurred, we can better infer incidence. That's what's shown on the left.

That is the dates at which infections actually occurred. Not surprisingly, it's not that different from diagnoses. But it's 38,700. We like to use

incidence because this is usually considered by us when we're looking at trends in what's going on with the new infections -- a more accurate way of looking at the data. What that means is, in the middle, that 1.1 million Americans today are estimated to be living with HIV infection of who estimate 1 in 7, or 14 percent, do not know they, yet, have the infection.

Annual infections have been declining very steadily since the 1990s. But since 2013, we've begun to see our progress stalling at around this figure of 38 thousand to 40 thousand new infections per year. Let me talk a little bit about lifetime risk for HIV diagnoses. I like to talk about it this way because I think it personalizes it more when you're trying to explain to people what risk means. This shows the lifetime risk by age, on the x-axis, over time. Not surprisingly, as people enter sexual debut in their teens and early 20s, lifetime risk increases substantially and then begins to level off in the 50s.

Lifetime risk for men is about 4 times that for women. That's also reflected by the prevalence and

incidence of HIV infection where there's a ratio of about 1 to 2, for 4 men for every woman who's infected. Because this meeting is concerned with men who have sex with men, I'm going to show you here, now, the estimated incidence among persons who are adults over age 13 by transmission category. You can see, as was described earlier, that among the entire population of people diagnosed with HIV infection, those living with the condition -- those -- sorry. Estimated when infected with HIV in 2016, 68 percent were MSM. And if you looked among men only, it's closer to 80 percent.

There is a substantial fraction among heterosexuals -- about one-quarter -- and about 8 to 10 percent among persons who inject drugs, either alone or who also are MSM. Looking over time, among MSM, what's been going -- sorry, by risk factor first, what's been going on since 2010. Again, these are incidence data and what I want to apply under a couple of things. Incidence of HIV infection among men who have sex with men has remained stable whereas, among heterosexuals and injection drug users, there have been substantial

and significant declines.

Now, honing in on men who have sex with men, there also are important differences by race and ethnicity. Black/African American MSM complies the largest fraction of MSM, and there has been no change over this time period in the incidence in this group. However, among whites, there's been a steady decline. Disturbingly, however -- and this is something that we're very concerned about -- there's been a very substantial and significant increase in incidence among Hispanic and Latino MSM.

Looking by age group, there's also an interesting point, which is that, although among older MSM, incidence has remained stable and generally low, there's been a steady increase in the group age 25 to 34. Recall that when I showed the diagram earlier of lifetime risk, that's when lifetime risk is accelerating and, generally, greatest. We're pleased to see that there's been a decline in the group age 13 to 24. We're looking to understand that better right now.

But the point that I want to make here is that, if you combine these two worst categories together and look at black or Latino men who have sex with men in the highest age for risk, 25 to 34, since 2010, we've seen a 65 percent overall increase incidence in that particular group. Another way of looking at risk by group is by looking at the lifetime risk in here, by transmission category.

Again, MSM have the highest risk, in terms of their lifetime risk, of acquiring HIV infection, followed interestingly by women who inject drugs and men who inject drugs. But heterosexual risk is comparatively quite low. Then, looking at these MSM in particular, again, as I mentioned earlier, the risk is substantially greater for African American MSM, who we estimate may have as high as a 1 in 2 chance in their lifetime of acquiring HIV compared to Hispanic MSM or white MSM.

Geographically, risk for HIV is also very different across the United States. In particular, I want to bring your attention to the southern part of

the country, which is where the problem is greatest at the present time. Although the southern states in the US depicted here account for only 38 percent of the US population, they bear the highest burden of HIV infection. 51 percent, over half of all new HIV infections, occurred in the South in 2016; 45 percent of persons living with HIV lived in the South; and 50 percent of undiagnosed HIV infections were in the South.

Looking more broadly, then, and asking, so, what's the lifetime risk geographically -- and this is essentially equivalent to lifetime prevalence because your risk increases by the opportunity to encounter the infection. So, when the prevalence is higher, your likelihood of encountering it is higher and your risk is greater. Again, the South has a very substantial increased risk compared to other parts of the country. Other areas that are notable here are the D.C. Metro area, Maryland, and Delaware, as well as New Jersey and New York.

The good news is that effective treatment has

done amazing work extending the life of people with HIV infection. Starting in this diagram from the UN AIDS, looking in 1995 up until 2010, with the advent of antiretroviral therapy and its steady improvement, the lifespan that a person could expect to live after diagnoses of HIV has increased steadily, so that in the current Europe, we can say that persons diagnosed in their 20s and given effective antiretroviral therapy can expect to live an essentially normal lifespan. This is due predominately to the advent and changes in the medical therapy used for treating HIV, which is now simple and very effective.

As many of you may know, it used to be a complex combination of tablets. This is actually a patient holding the pills that she was given for one day's dose back in the early 1990s. Had limited potency and very high toxicity, which dissuaded people from taking the medication. Today, however, we have at least 7, and soon -- I think -- to be 8, multi-drug combinations available as single tablet regimens that you take once a day. The regimen is very simple. The

drugs are more potent now -- in particular, the integrase inhibitors -- and these drugs have very few side effects. It's very easy now to manage HIV infection.

Treatment also has another really important benefit that's been brought to everyone's attention by a couple of studies; finally, the last one was published last year. And that is that effective treatment prevents sexual transmission. Shown here are the results of 4 seminal studies looking at sero-different couples, where there was an infected person and their sexual partner was uninfected, and the infected partner took antiretroviral therapy and achieved viral suppression. The uninfected partner used no protection, no condoms, no pre-exposure prophylaxis, no post-exposure prophylaxis.

In total, these company's studies included a little over 3,700 couples with a good mix of heterosexual couples and MSM couples. Despite over 125 thousand condom-less episodes of vaginal and anal sex, no single transmission of HIV was observed that could

be genetically linked between these couples. And I'll just tell you, having been in HIV medicine for 30 years and spending all of my time telling people that you have to be careful, this was a very stunning finding. But I now am certain in my belief that people who achieve and maintain a suppressed viral load have effectively no risk of transmitting HIV infection sexually.

But this good news is not reaching all Americans evenly. This shows what we call the cascade of care. Looking at the fraction of persons who have been diagnosed, received, or linked to care, who have been retained in care, and who have achieved viral suppression. I'll bring your attention, first, to the right side of the figure where we show we estimate that no more than 51 percent of Americans have achieved viral suppression.

Now, this varies a lot by individual clinic and practice. In the Ryan White AIDS Program here in the United States, they have achieved suppression rates over 85 percent. In the VA system where I see

patients, we've also achieved very high rates of suppression. But that's not true for all Americans. The biggest drop-off is in the area from getting diagnosed to staying engaged in care, and that's where we intend to spend most of our effort in the future, trying to make sure that people stay suppressed.

Breaking this down by different groups, I just wanted to highlight here that, for MSM, it's about the same. Roughly 50 percent are estimated to not be virally suppressed among those who've been diagnosed and undiagnosed. We also know, from data published earlier this week, that most infections come from persons undiagnosed or not in care. 8 in 10 new infections come from somebody not in HIV care. That fraction of persons who have either been not diagnosed who don't know they have HIV, or who know they have HIV but aren't in care, is only 38 percent of the population of persons we believe have HIV infection. But they account for 81 percent of new infections.

I wanted to touch briefly on pre-exposure prophylaxis. This is a single drug combination of the

drugs tenofovir and emtricitabine. It's currently the only FDA-approved drug for PrEP in United States. We know that it's greater than 90 percent effective for preventing sexual transmission, and we have a group back in my agency, now, reviewing these data. I believe we're going to come out saying it's probably even more effective. Curiously, the number of Americans that we have estimated who would benefit from pre-exposure prophylaxis happens to be about the same number who we estimate are living with HIV infection, or 1.1 million Americans.

These were data presented a couple of weeks ago at the large international HIV conference, looking at PrEP awareness and use among men who have sex with men. These are data from CDC's National HIV Behavioral Surveillance. These are not representative data, but they generally are -- they are taken from a large population of MSM. I say that to caution that I think these data may be over-estimating a little bit. But the trends are important.

Right now, we estimate that a very large

fraction of MSM have heard of or are aware of PrEP, 90 percent on average. But there are important racial and ethnic differences. Whites tend to know more about this or be more aware of it than blacks or Hispanics. And use of PrEP, it defines as "having ever used it at least once" has increased substantially, we think. As high as 35 percent of persons in this survey reporting having ever used PrEP before.

For comparison, our last estimate was that -- the previous estimate was that only 7 percent or MSM -- no, excuse me. I'm going to correct that. Only 7 percent of Americans had ever used PrEP, and the fraction of those who were MSM was about the same. So, we think that this is an intervention that's not only important and has a lot of opportunity to prevent new infections but is also getting out there into the public and being used. I don't need to spend too much time talking to this group about HIV testing. I just wanted to point out research we completed about a year and a half ago, looking at how different HIV tests performed.

You may be well aware that the antigen antibody-based technologies can detect HIV infection very early. Median, about 18 days. 99th percentile, that is the time at which, if a person tests negative, we would say there's a greater than 99 percent chance that they're uninfected was 44 days. Including in this table now, the Aptima RNA NAT test that was used in this study, the median period is down to about 11 days and the 99th percentile, where 99 percent of people who are tested negative would be considered uninfected, is 33 days.

With ART, HIV infection in 2019 is a highly preventable and manageable chronic disease. It's important to think that, now, we're near -- or 30 years later, where this infection has become something that's being managed as a chronic disease. I haven't shown you the data about what it's like to live with HIV infection today. But over 50 percent of persons infected are age 50 or greater, and clinicians who are taking care of patients who are receiving good care focus a lot more on the same things that everybody else

has to look out for. Don't smoke, manage your weight, get your blood pressure under control, and screen for cancer.

They can expect to live a "near normal" life expectancy if treated early and effectively. But this happy state is not easy for everyone to get to. You have to get suppressed, and that requires getting diagnosed and getting into ongoing care. For that reason, these steps and the continuum are a focus for us. Pre-exposure prophylaxis is a potent and very efficacious prevention tool. Although it's rising in use, it's still underutilized by MSM.

So, in summary, new HIV diagnoses continue to decline in the United States, although they appear to be flattening in the last few years. And they disproportionately and increasingly effect certain sub-populations which we must prioritize for prevention and treatment efforts. These include MSM, especially young Latino/Hispanic and black/African American MSM, as well as person living in the southern part of the United States.

With antiretrovirals, there really is a possibility of true HIV control. And I believe that future of no new HIV infections is fully within our grasp; and that with antigen antibody-based testing, or NAT-based testing, median time from last exposure to reactivity, in the context of testing a person for HIV, is 10 to 20 days -- those kind of liberal boundaries based on the data I showed you before; and that, if a person tests negative at greater than 45 days after last exposure, there's a greater than 99 percent likelihood that they are uninfected.

This is my name and contact information, and I think we'll have the questions afterwards. Is that right, Dr. Kaufman? Okay. Great. Thank you very much.

DR. KAUFMAN: Thank you, Dr. Brooks. Our next speaker is Dr. Alan Williams, from FDA. He'll be providing an overview of the Transfusion-Transmissible Infections Monitoring System, or TTIMS.

DATA FROM THE TRANSFUSION-TRANSMITTED INFECTIONS MONITORING SYSTEM (TTIMS)

DR. WILLIAMS: Good morning. Thanks very much. As mentioned, I'm with the CBER Office of Biostatistics and Epidemiology. I'm one of the persons who's coordinating the TTIMS program, which has been underway several years. In a long one-sentence definition, TTIMS, or the Transfusion-Transmissible Infections Monitoring System, is a representative and sustainable system initiated in September of 2015 to collect HIV, hepatitis C virus, hepatitis B virus, incidence and prevalence, along with risk factors, advanced laboratory measures, and associated demographic variables among US blood donors.

This is reflecting the US blood supply by collecting approximately 60 percent of the total US supply. This program has been discussed in public advisory committees numerous times, including to this committee. December 2015 was the first discussion where we discussed, in depth, recency testing as a potential predictor of incidence in first-time donors.

Also, in December of 2016, and then in December 2017, which was the first large data presentation from the program, largely including prevalence from each of the sites. There is a publication which provides background for the program, which is referenced here.

In terms of structure and governance, TTIMS is funded by the Food and Drug Administration, by the National Heart, Lung, and Blood Institute, and by the Office of the Assistant Secretary for Health in HHS. Operationally, it's run by two coordinating centers, the Donor Database Coordinating Center, or DDCC. This is a contract to the American Red Cross through 2020. The second coordinating center is the Laboratory and Risk Factor Coordinating Center, or LRCC. And this is a contract through 2021.

In terms of internal governance, there's a steering committee, which includes representatives from other vested PHS agencies as well as participants in the program. There's an executive committee that serves as the executive oversight, and there are various analytic workgroups conducting study analysis

and proposals.

So, to focus, first, on the Donation Database Coordinating Center, this is run by the American Red Cross under Dr. Susan Stramer. The data collection sites, which I report into the coordinating center, include the entire American Red Cross blood systems, Vitalant and each of their blood centers, the New York Blood Center, and OneBlood. And then, all of the laboratory results are coordinated and submitted to a central site from Creative Testing Solutions. In terms of work scope, the DDCC maintains a central database for TTIMS, representing 60 percent of the US blood supply and monitoring for the markers mentioned -- mainly hepatitis B, hepatitis C, and HIV.

This coordinating center built on the very substantial base established particularly by the REDS-II program and established consensus test result definitions -- because some testing processes do vary between centers -- validated all of the data exchanged within the program between centers and the coordinating center. And the DDCC also conducts quarterly data

analysis including prevalence calculations for donors, also for donations, and then ultimately provides incidence estimates which include the NAT yield, which is NAT in the absence of antibody reflecting very early infection, as well as the classic method of assessing repeat donor seroconversion.

Then, from these incidence estimates, one can drive residual risk estimates based on the incidence rate times the known window period of infection. Shown here is some of the HIV prevalence data presented by Whitney Steele at the December 2017 BPAC, showing, basically, some variation but largely prevalence of HIV among both first-time and repeat donors from September 2015 through July of 2017, which, as you'll note, encompasses the implementation period of the new MSM deferral which occurred throughout 2016. No statistical or measurable difference in prevalence across this time period, with a first-time prevalence of 8.8 per hundred thousand and a repeat donor prevalence of 1.4 per hundred thousand.

The second coordinating center is a Laboratory

and Risk Factor Coordinating Center. This is conducted by Vitalant Research Institute. Brian Custer is the PI for that program. This similarly uses data and samples contributed by the blood establishment participants, including Vitalant, American Red Cross Blood Services, New York Blood Center, and OneBlood, and the participation of Creative Testing Solutions for lab results.

The LRCC work scope includes an important program within this study, which is the design in conduct of the risk factor interviews within the program. And because of the large number of samples involved, interviews are conducted for all HIV-positive individuals, for hepatitis C virus-infected individuals who have yield infections -- in other words, reflecting NAT on the early infection -- and then, similarly, for hepatitis B, yield infection. And then there is a 2 to 1 ratio of controls for each of the seropositive subjects. So, a lot of interviews taking place.

The LRCC will, in the course of the coming year, integrate the risk factor data with the marker

data within the study. Additionally, this group houses a biospecimen repository within the program, which includes HIV, hepatitis C, hepatitis B samples collected within the timeframe of the TTIMS program, as well as historical HIV-positive blood samples from blood donors within the TTIMS sites. LRCC also conducts additional lab studies and is heavily involved in evaluating donor HIV antibodies, using L-Ag avidity tests, which are assays capable of characterizing a recent HIV infection.

The period of recency depends on the cut-off used between the assay, but typically, it's in the order of predicting infection within the past 130 days or thereabouts, depending on what cut-off is used. So, the LRCC has been conducting L-Ag avidity testing of stored donor samples to assess performance in blood donation settings, which was a new endeavor for that assay in this country. And then, ultimately, with that testing well underway, these recency data will be modeled to estimate infection incidence in first-time donors. This, of course, increases the power to assess

changes in overall HIV incidence over time, and particularly, pre or post any policy change that takes place.

The basis of the LAg-avidity assays is that persons with acquired HIV infections typically exhibit HIV-1 specific IgG populations with higher proportions of lower antigen-binding strength, also known as avidity. Those with longer term infections typically have higher LAg avidity. The mean duration of recent infection, known as MDRI, as I said, can vary, but typically would be something like 130 days and, therefore, reflects fairly recent infection. LAg avidity testing may also soon be available for hepatitis C virus infection and this will also be implemented within the TTIMS program.

So, again, just showing some of the early data presented earlier to the committee, from HIV-positive collections from 2010 through 2017, shown here are the numbers tested per year, the number positive, and the percentage. You can see that the percentage varies from the mid-20s up to 32 percent or so, and is

relatively stable over time from 2010 to 2017. Indeed, no significant differences by year. Additional research in the Laboratory and Risk Factor Coordinating Center is genetic sequence analysis of viral isolates from HIV, hepatitis B, and hepatitis C. Both provide sequencing data as well as assist drug resistance.

This would be a talk in itself; some very nice work by Brian Custer's group and his colleagues. But, in general, the genotypes and drug resistance mutations seen in donors with infection reflect the patterns observed in public health surveillance initiatives in the US general population and, therefore, serve as a representative group reflecting gene sequencing information in other parts of the country, in other populations.

In terms of overall accomplishments for TTIMS, as of the end of the year, 2018, TTIMS donation database from the participating vote centers totaled 23,982,000. This is from September 2015 through December 2018. December 2018 is an important cut-off because, as I'll talk about in a few slides, this would

be the data cut-off for some of the major analyses that are being done in the program, particularly incidence studies. Risk interviews are taking place regularly. All HIV risk interviews for HIV-positive individuals, there have been 144 interviews conducted so far; NAT Yield, for hepatitis C, 28 interviews; for hepatitis B, 13 interviews; and all controls, 296.

With HIV Recency testing conducted for all of the archive samples, as well as ongoing for the accrued HIV-positive samples in TTIMS, 1,012 tested of which close to 400 have been within the TTIMS time period. So, 2019 is going to build on this success of accruing samples and data and serve as a major analysis year. The major analyses targeted for this year will be based on two years of data and adequate power to assess prevalence and incidence time trends surrounding the MSM 12-month deferral change.

So, the pre-MSM 12-month period -- TTIMS defined data are available from September 2015 when the policy change was published through the implementation time period of 2016. This is defined as the blood

establishment “pre” period, because the centers changed policy at different times within 2016. Then, the post-MSM period for a 12-month deferral is defined as December 31, 2018. And this establishes a minimum 2-year time period for follow-up after blood establishment implementation at each of the participating sites.

That’s complex in a verbal description, but shown here is a diagram of implementation of the MSM 12-month policy change at the TTIMS sites. The bottom is a timeline for TTIMS with implementation beginning at September 2015 out through the end of 2018. The pre-MSM 12-month policy period really runs through August 8th of 2016 when the New York Blood Center changed policy, followed by Vitalant, OneBlood, and then Red Cross on December 12th, 2016. So, through December 12th, 2016, this comprises the pre-period, and then following that period, then, through the end of 2018 is the 2-year post period.

So, this was designed to provide adequate data and adequate power to conduct incidence analyses, which

is one of the major intents of the program. The analytic strategies for 2019 related to the policy change is, first, to continue the donation prevalence calculations by different strata, including first-time and repeat donors, sex, and US Public Health region. Second is the classical incidence calculations done for repeat donors by two different methods.

The first is to use equal MSM pre-implementation periods at each of the centers, along with some stated assumptions as to why this method could potentially result in different results from other methods. Then, the second method is to use modeling to minimize the bias related to the use of the true different policy implementation dates along with certain assumptions.

The whole idea of using the two different approaches is to really try to minimize bias because of these staggered implementation times. Since donation intervals are critical to the calculation of incidence -- and these would vary depending on the time periods involved -- it’s important to consider this as a

potential source of bias when they differ.

A third major analysis is estimates of first-time HIV donor incidence by using LAg avidity testing to estimate mean duration of infection. This will be done to determine data for recency of infection, but then modeling will be needed to estimate the HIV incidence as determined in first-time donors. There are discussions underway to determine the best way to conduct this modeling for this particular population.

Then, finally, using the resources established as I mentioned, the donor and control risk interviews from the program will be assessed in the context of the marker data and ultimately in comparison with the 2004 to 2009 REDS-III data from a very similar question there to look at behavioral risk factors involved with infection and potential trends over time.

An initiative developed this past year within the LRCC is to look at pre-exposure prophylaxis and antiretroviral therapy in donated samples from a targeted set of current donors as well as HIV-positive donors for ARV treatment. The reason for this is pre-

exposure prophylaxis for high-risk exposure and antiretroviral therapies for HIV infection are highly effective medications. However, dosing compliance failures can result in incomplete protection, and the theoretical possibility of transmissible HIV infection in blood that may not be detected by current blood establishment screening.

This is only theoretical. This has not been observed. But TTIMS felt it was important to establish a basis for whether or not some of the HIV seropositive individuals identified were on ARV treatment, or some of the seronegative individuals who are donating are currently using PrEP. So, for the PrEP study, TTIMS is studying PrEP use among current donors.

This was in collaboration with the Office of HIV/AIDS at the Centers for Disease Control and Prevention. This uses high-pressure liquid chromatography techniques to assess the presence of PrEP or PrEP metabolites in an initial sample of 1500 anonymous but geographically targeted first-time male donors. These are being tested anonymously and this

testing is underway.

The second program is to study antiretroviral use among HIV-positive donors, also in collaboration with Centers for Disease Control and Prevention. This will use all newly identified HIV-positive samples within TTIMS as well as the archive samples. Results should be available for these studies in the coming year.

So, in summary, since its initiation in September 2015, TTIMS has established a comprehensive and sophisticated monitoring capability for the safety of US blood supply. Major analyses are planned for 2019 to assist prevalence, incidence, and risk factors for HIV, hepatitis C virus, and hepatitis B virus infection among both first-time and repeat donors, and to assess time trends that may be associated with policy changes, such as the change to an MSM 12-month deferral.

TTIMS has been responsive to contemporary needs for data related to pre-exposure prophylaxis and antiretroviral therapy use among individuals who

attempt to donate blood. Data for this specific TTIMS studies described will be presented by the responsible investigators working within TTIMS in the coming year, both at this meeting and other venues. In terms of acknowledgements, first, a special thanks to the FDA, NHLBI, and OASH participation through continued funding of TTIMS.

Here is a list of -- the growing list of collaborators who participate in the program. Then, finally, a snapshot from our latest committee meeting. Thank you very much.

QUESTIONS FOR SPEAKERS

DR. KAUFMAN: Thank you, Dr. Williams. I'd like to ask if the committee has any questions for any of the speakers from this morning. Sridhar?

DR. BASAVARAJU: Thanks. I had a question for Dr. Goldman. So, what I had previously heard about the change in the deferral policy in Australia -- I had heard that there were some legal ramifications for people who did not answer questions truthfully. And in the countries where you've presented data today, where

you've made observations about compliance, I was wondering if you knew if there were any similar pressures, I guess, on people to actually answer the questions truthfully.

DR. GOLDMAN: I'm not sure I'm the best person to answer that question. I mean, many of us have, on our questionnaire, some legalese at the bottom, right? That said that I understood the donor materials, which is the pamphlet, basically, that we have, and I answered the questions to the best of my ability, and I'm aware I could harm somebody if I didn't. So, we do have -- in Canada, for example, we have verbiage around that. And I know Australia has very similar, and so do a lot of other countries. How legally binding that is, I don't know.

The compliance studies are usually anonymous and often done by a third party. For example, we use Ipsos Polling to do the compliance study because we don't want our name on it, so we can't really trace back the answers for the compliance study to a given donor. We just ask the donor certain demographic

questions on the compliance studies so we can say, oh, well, this was a male first-time donor because they told us that on the study. But we can't link to their blood record.

That would be the same with any of the other blood suppliers doing those compliance surveys. They're supposed to be anonymous to encourage people to be more truthful than they, maybe, were when they answered the questionnaire in the donor clinic. I'm not sure that answers your question, but --

DR. KAUFMAN: Dr. Schreiber.

DR. SCHREIBER: This is a follow-up question to the last question. I think honesty is one issue, but the other issue is accuracy. I mean, people don't generally keep records of the last time they had sex. It's been a while, yes, but has it been a year? Has it been 2 months? What about accuracy? How do you -- I mean, how is that calculated into the equation? Some people just don't remember the last time.

DR. GOLDMAN: Yeah, I think that becomes an issue when you're talking about especially more

complicated behavior-based questions and you're starting to ask people about how many partners and details about those partners and so on. I think, if you have a very long time period, it really can't be done. You know? So, to ask people, in the last 12 months even, about number of partners and were those partners having other partners and everything, I think it gets very sticky. I mean, not if the answer is no and you're talking about boring 50-year-olds. But if you're talking about young people that are getting it on, I think it's not realistic.

If you have a shorter period, I think you would get more accurate because people will remember more. We know, even with things like tattoos and piercings, people forget to tell you about ones that happened 11 months ago or even 4 months ago. You shorten your deferral period and you don't have half the number; even your deferral period is half. So why is that? It's because they were telling you about the ones that happened more remotely.

So, as the period is shorter, I think people

do remember more behaviors. On the other hand, to say exactly when something was, if it was 2 months or 3 months, I think that's a problem with all our criteria, that we ask about a lot of time periods and whether people are really doing all that math in their head for all those time periods is probably not that realistic either.

DR. KAUFMAN: Dr. Baker?

DR. BAKER: Thank you, and thanks to all the speakers for great presentations. I had a couple questions for Dr. Williams. Thanks. On the TTIMS system, the geographic spread -- can you tell us a bit of -- you know, in light of the FCDC epidemiology of HIV, and happening in the South and to Hispanics and blacks more prominently than other populations, what actually is the geographic coverage of TTIMS? Given that you say that it's 60 percent estimated US population, where exactly in the country?

DR. WILLIAMS: TTIMS is comprised of major blood systems such as American Red Cross and Vitalant, and these systems tend to be some favoring the

different regional representations. But the high prevalence areas, particularly in the South and Florida, are represented within TTIMS. Even, for instance, Vitalant, which is a West Coast operation, has centers throughout the country. So, in terms of population representation of donors within TTIMS, I think we probably need to calculate that a little more finely.

On the other hand, I would say the entire country is represented within the program, whether it's an equal numerical representation, I think it needs to be determined.

DR. BAKER: And the same thing with race/ethnicity, particularly with reference to the South and/or the West?

DR. WILLIAMS: That would really come along with the demographics. We don't target any certain race or ethnicity within entry into the program. We're covered, certainly, for urban areas and certainly for the Midwest and the coastal regions. But there's no specifically targeting to enhance racial or ethnic

subpopulations.

DR. BAKER: And one more question to clarify -- - in terms of governance and public access, for governance, are there any -- can you tell me a bit about any advisory groups or avenues for end user or consumer input?

DR. WILLIAMS: Well, we certainly have this committee. And I suspect, over the course of time, there will probably be data sharing within the HHS-level advisory committee. Other than that, there's not a formal association with other advisory groups. But certainly, all of the data is presented publicly, generally as soon as it's available.

DR. BAKER: And one more, if I may. Any thoughts about any discussions internally about plans for some kind of public-facing real-time information about what's happening in TTIMS or a public-facing minimal database -- data visualization about what's going on on a real-time basis?

DR. WILLIAMS: I guess the core answer is no, that hasn't been discussed. Because real-time, within

a large epidemiologic program like this, is relative often by the time the data gets cleaned, available for analysis, needing what you want to obtain for power, your months to year -- you know, a year or so after. So, real-time is relative. But it's certainly something that could be -- you know, see if there are possibilities to do that. There would be an advantage to it.

DR. BAKER: Thank you.

DR. HOLLINGER: Can you stay there a minute again? Sorry. Blaine Hollinger. I have about 3 questions. What are you anticipating will be the percentage of first-time donors here in these things? 20 percent more? Less?

DR. WILLIAMS: First-time donors overall?

DR. HOLLINGER: Yep.

DR. WILLIAMS: A little better than 20 percent. Historically, it's been 20; I think that it might be moving a little bit higher.

DR. HOLLINGER: Yeah. And also, when you were talking about PrEP and antiretroviral use, how many

patients actually come in and -- people, donors are coming in and donating that are on PrEP or antiretroviral? That's a little -- that's a pretty high-risk group.

DR. WILLIAMS: Well, that's not known at this point. That's what the studies are to determine. There's a certain increase to power in using biomarkers to assess a person's individual status in contrast to what answers are given on a questionnaire or other interview format. So, that's exactly what these studies are designed to look at -- ARV use in known HIV-positive individuals who are identified, and PrEP use in a targeted set of individuals who come in, answer the behavioral question, and provide blood samples.

DR. HOLLINGER: Yeah. And medication use is asked on the questionnaires usually, yeah.

DR. WILLIAMS: Medication use is asked. These particular drugs are not at this time.

DR. HOLLINGER: Yeah. And then, the final one, can you tell me after you get this data, and

looking at particularly the question about whether the time deferral can change from 12 months to something less or so on, how do you anticipate this data is going to be helpful? I mean, where is it -- what are you looking for to provide that kind of information, if we were trying to say we would -- we're making this decision?

DR. WILLIAMS: I think it's hard to pin down particular aspects that would strongly influence a policy. I think it's really considering everything -- the behavioral risks that are known to continue contributing to ongoing risk coming into the blood centers, what the actual incidence is overall, both in repeat and first-time donors, whether there's any sort of trend associated with that.

I think the ARV and pre-exposure prophylaxis data will provide some input in using biomarkers to determine risks that we were otherwise unaware of. I think you really have to consider all aspects and where interventions might still be necessary and where there's been progress.

DR. KAUFMAN: Okay, thank you. All right. Dr. Lewis?

DR. LEWIS: Two questions. The first has to do with the study we're using, HPLC, to look for evidence of PrEP among 1500 selected first-time male donors. I was just jotting out the two-by-two table I'd do if I was trying to do a case control study to determine whether PrEP was a risk factor for being in the window versus a protective factor, because it could go either way. In filling out that table, I thought the population you most need to figure out is the population that are HIV infected.

So, what I was wondering, was those 1500 subjects unselected? Or were those conditioned on being seropositive?

DR. WILLIAMS: The study of 1500 for pre-exposure prophylaxis are accepted donors. So, those are not seropositive donors -- conditioned on not being seropositive.

DR. LEWIS: Is there any effort to over-sample those -- because, you know, it's a very small number

who are seropositive. I think you probably need to over-sample those.

DR. WILLIAMS: Yeah. It's true. It's potentially a very rare event and a limited sample. You could consider it almost a pilot study. I think we have an estimated prevalence estimate of between 0.5 and 1.5 percent that we can get with a reasonable confidence interval, but we have no idea, at this point, what the prevalence might be. So, this was just an initial pilot effort. We could run larger studies and do over-sampling if we find that's appropriate.

DR. LEWIS: Do you have access to stored serum or plasma from HIV-positive donors' donations?

DR. WILLIAMS: Yes. As I mentioned, there are a total of over a thousand.

DR. LEWIS: That would seem like a wonderful biobank on which to run the HPLC. It helps you with your estimate.

DR. WILLIAMS: And in fact, we are -- I'm not that familiar with the HPLC, but I think there is a certain amount of overlap between the results between

the PrEP therapy and the ARV. So, I assume that can be distinguished at the HPLC level. But I think you wouldn't get a complete negative on one versus the other.

DR. LEWIS: Okay. And in the answers to the prior -- this is a new question. In the answers to the prior question, you talked about biomarkers. Can you just be more explicit? When you use that term, what are the list of things that are your top 2, 3, 5, 12 biomarkers? Hopefully not 12.

DR. WILLIAMS: Okay. Well, certainly, TTI markers, both antibody and nucleic acid testing. I think any biomarker which could determine the status of an individual from a biological standpoint, and use in comparison with answers given to particular questions which might answers to biomarker.

DR. LEWIS: I'm asking for specifics.

DR. WILLIAMS: Specifics, I'm not sure I fully understand.

DR. LEWIS: Okay. I'll just say, I don't understand what you mean by that phrase, so I'm hoping

you're going to help me understand.

DR. WILLIAMS: I'm talking about a biological marker that's detectable in a validated, reproduceable way in a subject from a biological specimen.

DR. LEWIS: I know the definition of a biomarker. What I'm asking is what -- in terms of biomarkers that you would measure that would help you understand where there's a disparity between an answer given on a questionnaire and the person's actual behavior, I'd like some examples of those. The presence of a drug, I get. I'm looking for the things farther down the list.

DR. WILLIAMS: Okay. Perhaps I could give an example.

DR. LEWIS: Great.

DR. WILLIAMS: The CDC HIV/AIDS group runs an HIV behavioral survey. They just published a manuscript in AIDS this year that showed of individuals who, when interviewed, indicated that they were negative for HIV or had not been diagnosed. When studied for ARV, half of the individuals were found to

be on the ARV treatment. So, that sets up the situation where individuals who indicated that they had not been diagnosed or were negative for HIV had evidence of antiretroviral treatment in their blood, and one needs to figure out that disparity.

DR. LEWIS: No, I understand that. Other than medications, can you give an example of another biomarker? Because you used a general term, and I'm trying to find out if you just used that to mean drugs, therapeutic drugs that are antiretrovirals or used in PrEP, or you mean something else.

DR. WILLIAMS: I'm specifically using it to reflect drug, yes.

DR. LEWIS: Thank you.

DR. WILLIAMS: Okay.

DR. KAUFMAN: All right. So, we're going to take a short -- oh, sorry. One last question. Dr. Ortel.

DR. ORTEL: Hopefully brief, for Dr. Brooks. Just a question about -- you gave us data on incidence and lifetime risk for HIV diagnoses by showing

differences in race and ethnicity, and then also in geographic location. Are those considered independent variables? Or do those reflect demographics in those regions?

DR. BROOKS: Those are -- well, they're -- yeah, it's hard to say independent variables because it's not really -- we're not predicting anything. But they are representative of the demography of the populations where this is occurring. Certainly, many people can fulfill multiple criteria. You can have an African American woman living in Alabama. But they're demographic characteristics. And the crossover I showed between race, ethnicity, and age was the one that concerns us the most. Does that help? Yeah? Okay.

DR. KAUFMAN: Okay. Meera, any questions?

DR. CHITLUR: No, thank you.

DR. KAUFMAN: Okay. So we're going to go ahead and take a short break and reconvene at 10:35. Thank you. I'd like to thank all the speakers.

BREAK

PRESENTATION OF THE HIV RISK QUESTIONNAIRE STUDY

DR. KAUFMAN: I'd like to ask everyone to please take your seats. Can I get a gavel? All right. Dr. Chitlur and Dr. Stramer, are you able to hear?

DR. CHITLUR: I'm able to hear. Thank you.

DR. STRAMER: Yes, I can hear.

DR. KAUFMAN: Thank you. All right. Just to stay on time, I would like to get going again. And I'm pleased to introduce the next speaker who is Dr. Barbee Whitaker from FDA, and she'll be talking about the donor HIV risk questionnaire study.

DR. WHITAKER: Good morning. Thank you. I'm Barbee Whitaker with the Office of Biostatistics and Epidemiology, and I will be talking about this donor HIV risk questionnaire study. So, to reiterate, the principles that FDA will use to move forward with the MSM policy are the following. We're committed to an ongoing evaluation of the deferral policy for MSM and to potentially advancing policy based on available scientific evidence. We're also committed to

maximizing the transparency of the process through stakeholder engagement and the use of public advisory committees such as this. This process will be based on gathering necessary scientific information while ensuring the continued safety of the blood supply.

So, this study that I'm going to talk about today is a pilot study. The idea is to cover, today, the description of the pilot study, the scope of work that will be presented here and then in the future, and looking at gathering population-based risk behavior evidence. I have a little bit of an update on this following bullet, which is that the Sources Sought notice was published on Friday on the FBO.gov site, and it has a deadline -- it was published last Friday, March 15, and it has a deadline of March 29. So, we do have something that has been -- that is available for you to look at on FBO.gov.

So, in background, Dr. Eder and others have covered the deferral history, both in the U.S., and Dr. Goldman covered the international background for MSM deferrals and other approaches to MSM safety. And I'd

like to remind you that there is non-compliance with the lifetime deferral that was, in the blood drop study, that was about 2.6 percent reported in the United States. And we don't have any updated data for non-compliance in the U.S. since the 12-month deferral was implemented. So, we feel there's a need for population-based evidence on which we can base any further regulatory decisions to be sure that we ensure blood safety.

So, I'll go through the details of this HRQ, High Risk Questionnaire, study, including more background on the study, purposes, study design, objectives, and so on. So, the background for this pilot study -- it was designed through a collaborative process to assess potential risk of alternative donor deferral strategies for MSM. It may help determine the feasibility and size of a larger study to assess whether reduction or elimination of the donor deferral interval for MSM is possible in the United States. And the larger study criteria are the identification through this pilot study of a set of behavioral

questions and responses associated with the absence of detection of recent HIV infection.

The purpose of the study is to provide us with evidence by which to consider these changes to the MSM deferral policy while maintaining the safety of the blood supply. Our primary objective is to assess the discriminate function of a list of behavioral history questions for predicting recent infection with HIV in MSM who wish to donate blood. The secondary objectives include evaluating the recency of HIV infection in those individuals by ID NAT, individual NAT, and/or antibody testing and identifying risk factors associated with recent HIV infection in individuals who are antibody negative yet HIV NAT positive, so the NAT yield donors for -- HIV NAT yield.

So, the outcome of this study may be that we can identify certain low risk MSMs -- MSM population that could be blood donors. The primary endpoint is the number of individuals who are HIV NAT positive but antibody negative. Secondary endpoints include the number of overall HIV infections, the number of recent

HIV infections, and the correlation of responses to the questions with HIV status.

So, we're looking for a study that will include 2,000 men who have had sex with men at least once during the past three months. This sample size was chosen to increase the likelihood that a recent HIV infection will be identified. Subjects will be enrolled from 8 to 12 geographically distributed sties with a high risk of HIV transmission among men who have sex with men and --not the LGBTQ community but men who have sex with men. The sites may be a combination of clinical facilities and venue-based locations.

Pilots sites shall be selected from locations in states and cities with the highest new HIV diagnosis rates based on the 2017 CDC HIV epidemiology reports. And some of the sites -- this might include states such as the District of Columbia -- or districts -- Georgia, Louisiana, Florida, and Maryland, which have rates about 20 per 1,000 adults and adolescents of new HIV infections. And the next category might include Nevada, Texas, Mississippi, South Carolina, New York,

Alabama, Delaware, and North Carolina, which have rates in the next tier, 15 to 20 per 100,000 adults and adolescents. And then certain cities that have particularly high rates of new infections include Miami; Orlando; Atlanta; New Orleans; Baton Rouge; Jackson; Jacksonville, Florida; Memphis, Tennessee; Columbia, South Carolina; Las Vegas, Nevada; and Baltimore, Maryland. But these are just a sample of potential locations where this study could be carried out.

The eligibility criteria -- inclusion criteria -- we're looking for males greater than or equal to 18 years of age and able to provide informed consent who have had oral or anal intercourse with a male partner at least once during the past three months. They can answer the study questionnaire, provide a blood sample, and follow the study protocol, and, as I said before, provide informed consent. The exclusion criteria include men who have prior use of injection drugs ever, exchanged sex for money or drugs ever, have a prior documented history of HIV infection, or a diagnosis of

syphilis, gonorrhea, or chlamydia during the three months prior to enrollment. And the point of the venereal disease exclusion is that that would normally be accompanied by HIV testing as part of standard of care and that, if they presented for the study, they would be -- we would be biasing toward a negative result. And that is assuming that they answered the third question accurately.

So, for the study, there would be two study encounters. The first would be the initial enrollment materials, completion of the questionnaire, and a collection of a seven-milliliter blood sample for testing. The subject would return within 14 days for a second encounter and receipt of test results, so that would include a second interview, counseling and referral if the subject is HIV positive. Study questionnaire must be translated into Spanish, and OMB and IRB approvals will be required. We can do a nine subject pilot prior to the OMB approval to identify issues associated with the questionnaire, in-person delivery, and data collection methodologies.

So, the questionnaire -- we have five questions on our questionnaire, and the first is how many different sexual partners have you had sex with? And that's defined as oral sex or anal intercourse during the past one month, three months, and 12 months. The second question is what kind of sex have you had during the past month? Oral sex, anal penetrative or receptive intercourse, both oral sex and anal intercourse, or not sexually active during the past month. The third question is, to your knowledge, have you had sex with an HIV positive partner during the past 12 months, yes or no? Do you always use condoms, use condoms sometimes, or never use condoms? And the last question is do you take pre-exposure prophylaxis or PrEP? And if the answer is yes to that, when was the last time that you took it?

So, these questions will be followed by HIV testing by the investigator, including blood screening for HIV using antibody and individual donor NAT testing. If the subject is HIV positive, then recency testing would be conducted for HIV. At the follow-up

visit within 14 days, there will be the interview to collect HIV risk exposure from those who have positive HIV tests of either NAT or antibody and counseling and referral for those HIV positive subjects. There'll be a sample repository established and maintained. The investigator shall submit an analysis plan to the FDA to include proposed data analyses, data specifications, data and table structures, a statistical plan to include any proposed modelling, and data quality control procedures. The investigator should plan to report to the FDA through monthly progress reports, study site selection reports so that we have a good understanding of where the geographic distribution is proposed, a nine subject -- one the pilot for nine subjects has been conducted, a nine subject pilot report, regular test result reports, and then data analysis reports including the mid-point, a draft, and final report, and then -- of the data analysis, and then a draft and final study report.

So, as I said before, the Source Sought notification has been published, and that is due by the

end of March, March 29 in fact. The RFP will be posted between May and June 2019. An award is expected in fiscal 2019, so that would be by the end of September. OMB and IRB approvals must be maintained. We'll need to initiate enrollment of MSM in late 2019 to early 2020, with full enrollment within six months, which would be late 2020, and then data analysis completed by early 2021. I'd like to acknowledge my colleagues in Office of Biostatistics and Epidemiology Anne Sieber and then also the contributions of the Blood Equality Working Group. Thank you.

QUESTIONS FOR SPEAKERS

DR. KAUFMAN: All right. Thanks. I'd like to ask the committee if there are questions for the speaker. Dr. Shapiro.

DR. SHAPIRO: I was just wondering if you had had any focus groups, in the development of these questions, to review them and look at the ability of individuals to understand them, interpret them, and answer them correctly.

DR. WHITAKER: So yes, there were focus groups conducted, but one of the questions today is to discuss the questions themselves.

DR. SHAPIRO: Okay. Two other questions. I was wondering if you had considered, besides these specific questions -- which individuals might have some hesitancy to answer -- whether you considered having all of the questions listed and, on the bottom, just say yes or no, qualify or not, in terms of comparing honesty of answers, overall, to the individual questions?

DR. WHITAKER: I don't know whether that was considered, but I think that there's some question study design methodologies which suggest that each question much be evaluated independently.

DR. SHAPIRO: Okay. And then, the third comment was you said one of the possibilities for recruitment of individuals might be at bars. I guess I would be a little concerned about the use of alcohol consumption or other drugs that might be prevalent in those areas for recruitment of subjects.

DR. WHITAKER: Well, I think we're looking for MSM who are interested in donating blood, so there are lots of opportunities -- there could be other events, festivals, gay pride events that might not include consumption of alcohol or other drugs and that it's up to the investigators to propose the way that they will be recruiting their subjects. So, this is just an example of --

DR. SHAPIRO: -- Right. I just might discourage the use of bars.

DR. KAUFMAN: Sorry. So, as I understand it, a goal of the study is to try to identify, within the global MSM population, which is currently considered as a single group, is there a low-risk population that can be identified. So, I was wondering if you had considered asking if MSM were married?

DR. WHITAKER: I don't know whether that was considered, but certainly that's one of the questions that we can discuss today as to whether that would identify a lower risk population.

DR. KAUFMAN: I speculate that it might, but I

have no idea. Dr. Stapleton.

DR. STAPLETON: Similarly, monogamy would be -- yeah.

DR. WHITAKER: Well, the number of sexual partners question I think will get at that, so that's one element of it.

DR. KAUFMAN: Dr. Baker.

DR. BAKER: Thank you. Can you tell us a little about this Blood Equality Working Group, the composition?

DR. WHITAKER: So, Dr. Eder had, in a slide earlier on -- so it included representatives from the LGBTQ community as well as blood collectors and public health professionals, as well. And that was a little bit before my time, so I don't know the exact representation on that. But perhaps other could comment.

DR. KAUFMAN: Can you comment a little about the power calculations and how many individuals with HIV that you anticipate finding -- or with recent HIV, and maybe a little more detail about how you would

determine that ability of this questionnaire to discriminate high risk from low risk?

DR. WHITAKER: Yes. So, hold on a second so I can go to my notes. Okay. The idea is to find at least one person in the high-risk cohort who is HIV NAT positive but antibody negative, so in the HIV window period. And this includes the highest risk incident rate for HIV, which would be African-American MSM, and the window period -- and also the window period calculation, so being the three-day net between NAT and HIV antibody negative -- so NAT positive, antibody positive. Actually, I'm not sure if that three days is completely accurate, but the annual infection incidence for -- whoops -- for the African-American MSM was quite high, about -- I have it here, but I can't read it.

DR. KAUFMAN: It's okay. I think it was in the range of 20 per 100,000.

DR. WHITAKER: 20 per 100,000 or maybe even -- actually, I think it was 50 per 100,000 for black MSM. So using the highest rate, we calculated that you would have to have 2,000 subjects to be able to identify at

least one.

DR. KAUFMAN: Dr. Basavaraju.

DR. BASAVARAJU: If the target is only to identify one, is that going to be enough to evaluate whether each question is effective in identifying enough infected MSM?

DR. WHITAKER: So this is a pilot study. So, if we get any kind of indication that there is an association between the questions and the test results, that's going to give us an indication of whether we should proceed to the full study where we would really have the power to be able to discriminate each of the questions.

DR. KAUFMAN: Actually, Dr. Bryant and then Dr. DeMaria.

DR. BRYANT: Thank you for your presentation. The question about the PrEP, will it be just -- is it a yes/no? I think when you went through --

DR. WHITAKER: -- Yes.

DR. BRYANT: Are you going to get any additional information if they answer yes, for how long

have they been on it or do they just take it occasionally?

DR. WHITAKER: So, the question is a yes/no question. The follow-up is "When was the last time you took it?" And then, I think the -- so in the follow-up -- 14 days later follow up period, if the subject is HIV positive, either by NAT or by antibody, then there will be additional questions about regular PrEP use and so on -- compliance.

DR. BRYANT: Okay.

DR. KAUFMAN: Dr. DeMaria.

DR. DEMARIA: Probably the most important determinate in terms of risk of exposure to HIV by having a sexual partner who's HIV positive is going to be whether that individual is virally suppressed or not. And obviously, maybe the subject doesn't know that, but it would be good to determine that to sort of put that in the perspective of overall risk.

DR. STAPLETON: You mentioned that the exclusion for a recent STI was -- one of those was you wanted to not have positive HIV test. But for PrEP

recommendations, they also receive HIV testing on a two, three-month basis. So, have you considered that?

DR. WHITAKER: Excluding for that? No.

DR. STRAMER: This is Susan Stramer. Can I ask a question?

DR. KAUFMAN: Yes.

DR. STRAMER: So, thank you, Barbee. So, for your solicitation, who are you soliciting or expecting to respond to the RSP? Is it groups who have not -- who have synergy or who represent MSM population? I'm just looking at who was supposed to respond to this.

DR. WHITAKER: So, for the Sources Sought, that's the small business set aside approach. Sue, can you mute your phone, please? Thank you. The Sources Sought is directed towards small business and the other categories that are included in that, but, for the next step, we would be looking for community-based organizations and, certainly, LGBT community-based organizations and investigators who might have contacts and good relationships within that community, as well.

DR. KAUFMAN: Okay. So, any other questions?

Dr. Ortel.

DR. ORTEL: Just a question about the way that you've got your questions written. If the purpose of question one is primarily to tell monogamous versus non-monogamous -- and we've already talked about the difficulty people might have with remembering numbers over the course of a year, so the quality of the data, if you're asking for a number -- would it just be simpler to say one month, three month, 12 months -- one or more than one, and then just have like a quick check box? Or do you really think that putting 8 versus 12, with a 12 month number, is going to give you data that you could use?

DR. WHITAKER: So, this is -- these questions are the proposed questions, and one of the requests for the -- what we would expect to see in the response to our solicitation request is indication about any suggestions about questions and any further -- how you would present them, what options you would give and so on. So, I think that's still there. Yeah.

DR. STAPLETON: Sorry to go back to the PrEP

question, but since PrEP may also alter serologic and nucleic acid testing results -- and I think we'll probably discuss that more later -- would be my guess -- it does seem maybe not to be a good -- that might be an exclusionary thing you might think about because they should be tested every three months. They are the highest risk, but if they take PrEP, we have good data that it's effective. So that may not -- you might -- do you have -- how important do you think that group is, I guess, would be my question?

DR. WHITAKER: Well, yeah, I think that's to be determined but certainly does give us an indication of risk, perceived risk, and then the follow up interview will provide additional information on the results of the test, as well as the results of the questions.

DR. KAUFMAN: Dr. Baker.

DR. BAKER: Hi. Thank you again. This question, then, is for Dr. Eder. Again, this Blood Equality Working Group -- can you give any more information about which advocacy organizations

participate?

DR. MARKS: Hi, Peter Marks, FDA. So, this was a group of a variety of different groups that was put together that included public health representatives from New York Department of Public Health. It included several different advocacy groups from -- with, actually, a national distribution, including G-M-H-C, a couple of other that I can't remember offhand. It included several academic institutions, including people from University of Alabama, University -- actually, from the Harvard system, including some representation from MIT and also from one of the California state universities. And there were probably a mix of others. It was not a deliberately -- one can't say that it was a nationally representative group, but it was a group that came together and discussed these questions. But there was, I think, a -- I think it's safe to say that there was a variety of opinions, in addition to -- it also included certain blood collection -- blood collectors, including representation from individuals from A-D-C and from New

York Blood Center. Thanks.

DR. BAKER: Thanks, and just a brief clarifying. So, was there anybody that you recall, or any groups, who used platelets, plasma products?

DR. MARKS: There were no users -- blood product users on that group.

DR. KAUFMAN: Dr. Lewis.

DR. LEWIS: For Dr. Whitaker, I'm sort of struggling with the -- and this is a hard study to do because you're trying to understand the predictive power of multiple questions that may interact. You're trying to identify predictive power for ruling out a rare event, and it's just tough. It just struck me that, with a sample size of 2,000 patients, there may be an opportunity to use the first 1,000 to figure out what you shouldn't do with the next 1,000. And so what I mean by that is that you may be able to find out from the first 1,000 that there are populations you don't want to include because you're not learning much from them and focus -- I would gently suggest that the agency consider suggesting a step-wise approach where

you split the sample and try to use what you learn in the first some percentage of the sample -- to use your resources as effectively as possible in the second half because you're trying to squeeze as much information as possible. And it's going to be very scarce.

DR. WHITAKER: Thank you.

DR. STRAMER: This is Sue Stramer, again. I have one other suggestion for Barbee and the questionnaire. There's nothing listed there about querying partners and perhaps including partners in this proposal.

DR. MARKS: Hi. Peter Marks, again. So that was discussed at length, and the feeling was that that was just not practical because it involves getting someone who is not involved in this. And in addition, in many cases, there're going to be multiple partners, so it's basically trying to overreach and overinterpret. So, we felt that -- the group was pretty unanimous, and this has been discussed both with other government agencies that it's too complex to try to go after the participants' partners. We have to --

in the blood donor center, ultimately, the questionnaire will be based on the individual at hand. And so if we were to rely on partners' responses, that could set up, again, something that's not generalizable from the study.

DR. KAUFMAN: I wanted to ask if you'd crunched the numbers for -- so assuming this study goes forward as a pilot, how big is the anticipated definitive study or larger study?

DR. WHITAKER: So, Peter's nodding, so the definitive study -- I'm not sure yet.

DR. MARKS: Sorry. So, the numbers that have been crunched before -- and that's why we need to do a pilot study. It would be a relatively expensive study on the order of something like 150 to 250,000 people, depending on what you see. And I think is well taken about wanting to essentially do this -- to refine things as much as you can, so we appreciate that feedback.

DR. KAUFMAN: Dr. Shapiro.

DR. SHAPIRO: Just one question. Is this

questionnaire administered in addition to the standard blood donor questionnaire to these individuals in this study?

DR. WHITAKER: No, it's just these five questions.

DR. SHAPIRO: So, you're not asking about IV drug use or other illicit drug use, which would also include another high risk population?

DR. WHITAKER: Well, actually, the exclusion -- so there would have to be some questions to identify that they're appropriate for the study before we get there. So, we're excluding the I-B-D-Us and getting money for sex or drugs. So that would --

DR. SHAPIRO: -- But you're excluding it base on what? Self-report?

DR. WHITAKER: Well, I mean, that's all blood donors ever do is self-report.

DR. SHAPIRO: Right. But if you're looking at specific questions that people either answer truthfully or not and may represent an analysis for this, I think you'd have to include that. Yes? No?

DR. WHITAKER: Include who? So, the excluded population?

DR. SHAPIRO: Yes -- that they're self-excluding -- that they're saying they're eligible because they don't use, say, for example, IV drugs. But then, you're going to look at these particular questions, and then that one person who ends up positive -- you may find a particular question -- I don't know how you do that in one patient, but you find power in a few questions. But it's actually a surrogate marker for something else.

DR. WHITAKER: So that's one of the reasons for the follow-up study, to really dig into how truthful they were, should they have been excluded, what risks do they have for HIV that might not have been identified otherwise. So that second interview is going to be very valuable.

DR. STAPLETON: Do you have plans to repeat those questions at the 14-day visit, once the person has meet you or the questionnaire -- the team and is more comfortable? Because that might be an opportunity

to seek out if they feel they were honest.

DR. WHITAKER: So, the investigator should propose the discussion for the follow-up interview, which would include what additional questions, what kind of discussion, what kind of probing would be done. And I would think that that would be a good approach to make sure that they hadn't lied there or misunderstood the question.

DR. STAPLETON: And would the people applying for this R-F-P have the opportunity to propose to save samples for future use for --

DR. WHITAKER: Yes. In fact, that is one of the criteria. Yes.

DR. KAUFMAN: Dr. Shapiro.

DR. SHAPIRO: So, are you testing for HCV and HBV in these samples, as well?

DR. WHITAKER: No, just HIV because that's the population of concern for HIV.

DR. KAUFMAN: I just want to echo Dr. Stapleton's comment. There was a paper from the Italian group that looked at individuals who had

donated, tested HIV positive, and then, on re-interviewing them, there was some really valuable information that was learned about did they interpret the questions right. And it was actually, in that particular study, a fairly high percentage of people didn't feel that some of the questions applied to them. So I think that probably would be a really valuable thing to do.

DR. WHITAKER: And I think Dr. Eder said this morning that the donors interpret the questions as "Is my blood safe?" not each one of the details of the questions. At least, that's been shown in some of the studies.

DR. KAUFMAN: Dr. Basavaraju.

DR. BASAVARAJU: So, I had a question about -- in the situation where a person states that they only have one sex partner, have you thought about asking whether they think the sex partner has only one partner as well or whether the partner may have multiple partners, as kind of a marker as to the person they're having sex with is high risk?

DR. WHITAKER: I don't know whether that was actually considered in the working group, but I think that there are certain questions about trustworthiness and how much can you really ever know -- that, you know, it's the same with a heterosexual couple.

DR. STAPLETON: But I take -- a lot of my patients say "I'm monogamous, but my partner's not." They're quite open -- people I know well that I've taken care of for years. But yeah.

DR. KAUFMAN: Dr. Baker.

DR. BAKER: Thank you. And have you thought about, in the design, to oversample for African-Americans and Hispanics?

DR. WHITAKER: So, we're asking the investigator to propose high risk populations from which we can capture this, and I would anticipate that that would be the case. And certainly, with the geographic distribution, we would hope to see that.

DR. KAUFMAN: Dr. DeVan.

DR. DEVAN: I just have two questions. Do you think you'll need to translate it into any other

languages other than just English and Spanish? And then the second question is question 4B to me just seems to be formatted a little differently than question 4A and 4C, just grammatically seems to have the adverb as the end. So maybe just for consistency, you could switch it.

DR. WHITAKER: Thank you, and regarding the other languages, I mean, I think mostly English and Spanish. And otherwise, that would be an additional exclusionary category.

DR. KAUFMAN: Can you comment as to whether this type of study has been done elsewhere?

DR. WHITAKER: Hmm. I don't think so.

DR. STAPLETON: One last thought. Not having thought through this, I don't have a lot of good suggestions, but since you're going to have this opportunity, will applicants have the opportunity to propose additional questions? Or is this fixed that these will be the five questions that will be asked?

DR. WHITAKER: It's fixed.

DR. STAPLETON: It seems like it might be an

opportunity to get additional information, so I don't know.

DR. WHITAKER: I think we'd like to see the follow-up interview really digging into any additional questions and any additional risk factors, and that would be the area where we would see more information coming. And as we said, this is framed as pilot study, so what we learn here could potentially be taken into a larger context.

DR. STAPLETON: Okay. But the follow-up, 14 day, they can ask much more extensive questionnaire.

DR. WHITAKER: It's more of an interview, a discussion, rather than just a questionnaire.

DR. STAPLETON: Okay.

DR. KAUFMAN: Dr. Baker.

DR. BAKER: But on that follow-up questionnaire, do you have a structured interview already created, and how fixed is that?

DR. WHITAKER: Not at this time, so that would be part of the proposal.

DR. BAKER: Thank you.

DR. KAUFMAN: Dr. Bryant.

DR. BRYANT: You mentioned that you would go to these areas where you felt like you would be able to recruit the most people to fill out the survey. Are you going to have fliers? Are you going to put it out on some of the websites that might services this community? Or how are you going to --?

DR. WHITAKER: So that would be up to the investigators' proposal, how they would be recruiting their sample.

DR. KAUFMAN: Dr. DeMaria.

DR. DEMARIA: There's been a lot of experience with venue-based recruitments. I think using that -- whoever applies for this, probably, will have that kind of experience.

DR. KAUFMAN: Any further questions from the committee? Dr. Shapiro.

DR. SHAPIRO: I just wondered if you considered adding a question regarding the use of alcohol or any other agent during sexual encounters because that's a risk factor for lowing inhibitions and

breakdown of safe sex practices.

DR. WHITAKER: I don't think that has been considered. It may have been considered, but it was not suggested by the community -- or the group that recommended the questions.

DR. KAUFMAN: Dr. Baker.

DR. BAKER: And was there any discussion about including any questions about donating blood within the scope of the questionnaire?

DR. WHITAKER: So, the population of interest is MSM who are interested in donating blood, so I think that would be part of the recruitment. You would want to gather information from people who think they would be able to donate, so hopefully, that is a safer population.

DR. KAUFMAN: Although, I suppose you could ask "Have you donated before?"

DR. WHITAKER: Mm-hmm. In your recruitment -- or as you go through your inclusion subject criteria.

DR. KAUFMAN: Drs. Chitlur and Stramer, do you have any final questions for the speaker?

DR. CHITLUR: No. Thank you.

DR. STRAMER: I do not. Thank you.

OPEN PUBLIC HEARING

DR. KAUFMAN: Okay. Thank you. So, thank you, Dr. Whitaker. And so, we'll now move on to the open public hearing. So, I have a statement to read. Welcome to the open public hearing session. Please state your name and your affiliation, if relevant to this meeting. Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the open public hearing session of the advisory committee 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 being to state if you have any financial interest 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 don't have any such interest, 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. Okay. So, I'd like to invite Richard Benjamin from Cerus to speak.

DR. BENJAMIN: Thank you, Dr. Kaufman. I was of the impression that my -- that my topic might be better after the MSM -- this afternoon's discussion.

DR. KAUFMAN: Yeah. That's fine, actually, if you would like to speak after that.

DR. BENJAMIN: Thank you.

DR. KAUFMAN: I'd like to ask, then, for Daniel Bruner to speak from Whitman-Walker Clinic in D.C.

MR. BRUNER: Good morning, Dr. Kaufman and members of the committee. Thank you for this opportunity to address you briefly. My name is Daniel Bruner. I'm the Senior Director of Policy at Whitman-

Walker Health here in Washington, D.C., and I have no relevant financial interest or conflicts. Whitman-Walker is a non-profit community-based health system serving the greater Washington, D.C. metropolitan area. We provide outpatient medical and behavioral healthcare, dental care. We have two pharmacies, community health services, youth services, legal services, and other health related services. We have more than 20,000 individuals and families who received those services last year.

We specialize in HIV treatment and prevention and the health and wellness needs of the lesbian, gay, and bisexual and transgender community, the LGBT community. Responding to the HIV epidemic has been at the center of our mission for four decades, since the first AIDS cases, even before it was known as AIDS, in Washington, D.C. We currently have more than 3,500 HIV positive patients, including more than 25 percent of all of the people living D.C. with an HIV diagnosis. We provide low barrier HIV and STI testing and counseling services at all of our sites and throughout

the metropolitan area, and we operate regular walk-in STI clinics, as well. We have more than 1,000 patients who are currently on PrEP, and we recently instituted a low barrier PrEP clinic to make it easier for individuals who would benefit from PrEP to start and adhere to that therapy. We've also been involved since the 1980s in clinical research of HIV treatment and prevention modalities and issues related to LGBT health.

Policies that effect men who have sex with men who identify as gay or bisexual, or otherwise identify as non-heterosexual, have been of great importance to us since the very beginning. Last year, almost 70 percent of our male patients who identified their sexual orientation identified as non-heterosexual, gay, homosexual, bisexual, or other. We've followed the MSM blood donation policy since the 1980s, and we were involved in submitting detailed comments in 2015, which resulted in the change of policy to a one-year deferral, and then also in 2016, as well, when the new proceeding was instituted. And we've been an active

participant in the Blood Equality Working Group since that was started in 2016 -- the group that's been referenced several times this morning.

For many years, the policy of deferring blood donations from all gay and bisexual men who've engaged in any same-sex sexual activity, even decades earlier, regardless of the type of sexual activity or the likelihood of HIV transmission, was widely perceived in the LGBT community as stigmatizing. And although there certainly has been improvement, the current one-year deferral policy still excludes many individuals who pose no risk whatever to the blood supply on the basis of their sexual orientation alone. We certainly support enthusiastically the FDA's efforts to explore how a focus on specific risk related behaviors the individual donors could continue to protect the safety, purity, and potency of the blood supply without labeling people as high risk based only on their sexual orientation. So, we're very excited by the potential of this proposed HIV risk questionnaire study to inform future blood donation policy, and we look forward to

opportunities to continue to be of assistance to the agency in this really important endeavor. Thank you.

OPEN COMMITTEE DISCUSSION

DR. KAUFMAN: Thank you. All right. So, at this time, is there anyone else from the public that would like to make a comment? Okay. So, hearing none. We will now move to an open committee discussion, and really, I'd just like to encourage everyone on the committee to contribute your thoughts to this really complicated area. So, the first question for committee discussion is to comment on what has been learned from implementing other MSM policies internationally, such as risk-based deferral methods or quarantine to retest for plasma, and how this information can inform the current U.S. MSM deferral policy.

Why don't I -- I have one thing that I wanted to ask about or maybe just comment on -- is I thought that the approach --the risk-based deferral methods that were put in in Italy and Spain were interesting.

These were put in without any data to support them. They were just instituted, and it's only retrospectively or after having done this that it's possible to go back and see how well these approaches have worked or didn't work. One thing that caught my attention was the -- related to something that Dr. Eder talked about at the beginning, which was that the rate of HIV per 100,000 in the general population in the U.S. is pretty high, over 100. I'm not exactly sure what the sort of exact number is. You get about a one log or a ten-fold reduction using the current screening methodology that we're using, such that first time donors have an HIV rate of approximately 8.8, maybe 10 per 100,000. And then the rate is about another log lower among repeat donors, since they get tested at the time of their donation. And that will catch most, although not quite all, of HIV infected individuals.

So, the thing that caught my attention was in the Spanish study. It looked like the rate in the general population was really not so different than the rate among donors. The authors of this one study --

and again, it was just one paper, though, comment that they were concerned that it didn't look like they were getting any real safety benefit from their strategy. So, I don't know if Dr. Goldman will want to maybe comment on that and if that's been seen in any other studies.

DR. GOLDMAN: Hi. Yeah. I think you've nicely summarized it. If you see the same rate in your first-time donors as in the general population, you have to ask yourself what are you doing with your screening? The other thing that's sort of interesting is we actually defer very few donors for MSM, so most of the screening that's happening is a self-deferral of people who know that they are in a risk group for donation and are just not coming into the clinic. It's not a very common reason for deferral at a blood donor clinic. So, I do think that that's a problem with that Spanish data, and there's not a lot of data.

There's that one article from Italy that also seemed to get at individuals not really understanding the questions well. And it's really hard to know what

that means in our context, right? They're being screened by a physician. What are they actually being asked? Do they understand what they're being asked? As questions get more complicated, it's harder for people to know what you're asking them about. So, I think that is a valid point, and it's a strength of our system, right, that the rates in our donors are very low. So either they're self-excluding and they're not showing up on the clinics, or we're asking them the right questions and deferring them or, probably, a combination of both.

DR. KAUFMAN: Dr. DeMaria.

DR. DEMARIA: I think in terms of the labor intensity of adding that kind of interview to the screening process -- I think with the results that's obtained seems to me to be more than it's worth. In terms of retest for plasma, it seems to me it's just a way of sort of allowing people to donate without really changing anything. You know, it just -- we'll take your plasma and then retest you to see if we should have or not. But I -- that again doesn't really

address the underlying issue of blood equality and changing the way we do things to allow people to donate blood but to still maintain the safety of the blood supply.

DR. KAUFMAN: Dr. Bryant.

DR. BRYANT: I think one of the things that I keep thinking about is this use of the PrEP. What is this going to do with the window period? We don't really know, in a group of people that are taking this drug, if the detectable limit needs to be change; in other words, their (inaudible) needs to be different on our testing.

Or is the window period going to go from 10 days to 20 days to 30 days? And then that brings in the question about does retesting of plasma. Would this be the population that we keep the plasma and test them four months later? Maybe the window period is longer. I don't know -- if they're on this drug. And I don't know enough about how this drug works and how the initial studies were done, but obviously, it's an effective drug or combination of drugs that has some

benefit. So how does it go about providing this benefit? Is it --?

DR. KAUFMAN: I think you raised a number of really interesting points. PrEP is -- I find the PrEP thing confusing. As one of the -- I think Dr. Whitaker mentioned it's not clear whether it would be considered a protective factor or a risk factor. Actually, it may have been one of the other speakers. Overall, it's clearly doing good in the world, in society. In this particular case, I don't know, and maybe I could ask one of our epidemiologists to sort of comment on your thoughts about this.

DR. STAPLETON: As a virologist -- I'm not an epidemiologist, but I think we don't know a lot about how this effects seroconversion. We certainly know it reduces viral loads. And so, you may delay detection of infection, but being a two-drug regimen, if someone becomes infected and stays on that, they're likely to develop resistance, in the majority of people, fairly rapidly, over three to six months. They should be getting tested every three months, as I mentioned. So,

I think it does throw a wrench into the works regarding the window period, and I don't think we have enough information. I think -- I know there are people studying this, and some of them might be in the audience, if they'd like to comment on it as well.

DR. KAUFMAN: Dr. DeMaria.

DR. DEMARIA: Yeah. I think if the ultimate question we're going to be discussing is going from one year to three months, I think from a public policy standpoint -- you know, we're trying to get everybody at risk, in Massachusetts, on PrEP to reduce HIV transmission. And defining everybody at risk almost excludes them during that three-month period because, if they're really at ongoing risk, they're not going to meet the requirements of not having an exposure during that three months. So, I think, for me, throwing PrEP into the mix of considering this is making it more difficult rather than less difficult to talk about.

If we're talking about anybody at risk for HIV infection should be thrown -- well, no. It makes it more difficult. I don't think it's relevant to the

discussion of three months versus 12 months because what we foresee is that people at high risk are on PrEP for the time they're at high risk. And not everybody is at high risk for the rest of their lives, so people are going to be going off PrEP because they're changing behavior, usually with getting older -- is going to put them at a less risk situation so that they're not going to get HIV infection. And then, five years later when they don't need to be on PrEP anymore because their risk has changed, they should be eligible to donate blood because they've avoided getting HIV infection.

DR. KAUFMAN: Dr. Bloch.

DR. BLOCH: This may be a little bit off topic, but I'm going to interpret that somewhat liberally as looking at risk-based deferral. So, in terms of the leading factor for what's going to impact risk, and one of the input parameters in risk-based deferral is going to be incidence -- in this case, eclipse-based infection. Now, it's a little interesting having today's session back to back with the zika session of yesterday. So yesterday, we voted

to be as aggressive as possible for a theoretical risk which effects one subset of the population. And to date, there's never been a clinical case of transfusion transmitted zika. Now, we're arguing to relax policy, which -- so going back, I fully appreciate the historical aspects of this where it really was, in terms of social chastise of it, was totally out of line.

Now that has been -- it's fallen in-line with other risk factors, and yet you want to relax -- single this out to relax it even more, despite the evidence which was shown this morning that the epidemiology is still focused in this population. It's not a judgement about sexual orientation. It's purely -- frankly, I don't think it's actually about donor. It's really not a donor problem. It's recipient risk problem. So that's the one piece of it.

And then the second thing is -- sorry. Going back to I think Dr. Brooks' talk from this morning where, if you look at -- if we look at donation at the moment, there's really underrepresentation from

minority donors, specifically African-Americans and Latino donors. And there's really been effort to engage those donor populations. Well, what he has shown is that there's -- this is one population which is specifically at risk of HIV. So, what we've learned, I think -- it's just interesting that this has been singled out specifically, and yet we know that there is sound medical evidence -- well, epidemiological evidence that this is -- this should not be done.

DR. KAUFMAN: Mr. Templin.

MR. TEMPLIN: Thank you. As a person with an arm in the game and a higher demand for a safe blood supply, I'm just concerned with the long-term ramifications of PrEP and all this antiretroviral therapy in the blood supply and how that may ultimately impact the donor health and the recipient health of that blood because, you know, we just don't know. This is such new technology, and people are taking it. And then they're not taking it, and then they're taking it again. I know people that are on antiretroviral

therapy, and the medicine itself is pretty hard on these individuals. So, it just concerns me that maybe there's not more studies being done on the long-term ramifications of this stuff. Thank you.

DR. KAUFMAN: Thanks. I think, in general, the approach that's been taking to individuals who donate who are taking some sort of medicine -- and that's most donors. It's certainly a lot of donors. The general approach that's taken by FDA is to -- certainly to exclude donors who are on relatively small number of known teratogens, with concern for the recipients. But for the most part, when individuals are excluded for being on medicines, the main concern is why were you on the drug versus what will it do to the recipient. The assumption is, if you're taking antibiotics, that -- let's say you're taking amoxicillin. The drug will be diluted in the donor's plasma, and then, if a recipient were to receive it, it would be diluted again in the recipient's plasma and probably wouldn't do much to the recipient.

But on the other hand, you have to ask the

question “Well, why are you taking the amoxicillin?” If you had a bacterial infection that could potentially see the blood product, well, that’s a different story. So, for the most part, that’s -- anyway, that’s how the drug issues are handled. And the PrEP is a whole -- or other antiretrovirals brings up a whole other, you know, kind of range of questions like we’ve been talking about. But thank you. Sorry. Sridhar.

DR. BASAVARAJU: So, I just wanted to say something, I guess, to follow up with what Dr. Bloch was just mentioning. So, one thing at CDC that we do is the NBCUS survey, where every other year we estimate how much blood was collected and how much blood was used in the U.S. And what we’ve noted is that, for several years now, there’s actually a declining demand for blood and, therefore, a declining number of collections of blood. But despite that, there’s still a surplus. Blood collectors are still collecting more blood products than are used. So there doesn’t seem to at least be, nationally -- at least based on evidence that we have -- there’s actually a demand for more

blood products to be collected, such that you'd have to potentially dip into riskier populations. Which is not the case -- for example, transplants, where there's not enough transplants for people who need them. So, people who want a transplant, for example, would be willing to take on additional risk.

DR. KAUFMAN: No. I agree with that point. I think collecting blood is difficult. I think it's fair to say, in general, the U.S. has been able to meet the demands year after year. So, I don't think there's really an argument to be made, truthfully, in terms of blood availability. I think the questions related to potential changes in approaches that might allow MSM to donate really are related to issues more of social justice, rather than availability.

Having said that, I think, as I mentioned at the beginning, the challenges -- are there ways that donation can be extended to individuals who are currently excluded without changing the level of safety that's been achieved? So, for example, I think it was -- we saw it took quite a while after Australia went

from a lifetime deferral to a 12 month -- it took quite a while for other countries to follow suite, and part of that was waiting to see what happened. We know the window period for HIV NAT is somewhere around 10 days, maybe a little less. That's not the same as saying, "Well, if we just defer for 10 days or 12 days, that ought to be completely adequate." What you do in terms of a population with a deferral policy really can have implications that maybe cannot be predicted. And so, anyway, I think that one of the reasons it took so long was just waiting for some data from around the world to see would there be any effect even from that -- what seemed to be quite a modest change. Dr. Hollinger.

DR. HOLLINGER: Yes. So, part of the issue is this early period, which you might call a window period. Virology might call it an eclipse period. Some other people use the word latency. It's a little difficult term to use virologically, at this stage. But one of the issues is how infectious or what's the data that, during this period of time if there's transmission to someone with a current sensitivity to

the assays today. I tried to go back and look at those groups of countries that do not have a time deferral, and it's really hard to find any information about transmission of HIV in those populations. It's either not collected. They don't have good surveillance, a whole lot of reasons.

But it is a very important piece of information because if there's going to be -- if the blood's going to be deferred or not utilized -- so it's only really in that one little period there where it's difficult. It has a lot of similarities, in many cases, to even, like, Hepatitis B, for example, in which there's some occult Hepatitis B. Most of the time, in occult Hepatitis B, you can find HPV DNA in the blood, but there are other times when it's just in the liver and it's not in the blood. And these patients do not appear to be infectious.

And even at very low levels, we know in many cases that the disease is not transmitted. Most of the disease, whether it's Hepatitis C, Hepatitis B, HIV and so on, there's a relationship between transmission and

the level of virus in the blood, so that patients who are treated, for example -- Hepatitis B and treated but may have some virus in their blood do not appear to transmit. So, I think these are the real problems. So, I'd like to know if there is some -- and there are probably some people here who may have that data about transmission during this period of eclipse. That's all.

DR. KAUFMAN: Just so I understand your question, are you asking about what is the chance that you can donate a unit that's truly infectious a day after acquiring HIV or five days --?

DR. HOLLINGER: In that seven to ten days.

DR. KAUFMAN: Yeah. Let me ask Sue Stramer or maybe one of the other people at the table can address that.

DR. STRAMER: Okay. Yes. Hi, this is Susan. In the United States, since we've implemented either P24 antigen or NAT -- so this is going back to about 1999, eight components have been collected from window period donates. And of those eight, five have

transmitted. And these all relate to transmission from large plasma containing components, either from FFP or FP24 or platelets in a large volume of plasma. The three that did not transmit were from red cell collections in which there was far less plasma available. So, there is differential transfusion transmission, depending on the plasma volume, that relates to the viral load in the infectious individual.

DR. HOLLINGER: But Sue, I'm not talking -- so let's get our -- the terms maybe necessary -- the window period. You're talking about NAT positive but antibody negative? Because you often speak of the fact that there hasn't been any transmission of HIV, HPV, HCV since 2015 documented. So, are we talking about NAT positive but antibody negative? Is that what you're talking about in the window period? Or are you talking about that seven to ten-day period where you can't detect anything? And if so, how is it determined, then, that there was transmission?

DR. STRAMER: I'm talking about the seven to ten days, and let's talk about one agent at a time.

So, if we limit this to HIV, we know this from reports of transfusion transmitted HIV and the investigation of co-components from the same donor who was responsible for the transfusion transmitted HIV case. So, from documented transfusion transmissions, there have been co-components, and the co-components that did not transmit were all from red cells.

So, the point I'm trying to make within the seven to ten-day window period is viral loads, of course, are dependent on how much plasma, which is where the virus is -- how much plasma is present in the components. So large plasma containing components are more infectious than something like red cells, which only contain a small amount. And we're talking now only about the window period -- the seven to ten days, which, Blaine, to go back and use your definitions, includes an eclipse period in which virus would not be able to be detected by current assays and window period which more sensitive methods of testing may be able to detect low levels of virus.

DR. HOLLINGER: If I may ask, Dr. Stramer, of

those five that transmitted, how many of those were tested with current -- with viral load assays with the sensitivity of 20 -- cutoff of 20 copies per mil?

DR. STRAMER: Well, we actually use more sensitive assays than quantitative viral load assays, and we do mini pool NATs. And really, the question is what's the differential sensitivity between doing something like ID NAT versus mini pool NAT? So, of the five that I referenced, one was a P24 antigen, a very early transmission, and the others were bi-pool NAT. Now, we don't know in most cases, if we would have done individual donation NAT, if those donors would have been interdicted because then most, if not all cases, residual samples are not available. We don't store samples from all donation, as they do in other countries like Japan, to see if we've had a transfusion transmission that we can go back and test those donors.

DR. HOLLINGER: So that's essentially my point of what I was bringing up. I'm still trying to look for the issues about the concern in that particular period of time of seven to ten days with individual

donations, detection, and so on. And that data's hard to come by. My gut feeling is that it's pretty limited in transmission, but that's the important question, I think, facing us, in terms of when to use a time deferral.

DR. KAUFMAN: Well, I'm -- I'm sorry. Go ahead, Dr. Bloch.

DR. BLOCH: But then if one's going to be completely reliant on the testing, then why have any deferral criteria? Why not just accept everyone?

DR. KAUFMAN: So, I think -- my understanding is that -- so first, if you -- I think the FDA has modeled this, and this is a part of it. We're talking about rates that are low enough that everything becomes really hard to study. So, you end up doing a lot of mathematical modeling. The FDA has modeled what would happen if there were no MSM deferral at all. What is we just got rid of it? And it's not like there would be an enormous number of infectious units entering the blood supply tomorrow, if you did it today.

The tests are really, really good, and we're

talking about residual risk, which -- and not to really belabor this point, but it's all window period donation. So there really aren't any other, like, meaningful sources of residual risk. But the FDA's modeling did suggest that you would increase the risk from its current level to something like fourfold higher. So, it's still really, really low. You wouldn't notice any day to day change, but the feeling of the agency -- and I think that there's fairly broad agreement -- is that that would not be consistent with what we're trying to do in the (inaudible) community or for the agency.

And so, I think that's an important place to start -- that is let's say, as a baseline, I think there should be agreement that we should not do anything that'll make the blood supply less safe. We may choose to do things that make it safer. But in that context, can we change how we do things without affecting safety? So, for example, I will say that England and Japan are going to a shorter deferral period. They're going from 12 months to three,

something like that. Will that make any difference in safety? I think it remains to be seen. Although, it sounds like from Dr. Goldman's presentation the data so far would suggest that it's no worse. And maybe you could comment if you thought maybe it was even a little bit better.

DR. GOLDMAN: I think it's a bitearly days for the data from the UK, but they haven't seen an increase in the HIV rate in their donors. And their HIV rate is really low to start with, with not a lot -- kind of no NAT only positive donors. So, they already are starting from a very low point, and they haven't seen any difference yet. I'm not aware of a lot of data from Japan, so I really couldn't comment on that.

DR. DEMARIA: Even without the data, I haven't heard anything that was just, biologically, there would be a difference between a year and three months. There's nothing to suggest -- and there is something to suggest you get better history, which is advantageous, at three months versus a year. So, it's hard for me to see that there would be a difference and there might

even be a benefit of going to three months.

DR. KAUFMAN: I think that's right, and I think one of the -- you know, I talked about potentially having things happen after a change is made that you might not be able to anticipate. So, for example, let's say that a country put in -- went from a year to three months. And then what if an unexpected consequence was that individuals who were at higher risk said, "Oh, well, maybe it doesn't matter anymore. They're kind of shortening it, so I don't have to pay attention to screening questions," or that sort of thing. I'm not saying that would happen. I'm just saying that you can't -- we're talking about huge numbers of people, and you can't really accurately predict what everybody's going to do or what the exact effects are going to be. So frankly, I was really -- this was the first I had really heard much about the TIMS program.

I think having a method that's rigorous that can be used to measure the effect of changes moving forward is incredibly important. So just having that

as a -- no matter what you do. Obviously, the number of -- the absolute number of infectious donations is incredibly important stat, but also the ratio of that to what's happening in the general population may also turn out to be -- to matter later if that goes down, in the future -- that sort of thing. Sorry. Dr. Bloch, did you have another comment? Sue, go ahead.

DR. STRAMER: Oh, sorry. I'm glad you brought up three months. I wanted to bring it up as an industry comment to keep the momentum of change moving forward and to add another potential way that we could decrease, at least, the time-based deferral. Certainly from TTIMS, we haven't fully evaluated it. Allen reviewed the changes in prevalence incidences and other laboratory-based factors that we're looking at. So, we have some time, and over two year -- 2019 to look at what the results of our studies are. But so far, the data, as Allen mentioned, are promising without change, and change hasn't been observed in other countries, as shown from Mindy's presentation. But as we gain experience with three months in Canada, the UK, and

Japan, I mean, I think we should look at those data very carefully, as well, because perhaps on our way to behavioral-based deferral, if we ever get there -- I mean, we can go from a 12 month to three months, and the data support that.

DR. KAUFMAN: Dr. Lewis.

DR. LEWIS: So, several comments. I've been storing them up, and I apologize. Number one, the comment about the juxtaposition with zika I thought was really interesting. There's a fundamental difference, which is that the epidemiology of zika, both temporally and geographically, is variable and unpredictable; whereas, the epidemiology that we've seen here is actually a lot of things have really stabilized. And there's a huge opportunity in that, in that you actually can study things and gain data that can be useful for estimating risk for implementing a policy change. And with zika, it's exactly the opposite. Studying what happened in 2016 tells us almost nothing about what's going to happen in 2020. So I think there's a real opportunity there that adds appeal to

study and then act, as opposed to theoretical things. The second general comment I'll make is that the risk here is really out in the tail, and there was the distribution of the time to detection. I think there was a comment about the 99 percent area under the time to detection under NAT being something like -- how many days is it? Thirty-three days?

DR. KAUFMAN: Thirty-three.

DR. LEWIS: And then it was stated by one of the speakers that that meant that, if you're negative at that point, there's a 99 percent probability of something. That was actually, in my view, likely to be an incorrect probability statement. I think that was a 99 percent sensitivity mark in time. And it's unclear whether things that might happen, like the use of PrEP or failure to use -- incomplete use of PrEP leading to unexpected seroconversions, might actually change that distribution out in the tail. And the hardest part of a distribution to both estimate and to be stable is out there in the tail on the edges. So, I think there's some uncertainty in that time limit that we just need

to be cognizant of.

With that said, the third part of my sort of pondering-ness has to do with the social justice blood equality argument. So usually when we talk about justice as one of the principles for consent, distribution of -- say, burden of participation in research, we're worried about the burden and risk of participation in research being borne by a population that will not share in the benefits of that research. And here, it seems just a tiny bit different because we are -- the prior deferrals excluded a population from the opportunity to donate, but that population is not being denied the benefit of the blood supply, given that -- if I understand correctly -- we, at least historically, have an adequate blood supply. So, the justice argument is based on a lack of an opportunity to contribute to a shared resource, but it's not on lack of access to that resource.

So, I'm clearly not an ethicist. So, I'm just wondering if there's anybody who can comment just with a little more clarity and precision about the social

justice and blood equality argument. What exactly is the harm that is being created by additional prolongation of -- for example, the 12-month deferral? And I did hear very clearly the point about a perception of stigmatization. I'm wondering is there anything other than that that I'm missing?

DR. KAUFMAN: Dr. DeVan.

DR. DEVAN: I'm not an ethicist either, and I don't think we should get hung up trying to fit this into one of the seven categories that are from Social Justice 101. I think this is a full participation in society question. I mean, I think we are trying -- we are taking a whole group of people and saying "You may not fully contribute. You may not fully participate in society. Period." And I don't think we know enough about certain risk factors, certain -- I think we just need to dig a little bit more. But for me, you're not benefiting from the blood supply. It's you're being told that you cannot do something that other people can do, potentially unfairly or without good science that blocks you from doing it.

DR. KAUFMAN: And I think it's complex. That is blood donation is -- it really cannot be conceived of as a civil right, I don't think. We exclude people for many things. I live in Boston. There's a big community of people who've lived in Europe between '80 and '96, at a time when there was worry about a variant in CJD. And they're deferred from donating. We defer lots of different people for lots of reasons, and it's not -- with the best of intentions. It's not to be discriminatory. It's to protect the patients. And truly, that's the -- I think that that's really FDA's intent, that is the goal is truly not to discriminate against any group, but rather to reduce risk based on evidence for the safety of patients.

And we're kind of at a time when it may be appropriate to reflect on, and potentially change, ways that we have addressed risks to the blood supply, given new testing, new science, and so on. This has been, in the past, of course -- this deferral for MSM has been obviously, I think by many people, viewed as discriminatory. I truly do not believe that it is, but

I think, at the same time, it's a worthwhile endeavor to try to see what can be done with the -- anyway, with that in mind, if that makes any sense. Dr. Schreiber.

DR. SCHREIBER: So, summarizing a little bit, we all agree, I think, that patient safety is paramount, and no decision made any time by the FDA should result in any diminution in the safety of the patient. I think we all agree that anyone should be allowed to donate that does not reduce the safety of a patient, regardless of any other arguments about discrimination. If it's safe for that person to donate, they should be allowed to donate.

We're presented with, I think, today, three strategies. The third we'll talk about, which is pathogen reduction, this afternoon. That kind of makes all the rest of this discussion today irrelevant. Because if you can pathogen reduce universally, then the question -- then a lot of these questions become less relevant. But that's for this afternoon.

That leaves us two strategies. One is the time-based deferral strategy, and I think that -- I

would hope that we would agree that that time-based deferral -- that time should be the minimal amount of time necessary until, essentially, 100 percent of the people who will convert -- or the window period is over. And I think -- it seems to me that a year is too long, and probably three months is adequate for that to occur. And there does not seem to me to be -- I can't think of a biologic or scientific reason that one year is better than three months, right? Because everybody that's going to become positive will do so by three months. And in fact, maybe three months is better because people can remember the last time they had unprotected intercourse or sex better at three months than they can at one year.

So, we also have another country, albeit one with a very low incidence, England, who's gone to a three-month period. So, there's a precedent. So, to me, that seems quite reasonable. I think the question of the quarantining -- to me, the issue of quarantining is more of a logistical and economic question. Is that feasible logistically and economically? I have no

idea. If it is feasible logistically and economically, then I see no reason not to do that because that seems very safe and won't harm the safety of the patient. So, to me, these are the issues as we're presented at this time.

DR. KAUFMAN: Thank you. Dr. Marks.

DR. MARKS: So, we really appreciate the comments. I think -- we understand the issues here. I think one of the issues that we've discussed what the UK has done. And with all due respect to our European colleagues, there's just not data, and the idea here -- just to refocus on this study, which will take some time to conduct and which is only a pilot study for potential subsequent study -- is to actually have data. Because when we look at what the United Kingdom did when they made their change -- again, with all due respect to their change process. If you look over the report of a scientific advisory board, it was solely based on, essentially, theoretical considerations, not based on data.

We also know that the United States has a very

different epidemiology of HIV -- and I think Dr. Brooks could comment more on that -- than the United Kingdom and other places. So I think what we're looking to do here is, I think, think about this pilot study -- and that's what I think we were looking to get comments on -- as a way to try to get some data that could potentially help us see a way forward in the future where you might be able to get away from a time-based deferral.

I will tell you from the last docket we had open -- we got feedback to the last docket -- the LGBTQ community in general finds any time-based deferral discriminatory because -- again, we can argue all the aspects of this, but this study is being done -- is being proposed in an effort to find is it possible in the United States, with the existing testing strategy that we have in place -- because I agree that pathogen reduction, potentially, adds a whole new realm to this. But with our existing testing structure, is there a way to come away from this without the need for a time-based deferral? Can you ask questions for at least

some subset and not need that deferral? So that's what -- but the discussion here today has been fantastic because it's bringing up the questions and a lot of the issues that we've been grappling with. So, thank you.

DR. KAUFMAN: Let's put attention then to discussion question two, which is on the screen. Comment on the questions proposed for the study in the HIV risk questionnaire, whether there are any additions or modifications to the study in order to best identify behavioral risk questions to predict the risk of HIV transmission in the MSM population. So, I'll open that up to the committee. Dr. Lewis.

DR. LEWIS: First of all, to Dr. Marks, that was very helpful. So, I think one of the things we saw from the international experience is that there is geographic heterogeneity in the characteristics, and one of the things we have in the U.S., as you pointed out, is we not only have a very different epidemiology of the epidemic. We actually have heterogeneity within the country. I'm sorry. I don't want to get into Spanish politics, but we have some of the similar

divides of different parts of the country seeming like they're different countries.

And so one of the things -- and I think this addresses specifically the issue of modifications to the study -- so I think that, even in the very large study that you propose, but certainly in the pilot study, it's going to be difficult to understand whether you would have gotten different results based on the areas in the country in which you sampled. You have a pre-specified approach to sampling particularly high-risk areas that may yield data that are not applicable to other areas of the country that you didn't want to include in your study because you know you would have gotten nothing useful. And so I guess what I'm saying here is that in the pilot study, but also in, especially, the follow up study, trying to capture prospectively measures of differences in the epidemiology of the HIV infected community, or at-risk community, that will help you understand whether, in fact, the non-time-based strategy you ultimately propose needs to be different based on the demographics

or the geography in which they are applied. Because it seems very difficult -- just as there's not a one size fits all across Europe -- that there's actually going to be an appropriate one size fits all across the U.S.

DR. KAUFMAN: Well, maybe we can -- I guess I have some, potentially, more detailed questions just about the pilot study itself. One thing that I would like to ask is what are the main primary -- main outcomes, primary and secondary outcomes from it? That is, many pilots that are done for questions of feasibility. I don't know. Maybe Dr. Marks or Barbee can comment on that. My worry is just that, if it's a big enough study just to catch one recent infection, what can be learned from it?

DR. MARKS: So, thanks. So, I think Barbee can also answer this. There's a range -- because we don't know exactly what the numbers we're going to actually predict are, depending on how you essentially run your numbers, it could catch at least one. It could catch five. It could catch. We don't know, and that'll depend on -- and I think that last comment

about where you are in the country is very key to this. We decided -- we actually went back and forth in thinking about this, whether it made sense to do a more representative sampling upfront or to essentially concentrate on areas. But we thought it would be important to try to at least see if we get a signal first, and then see if there's some correlation that we can make, see if at least the test questions work -- if they're acceptable.

It turns out some of these questions may not be fully acceptable in certain regions of the country, but we'll at least get to -- in terms of general use. But at least we'll get a sense of these. It will give us some correlation here. We will have a sample bank, then, afterwards, which will, I think, be useful for being able to go back and try to do some more refinement. So again, we don't know exactly, but this is to catch at least something, hopefully, and get some idea. I mean, I think if we -- the study might be a failure, in one sense, if we catch zero.

But I would put it to you that this is a study

worth doing, in any case, from the public health perspective because, as we know -- and I guess I'd ask Dr. Brooks -- we know that, depending on where this is done -- and we'd hope it's done in places where there are increasing incidences in some ways of HIV in certain populations -- you are going to identify men who didn't know they were infected. And they will benefit from being identified. And so even if it's a -- I guess this is one where we can fall back on even if the ultimate primary and secondary objectives fail, the tertiary objective not stated will actually be beneficial to participants in some way.

DR. HOLLINGER: Just a question while you're still up. Doesn't Washington, D.C. have probably the highest risk of HIV in MSM? So that seems like a great place to do a study.

DR. BROOKS: Washington, D.C. would be an excellent place to do a study, as well.

DR. HOLLINGER: Yeah. I mean, several pooled hard.

DR. BROOKS: It's a lot closer, too.

DR. HOLLINGER: Absolutely.

DR. BROOKS: I just wanted to add one thing to Dr. Marks' comment, which is one of the reasons -- when we do HIV studies related to prevention, in general, in high prevalence areas is to the point that we want to demonstrate either that you can measure something or that it's effective as quickly as possible. We have no reason to believe that when we translate something we've learned in that circumstance to a low prevalence area that the risks are any different. We may turn up less infection, but there's no reason to believe that anal sex practiced in Georgia is substantially different than that practiced in Montana. So, if we're asking that same question, we would expect to have the same a priori sensitivity -- probably not going to yield as many positives, however.

DR. KAUFMAN: Dr. Basavaraju.

DR. BASAVARAJU: So, for Dr. Marks about this plan. So, if you do the pilot and you find zero infections, what are you going to do with that information? Like what does that mean for the larger

study? What does that mean for the questionnaire?

DR. MARKS: It may mean that we go back to the drawing board and bring the advisors together and think more about it. I think it would all depend on what we actually find. Yes. If it was a total no findings, that would be -- we'd have to go back to the drawing board. But I think, from looking at what we've done with the statistics, we think that if we go and do this in the right -- and that's why we're going -- to the idea of going to the Washington, D.C.s, Atlanta, Miami -- I'm sorry to call these -- for the mayors of these cities, I'm sorry to call you out. They've heard it before. Right -- Chicago, Los Angeles -- if you go to those cities, the calculation you can make is that we should at least see one. We've done some calculations where you might see as many as ten, so it just -- hopefully, we'll see something. Do we know -- if it's zero, I guess we're back at the drawing board.

And then, I would agree with you. We would have wasted this time from the standpoint of advancing the policy. On the other hand, we still would have

benefited some people from helping them be diagnosed and also putting together a study infrastructure that might be beneficial in the future to work with.

DR. KAUFMAN: Dr. Shapiro and then Dr. Lewis.

DR. SHAPIRO: Thinking about this pilot study, it really seems to me that there's two questions imbedded in this. One is the applicability of these questions in terms of defining risk for a certain population, and then the other is, looking at patients who convert, are they being honest? Are they reporting this information? How likely are you going to be able to use this information for your blood donation policy?

It would seem, based on that, then you really need two studies -- two subpopulations to apply this to. One is to an overall MSM population to just look at the questionnaires and do the testing and say are you likely to get honest answers and relevant answers from this. And the other is to look at populations who are antibody-negative NATpositive and to apply this and to determine if any of these particular questions come up as a question that can identify that group more than

another question. It just seems like you can't necessarily do both things in one study. Did I explain that or not very well?

DR. MARKS: Are you trying to say that you would need a study where -- you'd like a study where there would be -- you would actually look for window period or eclipse period individuals and ask these questions of those individuals? I think the problem is that putting that sample together, in retrospect, it's hard to know -- retrospectively, it would be challenging to know that you were getting reliable answers --

DR. SHAPIRO: -- Not retrospect.

DR. MARKS: But do it prospectively.

DR. SHAPIRO: Go to a population where you know you're not going to get one, but if you test 500 people, you're going to get 50.

DR. MARKS: So that's the whole point of this study -- of trying to do this in a population of -- we're trying to stilt this population to the highest risk group, so they have to be MSM who are active

within the past three months in cities where potentially the risk of transmission is, if anything, stable or increasing. Without just increasing sample size, I'm not sure we can -- to get more in that -- maybe I'm misunderstanding you.

DR. SHAPIRO: If you look at your eligibility and exclusion criteria, if you change that for the two groups that you might study, you would enrich one population. So, you're looking for people who want to donate blood. My question is what difference does it make? If you're looking at the validity of the question to detect a potential seroconversion, it doesn't matter if they want to donate blood or not.

DR. MARKS: But ultimately, for application of this -- for our purposes -- if you're a person who has sex with other men but you never want to donate blood, then it's not relevant because you're never going to put yourself into the donor pool in the future. So, the idea would be --

DR. SHAPIRO: -- It is in picking out a question here that may show a seroconversion

probability rate. If you just look at these questions in terms of people who want to donate blood, then you'll look at the applicability of those questions to that population, the acceptability and how honest those people are in terms of answering that question. Because you're relying upon two things for this. You're relying upon the testing capability -- the accuracy of the test and the false negative rate. And you're relying upon the honest of the donor.

DR. MARKS: Yeah. I guess I'm going to just say something from a practical perspective. I take your point, but I think, from a practical perspective, since no one is actually donating a unit here, the question of whether they'd be willing to donate a unit is quite hypothetical. And how many of them would run away when I come at them with a 19-gauge needle and not donate? We're not going to be actually -- we're not going to be testing that. So, your point's well taken. I just don't know that -- this was felt -- the group felt that this was a way of at least kind of focusing the question. But I think we'll take that back and

discuss whether just dropping that as an eligibility criterion may make sense.

DR. SHAPIRO: I just don't understand, if you get one or ten people here, how you really evaluate any of these questions for applicability to say that that picks out a high-risk group.

DR. MARKS: I think what it does, at least, is it helps at least start the -- it helps you develop a hypothesis for a larger study as a pilot -- that you at least know how to size the next study, and you might be able to refine these questions further. I think the bottom line is you have to start somewhere, I think.

DR. KAUFMAN: Sorry. Dr. Lewis and then Dr. Schreiber.

DR. LEWIS: So I'm increasingly struck by how difficult this problem is, and so I appreciate and fully support the point that you want to make a policy decision based on data. But it sounds like it's going to be impossible to get the data that directly answers the question. Because if I understand correctly, what you're trying to pick up here are -- when you say

you're going to try to find one or ten, are they NAT positive, antibody negative? Is that what you're looking -- what is that case you're trying to pick up?

DR. MARKS: That's correct. NAT positive, antibody negative.

DR. LEWIS: But we screen the blood supply with NAT, correct? So even that case isn't the case you're really worried about. You're using that as a proxy for the risk of them having been in the window -- eclipse, whatever.

DR. MARKS: That's exactly correct.

DR. LEWIS: Okay. So, you already have your case defined as something different than what you're really worried about. So that's one area of extrapolation. Then, you're extrapolating from a higher risk population based on practices or geography to try to understand how to screen more globally. That's another area of extrapolation. You're trying to extrapolate from a population who's willing to participate in two interviews and a seven mil draw to a population that will voluntarily donate blood and

actually look at 19-gauge needle in the face, which is a very different thing. Okay.

And so, there's -- this is -- even though you're trying to get data that will inform the policy decision, at the end of the day, you're going to be making multiple extrapolations and assumptions about the linkages. So where I'm going with that is that it seems to me that the cases -- since you're already going to have to extrapolate from NAT positive, antibody negative back to the risk of having been in the window, that you might as well also take advantage of any other evidence of early infections because the patient who's more early infected, even if they're now antibody positive, also gives you their information.

So, believe it or not, this was an incredibly long-winded attempt to answer your question about the endpoint for this. I suggest that you don't define your cases just as NAT positive, antibody negative, but you actually develop an ordinal scale for the interest of the case to you in which that's the highest -- that's the most interesting case. The next one is, by

other markers, a recent infection.

DR. MARKS: Keep going. You're right on -- we're on the exact same page. Keep going.

DR. LEWIS: Okay. Well, I may be about to drive off the tracks. Just watch. And the problem with this is that it, if you have a subject you identify who has a relatively recent infection but it would have been picked up by current screening, your time-based questions, in terms of their individual practices, now have to be adjusted for the estimated time of that infection. And that raises a really interesting statistical analysis question. So, my point is to get away from the binary outcome, try to order the importance in terms of their evidence of risk for being in the window of multiple ordinal outcomes, and then try to time adjust your questions so that you can interpret each one of those outcomes as well as possible.

DR. MARKS: Thanks very much for that, and, in fact, you've -- I really am greatly for that comment because that was something that we'd discussed. And we

actually neglected to present that way -- that they're actually -- for instance, the avidity assay will give you another bite at the apple, so to speak. But you're right. We'll have to take into account the other corrects in the statistics.

DR. KAUFMAN: Thanks. Can I ask those on the phone to please mute their lines? Dr. Schreiber and then Dr. Bloch.

DR. SCHREIBER: So, I want to make two points. Number one, I believe there to be a problem with the questionnaire in that none of the questions ask about the gender of the partner, which I think is critical and should be included.

DR. MARKS: The entry criteria is male.

DR. SCHREIBER: Right. But when you say how many different sexual partners have you had, maybe they had sex with three men and two women.

DR. MARKS: Point well taken. How many male sexual partners --? Right.

DR. SCHREIBER: Yeah. So that was point number one. I think that's really critical. The

second thing is I wanted to just address a point that you made earlier, which was the issue of the deferral period, and I understand that you would prefer that there be no deferral period. But I think that we get into problems when we talk about having to have data to change rules when the rule itself has no data. So, you've got a one-year rule in place, and, to my knowledge, there's no scientific basis for that one-year rule. And it actually probably doesn't make sense because it's too long. So, could you comment on what is the scientific basis for the one-year rule that we don't want to change to three months because there's no scientific base for the three-month rule, which makes biologic sense?

DR. MARKS: So, point very well taken. I think what Dr. Kaufman already mentioned, though, is one of the concerns that has been articulated is that when one reduces the questionnaire from a certain length to another time -- and again, with deference to what Canada's done, the question is do you know what that signals to people in terms of their recent

behavior? So, will that change at three months? I'm not saying it will or not, and I think points all well taken. We'll be happy to go back and think about this some more.

We did go from indefinite to 12 months on the basis of epidemiologic data, and that was because of the desire not to increase risk because we do have to have the end user -- the patient who's going to receive products in mind. So again, I totally take your point, but if we take the natural extension to your point, then we should have a 30-day deferral. And that's been brought up as well. So, I think points all well taken. We can go back and think about this, and I appreciate that.

DR. KAUFMAN: Thanks. Dr. Bloch. Any other comments on the proposed study? Dr. Baker.

DR. BAKER: Thank you. Just a general comment that brings in my questions about TIMS, as well as this. Has there been more consideration about communication and dissemination to the public at large about these -- both TIMS and this effort to ultimately

demonstrate or increase the blood supply safety -- the safety of the nation's blood supply? I don't think that that's been thought out very well about how that's being communicated to the public -- not just the public community of scientists but just the lay public and the end users.

We started BPAC because of blood safety issues affecting the public at large, and, yet, that seems to be a piece that I'm missing. In all of our well-intentioned interest to get the study design correct, is how are we communicating what the important work of TIMS is doing and what this important pilot project will do for -- to try to assure the safety of the nation's blood supply. Not to release data inappropriately, but just I've been doing some internet searches on TIMS. And you really just can't find a more external face of what's going on -- that this exists, why it exists, how it's contributing to the nation's blood supply or what we know about the safety of the nation's blood supply. And the same thing that why we are doing this, there's plasma users and others

who rely on blood components, and we want to make sure they're safe. But yet, there's no central place where that information is really out there to the public. So that's a consideration.

DR. MARKS: This is Peter Marks. So, I appreciate the comment, and I think we can go back again and think about whether we can figure out a place to post this on webpages -- also think about whether a publication in an appropriate journal makes sense. Because there will be publications forthcoming in addition to ones that have appeared.

DR. KAUFMAN: I was just saying there are groups that are in a position to communicate with the public about these sorts of issues. I'm thinking of the A-B-B, America's blood centers and so on -- I-S-B-T, in addition to the agency itself. So, I think that there are channels available. Dr. Stapleton.

DR. STAPLETON: I hate to raise whole new study designs, but one of the concerns is that you're not going to have enough endpoints to draw any conclusions. Did you consider doing a rapid testing

first visit with a blood draw with the opportunity to schedule a follow-up for the NAT-only positive people? Because then you could do a case control for your cases.

DR. MARKS: Yeah. So, it's a very good question. It actually was considered, and it just was a matter of thinking about the complexity of trying to have the fewest number of visits to operationally be able to do this because we needed to think about doing this in a way that was not very -- you know, the least expense. But that was absolutely a reasonable thing to consider.

DR. STAPLETON: Because you would save a lot of second -- if you did case control. And is it too late to -- probably is. But in the RFA, could you give people the opportunity to propose different study design?

DR. MARKS: It might be a little bit late to be thinking about that, but, you know, it may be that, again -- if this doesn't turn out the way that we would anticipate, that might be another thought to go back

and try to get these data that way.

DR. KAUFMAN: Okay. Any other comments or questions? Okay. Well, thanks very much. So, we will break for lunch, and we will resume with Topic 3B at 1:30 p.m. Thank you.

LUNCH

INTRODUCTION TO THE TOPIC

DR. KAUFMAN: This afternoon session, we'll be discussing pathogen reduction of platelet donations as an alternative procedure to MSM donor deferral. I'm pleased to introduce the next speaker, Dr. Carlos Villa, from FDA. He'll be talking about pathogen reduction of platelet donations as an alternative procedure to MSM donor deferral.

DR. VILLA: All set. Thank you. My name is Carlos Villa. I'm the medical officer in the division of blood components and devices in the Office of Blood Research and Review at CBER. Today, I'll be

introducing pathogen reduction of platelet donations as an alternative procedure to MSM donor deferral. I'd like to begin by providing the issues for discussion before the committee today. And these are to discuss the use of pathogen reduction of apheresis platelets as an alternative to the current MSM deferral policy, and to discuss any associated risks and possible mitigations. I will reiterate these issues for discussion at the conclusion of my presentation.

I'd like to begin with an outline of what I intend to cover today. First, I'll provide a background, recapping some of what we heard this morning, including FDA's approach to blood safety as well as FDA's current recommendations for MSM donor deferral. Next, I'll introduce the idea of alternative procedures described in the Code of Federal Regulations under 21 CFR 640.120 and describe a particular alternative procedure request to MSM donor deferral that involves the use of pathogen reduction. I'll also provide a bit of background on pathogen reduction technology. Finally, I'll provide some issues for

consideration for the committee as they discuss this topic today.

FDA's approach to blood safety, as we heard this morning, consists of a multi-layered system of protections for donated blood. These layers of protection include: donor education and screening; donation testing; donor deferral lists; quarantine, recall and lookback for blood components; and systems for investigation, correction, and reporting of problems and deficiencies when they occur in distributed products. It is the first of these layers of safety -- in particular, donor screening -- which are the topic for our discussion today and for which I'd like the committee to focus their discussion.

Again, as we heard this morning, FDA's current recommendations for HIV risk deferrals include a number of criteria. But I'd like to reiterate a couple aspects. First, donor deferral recommendations for HIV risk apply to all collections even if the components will be pathogen reduced. Second, among a number of criteria -- the full list which was provided this

morning -- are the following specific recommendations for donor deferral. These are to defer for 12 months from the most recent contact a man who has had sex with another man during the past 12 months, and to defer for 12 months from the most recent contact a female who has had sex during the past 12 months with a man who has had sex with another man in the past 12 months.

These specific criteria I will refer to as the MSM deferral criteria for the remainder of my presentation. And it is these specific criteria for which we are asking the committee to discuss alternative procedures. Alternative procedures are described under 21 CFR 640.120. And under these regulations, FDA may issue an exception or alternative to regulatory requirements, commonly referred to as a variance, regarding blood, blood components, or blood products. FDA's approval of such exceptions or alternatives are based on the availability of adequate information, showing that the alternate process ensures the safety, potency, and purity of the blood component or blood product.

FDA has received a request for an alternative procedure to MSM donor deferral per those criteria I mentioned earlier. Under such an alternative procedure, donors will be screened and determined to be otherwise eligible to donate. However, instead of donor deferral per MSM criteria, apheresis platelets will be collected and pathogen reduced using an FDA-approved device according to its instructions for use. Importantly, donations will be tested for all relevant transfusion-transmitted infections, including HIV, as required by the FDA.

As this alternative procedure request involves the use of pathogen reduction, I'd like to, next, provide some background on this technology. There is one device, the INTERCEPT Blood System, currently approved by FDA for the treatment of apheresis platelets and plasma. This device is based on Amotosalen/UVA technology, which is depicted on the right-hand side of this slide.

In this approach, Amotosalen is added to the blood component. The Amotosalen intercalates within

nucleic acids in the blood component. And following UVA elimination, crosslinks are introduced within the nucleic acids. This blocks subsequent replication, transcription, and translation of the nucleic acids, thereby inactivating infectious agents. The device is intended to reduce the risk of transfusion-transmitted infection, including sepsis.

The treatment is performed within 24 hours of collection. Following treatment, residual Amotosalen is removed and the component ready for transfusion. The viral reduction of HIV with the INTERCEPT Blood System, according to the package insert for the device, is based on input titer and post-treatment titer. This viral reduction ranges between greater than or equal to 2.4 to greater than or equal to 5.6 log10 reduction depending on the viral strain and the suspending media, whether that is platelet added to the solution or plasma.

Next, I'll provide the issues for consideration before the committee as they consider this alternative procedure request. These include the

extent of HIV log reduction to prevent HIV transmission by transfusion, the possible effect of the variance request on the platelet supply, as well as the manufacturing process for pathogen reduced platelets, which includes the controls necessary to prevent process failures, as well as -- as currently stands -- the limitation of pathogen reduction to specific platelet platforms.

Additional issues for consideration before the committee include the processes for managing a dual inventory of pathogen reduced and untreated components, as is often the case in blood establishments performing pathogen reduction today. Additionally, adequate measures to prevent release or distribution errors should be considered. For example, the use of blood establishment computer systems, or BECS. Finally, the committee should consider the risks and consequences of biological product deviations. For example, the failure to perform pathogen reduction on a platelet component that was collected from a donor not deferred for MSM deferral criteria.

With these issues of consideration, I'll reiterate the issues for discussion before the committee today. And these are to discuss the use of pathogen reduction of apheresis platelets as an alternative to the current MSM deferral policy, and to discuss any associated risks and possible mitigations. I thank the committee and everyone for their time today.

DR. KAUFMAN: Thank you. I'd like to introduce the next speaker, Dr. Jim AuBuchon, from Bloodworks Northwest. Thank you.

PROPOSAL FOR PATHOGEN REDUCTION OF PLATELET DONATIONS FROM MSM

DR. AUBUCHON: Thank you, Dr. Kaufman. Across my career, I've had the opportunity to propose a variety of practice and policy changes, but none more historic and significant than this one. I appreciate the agency's invitation to do so today. Just to set the stage, I want to make sure that the committee understands who Bloodworks is. Our not-for-profit mission statement is focused on saving lives, and our

vision is one of advancing health and the practice of transfusion and transplantation medicine. And I believe that the steps that I'm going to propose today, indeed, fall in line with those tenants.

So, as a quick outline, I'd like to, first, review what we are requesting -- I thank Dr. Villa for doing that already -- tell you why we are doing this, how we think we can go about doing this and maintain the safety of the blood supply, how we're going to manage a very different kind of recruitment of an apheresis platelet donor than what we do today, how we hope to be able to add to knowledge as well as to the platelet supply through this variance request, and then give you some thoughts on where this is all headed.

So, in a nutshell, as Dr. Villa stated, we propose to accept, as an apheresis platelet donor, someone who is currently deferred for having sex with another man in the last 12 months or a woman who's had MSM contact in the last 12 months. An apheresis platelet would be collected and, after negative test results, would be converted to an INTERCEPT pathogen

reduced platelet. So, in essence, we are proposing applying new technology to offer new donor recruitment and donor inclusion possibilities.

Now, how did this all get started? A little over a year ago, I was asked to speak at a seminar, an open session, at Gay City in Seattle. Gay City is an LGBTQ community resource center and there were 50, 60 people in attendance. It was known ahead of time that I had been vociferous in advocating for the application of scientific objective evidence in setting all donor deferral criteria. And, because of that, I was willing to accept this invitation and was not pilloried at the meeting. In fact, I was thanked for my advocacy on behalf of the gay community.

They wanted to talk more about why this current criterion was in effect, and what had been done and what could be done to change it in the future. Toward the end of that two-hour session, one person stood up, thanked me for my advocacy, and then said, “But what more can you do?” And I didn’t have a good answer for that.

I'm good at writing letters. I'm good talking with people. But I didn't have another idea in my back pocket. So, I had to punt on the question when it was posed. But it clearly stayed with me. It was only a couple of months later, while sitting with some friends and a glass of wine, that I first had a brainstorm about something we might actually do to change policy.

With discussion with other colleagues, other ideas came forward. The first idea we had was to go with a whole blood donation approach for MSM with a quarantine and retest approach. The idea here would be that we would accept an MSM who was currently deferred, collect a unit of whole blood that would, then, be converted into red cells and plasma. But both of those units would be quarantined. We would ask the donor to return 21 days later after the window period for a mini-pool HIV testing for a retest. When that retest showed that all the test results were still negative, the units would be released into inventory. So, this was the first idea that we came up with.

There were a couple of concerns that came up,

however. One was the donor inconvenience factor because we'd have to expect the donor to show up, not once, but twice before we could use the unit of blood. If the donor didn't show the second time, we would have lost that unit. We were also concerned with some expressions in the scientific literature we were seeing, that when pre-exposure prophylaxis, or PrEP, failed, it yielded a very low level of viremia in the infected individual; so low that we might miss it in HIV NAT testing.

So, this was a concern that we might get a false negative when we were depending solely on the test to ensure the safety of the blood supply. And then, also, we would only have half the usual red cell shelf time to use the unit. The other idea that came up in discussion with colleagues was to go with what we ultimately submitted as a variance request -- an apheresis platelet donation with, then, subsequent pathogen inactivation.

We recognize there are some concerns about this and we'll be talking more about these, including

how would we recruit prior to having any knowledge of the individual's test marker status? And we would be creating a new type of platelet, not just pathogen reduced platelet, but a pathogen reduced platelet from a different donor source than we had used previously, which we have complete confidence in as I hope I will be able to convince you of in the next few minutes. But would the community regard these units, then, as suspect and essentially, perhaps, avoid all pathogen reduced platelet units even though the majority might not come from this source?

Both of these approaches require a different treatment for this group of donors, and that's unfortunate. There's no way around that at present. In discussion with various MSM leaders in the Seattle area, the option was clearly for the second approach: using apheresis platelet donation converted to INTERCEPT platelets. So, that's what we have been pursuing since that time.

Now, to give you the geography here which relates to the numbers of potential donors, Bloodworks

serves the I-5 corridor from the California-Oregon border up to the Canadian border, and then extending up into the panhandle of Alaska. We have 11 different collection centers, plus 15 or 20 mobile blood drives operating daily, and 3 laboratory locations. There are two primary urban centers in this area. But, overall, there are about 6 million people across 45 thousand square miles that we serve with a large number of employees and volunteers in collecting blood from about 225 thousand donations annually.

In the greater Seattle area, with a population of about 4 million inhabitants, it's estimated that there are about 200 thousand gay males. Whether these would all qualify under MSM criteria as we use that term is not known. But it's a good starting point, an approximation. In the Portland metro area, slightly smaller. There are approximately, it is believed, about 70 thousand gay males. So, that is in the range of a quarter of a million new blood donors that we might ultimately find presenting themselves. Now, how many would actually come and donate blood where the

criteria changed is not known.

However, recently, Israel opened up the possibility of plasmapheresis donation with a quarantine and retest system, similar to what I described, possibly for whole blood. In that case, they surveyed over 12 hundred MSM and found that almost two-thirds said they would donate. In addition, we know that there are many in the LGBTQ community and their supporters who self-defer, not because they do not meet any qualifications we may have, but they self-defer out of protest over the current requirements. So, the number of donors that we may encounter for the first time could be quite dramatic.

Maintaining the safety of the blood supply is absolutely paramount, as was pointed out by the committee in their discussions earlier today. So, I'd like to offer a few comments about the levels and limits of our logic protection, and the process controls that we would use to ensure that we are delivering what we think we are delivering. I'm not going to spend much time talking about bacteriologic

safety, but I do want to point out that, although the various pathogen inactivation techniques that have been developed over the last several decades were not focused on bacterial contamination of platelets when they were created.

This is the primary reason that many blood bankers are very excited about having PRT platelets available, because we recognize that approximately 1 in every 250 patients who receives platelets -- and most receive multiple units of platelets -- will encounter a bacterially contaminated unit during their course of therapy. And that's scary. So, we are looking forward to using PRT as a simple, quick, and effective means of avoiding this most common form of pathogen transmission in blood transfusion.

The limits of detection with the NAT system that we are using have been published, and they are incredibly sensitive. As you can see, the number of copies per mil at the 50 percent limit of detection is very low and the infectious window period that this represents is very short for HIV, HCV, and HBV.

Compare these limits of detection with what you have already seen as the probability of a reduction of any viral contamination, and we are looking at multiple orders of magnitude of safety. So, even if an individual is just below the limit of detection in the NAT testing that is currently performed, the INTERCEPT system will be able to produce a unit that has had HIV, HBV, and HCD effectively reduced.

Now, there are many process controls that need to be included in this new process that we will be doing. Certainly, we have to make sure that every unit is tested and any unit that is positive in HIV or any of the other tests that we do is appropriately interdicted. But this is standard procedure. This is something that we do every day anyway. So, this is not new. It does not require any new approaches.

We have to make sure, though, that we identify who is an MSM and capture that information in our system so that we handle them and their unit appropriately; have to make sure that we don't create any other components that could not be pathogen reduced

through the process; and that we manage any units that are unsuitable for the INTERCEPT system.

So, how would we do that? Well, today, if a donor comes in and donates and answers yes to one of the MSM questions, this yields an automatic deferral and no collection of any blood component is possible. But, in the future, if this variance is authorized, we have to have our BECS system be able to accept them as a donor, but only for apheresis platelet collection, and then further require that that unit is converted to INTERCEPT platelets before the unit is released. This will be handled after examination of our computer system and how it's structured.

With the step that -- when the deferral, which is now automatic for positive response to the MSM question, is overridden, that will cause an attribute to be created, related to that donation, which is automatically applied. The attribute will only allow apheresis platelets to be collected and will require conversion to INTERCEPT platelets before release of the unit. This is absolutely key and will be automated.

When the unit is collected, it will, then, proceed to the laboratory as do all the other apheresis platelet units. It has to be found within certain platelet content and volume limits in order to be handled through the INTERCEPT system, meeting the so-called guard band requirements.

When these have been verified as having been met, the unit would be treated in the INTERCEPT system and could be labeled, then, as a pathogen reduced apheresis platelet unit. The BECS system is in control of this and, obviously, is interfaced with the systems to make sure that the unit has actually passed through the eliminator and has received the Amotosalen and that everything has been handled according to package insert requirements before the unit can be labeled and then released. It would be released into our inventory, and we receive orders against that inventory from hospitals as they need their platelets.

This is not a matter of a new product creating a dual inventory. As you can see, we have multiple flavors of platelets already on the shelf. We have

apheresis platelets that we will soon be converting, if they're not pathogen reduced, to a large volume delayed sampling approach. We provide individual whole blood platelet units for pediatric platelet transfusions. We provide pre-storage pooled platelets from whole blood donations. And any of these forms of platelets may be requested to be irradiated.

So, as you see, there are many different forms of platelets. And having one new form from a new source is not really any change to our operations. If the unit, when it reaches the laboratory, is found not to have appropriate content or volume, it cannot be processed through the INTERCEPT system. It would be quarantined and discarded. Again, because the BECS would require that the unit be treated through the INTERCEPT system and have a pathogen reduced label before being able to be released, the unit would not be able to be released for transfusion. So, the process controlled through the BECS is very important.

Picking up test positive units, picking up the unit or any portion of the unit that hadn't been

INTERCEPT treated, and if any co-component were created -- and the system wouldn't allow for that, but if it would, it, too, would not have passed through the INTERCEPT system and could not be labeled and released. Now, the donor recruitment for this process is going to be different than what we do today. We recruit, as plateletpheresis donors, individuals who have given multiple whole blood units already. We are looking for a level of commitment. Because when we need platelet donors, we need them. We need them to show up and we need them to be reliable. We need to know that they live close to somewhere where we routinely collect platelets.

Although we do have mobile platelet collections, most all of our apheresis platelets are collected in our fixed collection sites, so they can't live a great distance from there. We know their test results; they've donated on multiple occasions. We know their infectious disease test results are negative. We know their blood type, which also would steer us toward collecting platelets from certain types

and not others. And, importantly, we know their platelet count, because we would rather have an apheresis platelet donor with a higher platelet count. With all of that information, we can make the decision to recruit them as an apheresis platelet donor.

That has worked very well for us and is similar to what many other blood collectors use. In this situation, however, we're going to be dealing with a donor that we don't know. We don't know any of that information when they first present for donation. We're going to be approaching recruitment in two different ways. One, something that we do already, is we recruit MSM to donate through our in vitro research product program. We have a large biologic products division that collects blood that is usually used for in vitro research. And when it is used in vitro research, we don't apply the MSM deferral criteria. When it's used in some in vivo method, then, of course, we do apply that.

So, we have the opportunity to meet these donors ahead of time, make sure that their donor

questionnaire responses are all acceptable other than the MSM question, and that their test results will be satisfactory. If someone walks in and says, I'd like to donate in your new program, we would give them a complete donor history questionnaire to fill out and we would draw a sample to be run through all of the standard infectious disease tests to ensure acceptability of the donor before we commit a slot on our platelet collection schedule, an apheresis collection kit, and potentially even an INTERCEPT system -- an INTERCEPT kit. So, once we know the donor would be acceptable, we would, then, set an appointment for their donation and then recruit them.

Also, as part of this, we would create what's called a donor profile, or donation profile, that would restrict them to this system. So, the only thing that would be able to be collected from them would be apheresis platelets and the only thing that would be able to be generated from that donor would be an INTERCEPT platelet.

So, this is a second layer of safety in the

variance request that goes along with the donation attribute that I talked about earlier that would be invoked when an MSM deferral was overridden after the MSM question was answered with a yes. So, we have two different BECS systems that will both ensure that only the right component is collected and a right component, ultimately, is produced.

Now, this morning, you heard Dr. Whitaker talking about a study to gather more information about the sexual practices of potential MSM donors. The agency has asked if we would be willing to consider participating in that. The idea is that an MSM donor, after donating apheresis platelets, would participate in a study, giving written informed consent to provide some information that would allow us to correlate their sexual practices with a infectious disease test result.

This would be optional. It's not required. And it would be an IRB-approved research study that would attempt to associate certain sexual practices with donation proclivity and testing results. We would intend to use the same questions that the FDA-sponsored

study would be using.

I hasten to add, however, that the collection in transfusion of PRT platelets is not a study. We would be generating a licensed PRT platelet unit as a result of being granted the variance. This would be an additional study. It would be a research study that donors may decide to participate in, if they would like to give us additional information. That would help the FDA ultimately see if there are some risk-based questions that could be used rather than asking a question about membership in a group.

So where is this all headed? Well, we began several months ago, shortly after we submitted the variance request to the agency with partnership with the LGBTQIA community for potential recruitment of donors and publicity in the gay community about this process once it's been approved. We have approached them already about participating in research product donation, and they are very interested in helping us get the word out in the future about platelet donation.

We're also preparing our hospitals for PRT

platelets. We have not seen the uptake that we would like in interest in PRT platelets, but several hospitals have indicated that they are interested and willing to use PRT platelets. We believe that it increases recipient safety, and that is the primary reason that we should be using PRT platelets -- to avoid the bacterial complications. As hospitals become more aware of the complicated processes they may be required to follow in the future if a unit is not pathogen reduced, in order to mitigate the bacterial risk, they may become more interested in using this simple approach.

We believe that this approach also provides a new means to bring additional diversity into the blood supply. We struggle with the fact, as all blood collectors do, that all minorities are underrepresented in our donor lines. We would like to have the support of all communities, and for no other reason than we certainly attempt to provide blood to all those communities, but the dispersion of different red cell anagens are not equal across different ethnic lines.

So, we need all communities to participate so that we have the ability to have the blood available to make sure all can be supported.

We are very interested to find out what recipients of platelets feel about this variance request. We are working with a local company that works for a number of pharmaceutical companies in putting together patient focus groups, and patients who appear in commercials and appear before other groups of patients. We're using them to see if we can put together groups of patients who have received or continue to receive platelets to get their impact to make sure that we are crafting our messages to the community about the safety of this approach in a manner that patients are not concerned. We have also begun some internal preparations in the hope of ultimately having this variance be approved.

Developing appropriate SOPs, making sure that the BECS system is appropriately programmed and validated to operate in the manner in which we believe it needs to, making sure that the staff is

appropriately trained. In knowing that this meeting was a public meeting and not knowing how well it would be covered by the media, we have to be prepared for MSM showing up tomorrow at our donor centers, wanting to donate blood. So, we have already created a system to not only advise our staff of this variance request, but to create a system to capture the interest expressed by MSM donors before we can actually take them as regular blood donors.

We believe that this approach is essentially analogous to the approach which the agency has already approved for one blood collector, and that is the ability to accept donors who are current -- or have otherwise currently been deferred for travel to malaria areas or having been born in malarial endemic areas, providing that the apheresis platelet is treated with the INTERCEPT system.

So, the idea is that, again, we can apply new technology to expand the diversity of our donor pool. Because, in the end, it is all about diversity. It's about supporting the community that we support. We

depend on the community's support in order to be successful, and we believe that it is appropriate for us to seek social justice and provide an equitable approach to blood donation while maintaining safety -- you could even argue improved safety -- with an increased availability of PRT platelets, having a boost to our donor recruitment.

There were some discussions earlier today about whether or not there was enough blood in the country. And I would just caution the committee about looking at annualized data about collections and assuming that there's enough blood. Because, on a day to day basis, I can tell you that many blood centers, strictly those in larger cities, are exceedingly pressed to make sure there is enough blood on the shelves.

We are all spending additional time, additional resources -- that is, additional money in recruiting in a new sociologic framework, in a new demographic distribution of our population. And it is exceedingly difficult to keep enough donors coming

through the door, even if not as many red cells are being used as in the past.

In this variance request, we're talking about platelets. Our platelet utilization continues to climb. It's gone up 15 percent in the last 4 years. We are looking at the future of a likely bacterial risk mitigation guidance from the agency that will probably put whole blood platelets out of business. That's unfortunate in our opinion, but we understand the rationales. So, we are going to have to turn more to apheresis platelets. 25 percent of all of our platelet doses today come from whole blood derived platelets. That's going to decline in the future, and we need to find more donors to provide those platelets. Because, today, we just don't have them.

So, for all those reasons, we are very excited about this proposal to the agency. I look forward to hearing what the committee has to say about it. Thank you.

QUESTIONS FOR SPEAKERS

DR. KAUFMAN: All right. Thank you very much, Dr. AuBuchon. I'd like to ask if there are any questions from the committee for both Jim AuBuchon and Carlos Villa. Dr. Schreiber?

DR. SCHREIBER: I'm curious to why the discussion is limited to just platelets. Pathogen reduction for plasma is approved as well and your platelets are suspended in plasma, if I am correct. Why not -- one of your last statements were, you know, we're worried about the shortage of blood, so we could also make -- potentially make plasma available this way. Why is that not in the discussion?

DR. AUBUCHON: You are correct. It certainly is possible. A couple reasons: one, we don't have a shortage of plasma. Occasionally, we are a bit short on AB plasma. We do have an AB donor plasmapheresis program, so I suppose we could certainly use some MSM donors in that and treat them in the same manner. That's possible. I think the reason we didn't propose it initially is because the primary impetus, primary driver, for adoption of PRT is avoidance of bacterial

risk. And that just isn't present in platelets.

So, if the agency likes our proposal here for platelets, we certainly could consider applying it to plasma. We would probably only use it for AB MSM donors, but then, we rarely have enough AB platelets anyway. So, any AB donor that we found through this program, we'd probably want to collect platelets from them anyway.

DR. KAUFMAN: Dr. Shapiro?

DR. SHAPIRO: Did I understand you correctly that you're only going to apply the PRT technology to MSM donations and not to the general pool of donors?

DR. AUBUCHON: Thank you for the opportunity to clarify that. No, that is not the case.

DR. SHAPIRO: Okay.

DR. AUBUCHON: I don't know how many MSM donors are going to present, but I am expecting that the vast majority of our PRT platelet units that we produce will come from our regular donor pool. The MSM donors will augment that, but I -- unless we receive a far stronger outpouring than I could imagine, it'll

probably be mostly from the regular donor pool.

DR. SHAPIRO: So, they're using the technology on all the pheresis platelet --

DR. AUBUCHON: Now, we are not yet providing PRT platelets to any hospital. Truth in advertising here, several hospitals are getting ready for that. We have done all of our validation work with the INTERCEPT system. So, we're ready to produce INTERCEPT platelets; we just have to get some hospitals to be able to use them. It's complicated. The committee may wonder, well, if they like it, why don't they just use it?

One of the problems is that the hospitals are interested in using PRT to avoid the need to irradiate the platelets. But that means they have to make some fairly substantial changes in their hospital laboratory information system, so that a unit that comes into their inventory as a PRT platelet is regarded as the equivalent of an irradiated platelet. And that is causing them some difficulties.

DR. SHAPIRO: Another question I had about

this is the website for this agent says that it's very effective in a susceptible pathogen. What constitutes a susceptible pathogen versus an unsusceptible pathogen?

DR. AUBUCHON: I will defer to an expert sitting in the audience, Dr. Richard Benjamin, if the committee would like to hear him speak to that.

DR. BENJAMIN: Hi. Richard Benjamin, Chief Medical Officer for Cerus Corporation, the manufacturer of the INTERCEPT system. Our pathogen set describes a broad-spectrum ability to kill pathogens across enveloped and nonenveloped viruses, bacteria, parasites, and leukocytes. But, like any pathogen reduction system, we do not claim that it inactivates all pathogens and there are some specific pathogens that we are less effective at killing. Specifically, spores or bacteria such as bacillus and some of the small nonenveloped viruses, such as hepatitis A and hepatitis E, are not effectively killed as HIV is. So, we need to be very careful about what our claims are.

DR. KAUFMAN: Dr. Basavaraju?

DR. BASAVARAJU: So, you know in transplantation when a transplant recipient is offered an organ from a donor who is at increased risk for HIV? Even when that infectious disease testing is negative, the recipient is still told of the donor risk factors and subjected to inform consent. Do you have a plan or are you planning to have an informed consent process for recipients who might receive these products or hospitals that might buy them?

DR. AUBUCHON: No. We believe that we can make a strong case to the public and to our hospital-based colleagues that these units will be absolutely safe and that there is no increased risk to the recipient. In fact, we believe that by having these additional donors, we will be able to provide more PRT platelets than we would otherwise. Therefore, we will be providing a platelet inventory of increased safety, not decreased.

DR. KAUFMAN: Dr. Lewis?

DR. LEWIS: So, following up on that question, I want to try to understand the quantification to the

extent that we can about the potential risks. There are two changes that are being made. One is you are expanding your donor pool criteria. So, potentially, your donor pool will have some increased risk of being in that very short window before the NAT testing is positive.

DR. AUBUCHON: That's correct.

DR. LEWIS: That's the increase before treatment. And that's being counterbalanced -- if I understand your prior comment, you believe more than counterbalanced -- by the two or more log reduction associated with the treatment of the platelets. Is that correct?

DR. AUBUCHON: That's correct.

DR. LEWIS: So, to argue that the net effect is an increase in safety, that means that you believe that the increase in risk of being in the window period is less than a couple of logs?

DR. AUBUCHON: No. I use the term "increase safety" in relation to reduce bacterial risk, because we know that our current culture methods are only

approximately 50 percent sensitive in detecting bacterial contamination. And 1 in every 1500 units, or 1 in every 250 platelet recipients, is receiving a unit that has bacteria in it. I don't like that and I would like to get away from that.

So, as we make more PRT platelets and have them become a larger proportion of the entire inventory, the safety of the recipients will increase. By increasing the donor pool, particularly those people who have to have their platelets go to PRT platelets, we will be ultimately increasing the safety of the blood supply.

DR. LEWIS: Okay. So, you're making one of the changes to increase the donor pool; could at least, theoretically, increase the risk of HIV not detected in the -- because it's in the window period. But you -- but the in vitro work demonstrates that the pathogen reduction gives more than a 2-log reduction of that pathogen. But, overall, you're arguing the safety is based on the increased safety with a stricter bacterial contamination?

DR. AUBUCHON: That's correct.

DR. LEWIS: Okay.

DR. KAUFMAN: Dr. Schreiber, and then coming from Dr. Benjamin.

DR. SCHREIBER: So, I think the -- using more platelets to 5-day shelf life, which is very short, is limited by the potential bacterial contamination. Does this process potentially lengthen the lifespan of the donated platelets?

DR. AUBUCHON: Some countries are using INTERCEPT platelets for storage up to 7 days. That's not currently approved in this country. One benefit from using INTERCEPT treatment as opposed to the culturing approaches that have been proposed is that the effective useful storage period for the platelet increases. Because the processing to INTERCEPT platelets is done within 24 hours of collection and since the infectious disease test results come back within that window period as well, the unit can be released on day 1. And that's not the case for the large volume delayed sampling.

Although that has been discussed as possibly leading to a 7-day storage period, it won't be possible to get those platelets out into the market, get them out into inventory and distribution, until probably day 3 of their lifespan. So, the effective amount of time that the unit is available when it's an INTERCEPT platelet will probably be greater than when it's handled with the new culture systems that are being proposed.

DR. KAUFMAN: Dr. Benjamin?

DR. BENJAMIN: Richard Benjamin, Cerus Corporation. I'd just like to clarify something about the 2-log cure for HIV that you saw on the two clinical isolates. All of those strains, you'll have seen a greater than or equals to sign before the number, which signifies that we've cured the -- or we've activated the virus, but to the limit of detection. So, we are constrained, then, about how much virus we can put into the product. And those clinical isolates do not grow to high concentrations. So, the maximum amount of virus we could put in was only 2 to 3 logs.

For the laboratory strains, we could grow them to higher concentrations and you would've seen a 4.7 or 5 logs. But again, it was to the limit of detection. So, I wouldn't get focused on the 2 logs as we have not seen heterogeneity in our ability to cure different strains of a virus. When I see 4.7 or 5 logs, I think that's probably the more realistic minimum number for cure rate on HIV.

DR. KAUFMAN: Dr. Bryant?

DR. BRYANT: In your presentation, you talked about the safety engagement with the recipient groups. Are you referring to patient groups or are you referring to hospital customers?

DR. AUBUCHON: I'm specifically referring to patient groups. We'd like to hear directly from patients. We are pursuing getting those groups set up right now. We are working with our hospitals as well. We have made known to them this presentation today and what we are asking the agency to approve. But we look forward to further engagement with them and discussions with them. We've had many meetings with our hospitals

over the last year and a half, talking about PRT platelets and their advantages. They appear to be well-accepted theoretically. The problem comes down to cost.

DR. KAUFMAN: Dr. Shapiro?

DR. SHAPIRO: I just want to clarify if I understood what you said in your presentation. You said you were going to be using the questionnaire that the FDA developed in MSM individuals who were donating for platelets, but are not these individuals already testing negative for HIV so you already know their status?

DR. AUBUCHON: Yes. It is true that we will already know that these individuals are negative in all infectious disease tests before they ever come in to donate. At the break I was talking with Dr. Whitaker, saying that perhaps if we participate in this, we should apply the questionnaire to all those individuals who present with interest to donate so that we can capture some who, perhaps, are test-positive.

DR. SHAPIRO: Okay. Okay. Thank you.

DR. HOLLINGER: So, Jim, just a question again. Is -- so, with the current techniques that are used, there's some benefits you see with the pathogen reduction in terms of bacterial contamination potentially and other things. But what has been the risk with the current -- forget the pathogen reduction. But what is currently available for looking for bacterial contamination for serology and everything else? Has there been a problem with that that you can see? And I can understand the practice eclipse phase. If you figure that some patient who is in this eclipse phase actually is expressing virus in the blood, which that is going to come out in the donation, it'll be a -- should be a very low titer. But can you give me some idea about risk?

DR. AUBUCHON: Well, I'm not the expert in that field of transfusion medicine. But as the committee has already discussed today, the risk of HIV or hepatitis transmission currently through the blood supply is unseeable and occurs very infrequently. It's one per millions of units transfused and it is very

difficult to quantitate because it is so low. Bacterial risk is much higher.

Now, I don't know if it's the clean living of the people who live in the Pacific Northwest or not, but we have not had the magnitude of bacterial contamination cases that other collectors have seen. I'm grateful for that, but I also know the literature that says, still, 1 in every 1500 units is contaminated with bacteria.

So, I don't go to sleep at night worried about HIV or hepatitis transmission because, effectively, it does not exist in our blood supply at present. If someone from the public asked me, "Is the blood supply safe?", I'm very quick to give an unequipped glance or, "Yes, it is safe." And I want to keep it that way.

DR. HOLLINGER: So, just a follow-up, maybe somebody in the blood banking community can tell me, which is what -- how many deaths have occurred each year with the bacterial contamination from platelets?

DR. BENJAMIN: Just the FDA fatality rates, I believe it's two to three a year -- is the number that

appeared.

DR. AUBUCHON: That's recorded.

DR. BENJAMIN: That's recorded by -- the FDA can talk to that.

DR. HADDAD: Based on the estimate and based on the rate of contamination and how many contaminated units actually lead to a septic reaction and to death, you really can estimate between 10 and 20 death a year.

DR. HOLLINGER: All right. Thank you.

DR. KAUFMAN: And with -- and just to follow up on that, there are -- this pathogen reduction technology has been used nationwide in some places. Switzerland, they've had zero septic reactions since implementation over a period of some years. So, it is quite effective for them.

I had a question. And this, as you stated, would not itself be a study. That is, you'd end up at the end with a -- I assume the label would be exactly the same.

DR. AUBUCHON: Correct. These units would not be distinguished in any manner.

DR. KAUFMAN: But at the same time, I was wondering if you were interested in capturing -- kind of processing information or some data about the logistics of the process. How many units, for example, above expectation were you able to get? Or how many did not meet the guard bands? Or things of that nature.

DR. AUBUCHON: Oh, absolutely. I mean, we will set up to make sure that we are able to track all of these units and understand not only the donors and how frequently they've come to donate, but how successful we are with collecting the units, what impact they make on the overall supply, and if we're able to collect, within the guard bands, better with them than other units -- other donors perhaps. I don't know.

DR. KAUFMAN: All right. Dr. Bryant?

DR. BRYANT: Jim, will the donor be -- in your computer system, will it be per donation? In other words, when they answer the question yes, that's when it tags that donation. Or will the donor carry a tag

as well?

DR. AUBUCHON: The answer to both of those options is yes. The donor will carry a tag, if you will --

DR. BRYANT: Notation. Notation.

DR. AUBUCHON: -- indicating that they can only donate apheresis platelets and only INTERCEPT platelets can be made from their donations. And then, whenever the MSM deferral, which is automatically imposed when someone answers yes to that question -- whenever that deferral is removed or overridden, then an attribute is added to that donation that requires a donation to be apheresis platelets and the ultimate unit produced to be INTERCEPT platelets.

DR. BRYANT: So, if the donor answers no, they would still be tagged for --

DR. AUBUCHON: That's correct. If a donor came in and answered no to the MSM question, the same requirements would still be placed on them. Now, we may have to ultimately work out a system if we find that there are donors who previously were MSM with a

12-month deferral, and then they say, well, I've been abstinent for 14 months. And they would, then, qualify as a regular donor. Or if the time deferral were to shift from 12 months to something shorter, then perhaps some of these gentlemen would, then, not be caught by that new question. We'll come to that, and we'll deal with that when we come to it.

DR. BRYANT: Okay.

DR. KAUFMAN: Dr. Stramer, did you have a question or comment?

DR. STRAMER: Yes. Actually -- can you hear me?

DR. KAUFMAN: Yes. Go ahead.

DR. STRAMER: Okay. Jim, thank you. Have you discussed with the advocacy groups that you've been working with that via the guard bands, you probably won't be able to pathogen inactivate all units, and perhaps 50 percent of them, from donors who you will be accepting as MSM, will not be acceptable for distribution; unlike donors who won't be MSM who we can apply different bacterial mitigation sets to? And what

was their reaction to that?

DR. AUBUCHON: We do not yet have the collection experience that your system has, so we will be devoting a lot of attention to the platelet count in these donors and exactly how much we collect from them. Because, if we don't produce a PRT platelet, we're not producing anything from them. And that's obviously a large expense that is lost.

So, we are looking to gain more experience in how to collect platelets within the guard bands for all donations. But in particular, for these donors, we will have to be very careful to make sure that we get it right, otherwise we've lost all of our investment.

DR. KAUFMAN: Dr. Lewis, and then Dr. Ortel.

DR. LEWIS: I'm sorry. I want to come back to this issue of the two different possible effects on the overall safety of the platelets that are provided. So, in principle -- and don't interpret this question as my advocating for this approach. But, in principle, you could institute the pathogen reduction with your current donor pool which would gain you the increase in

safety associated with the bacterial contaminant reduction without expanding your donor criteria.

DR. AUBUCHON: That's a logical and reasonable question, but not exactly. First, we have the problem of the 25 percent of our platelets that are produced through whole blood donations. There is no pathogen reduction system available for them, so we have to collect more apheresis platelets in order to do the full conversion, I think, as you're talking about.

Now, we have the additional problem that Dr. Stramer was just mentioning, that the guard bands are tight. We are hoping that Cerus will be able to submit data to the agency to expand those guard bands. But not every unit that's collected can be converted, by product insert, to INTERCEPT platelets.

So, we know that the discard rate becomes higher or the split rate goes down. That is what might, today, be regarded as a double unit collection. It could only be a single unit INTERCEPT unit. So, we anticipate we are going to have to collect more units of platelets to, someday, convert to 100 percent PRT.

And we don't have those donors today.

DR. LEWIS: Okay. So, the connection you're making between the expansion of the -- or making the donor requirements less restrictive is because the use of the pathogen reduction technology will cause other issues that may decrease the actual availability of platelets?

DR. AUBUCHON: I would agree with you, but I wouldn't regard what we are proposing as making it less restrictive. I just say that we would be avoiding an unnecessary deferral.

DR. LEWIS: Eliminating a deferral?

DR. AUBUCHON: Correct.

DR. LEWIS: Okay. And then, just to quantify for a second, the numbers that you gave on the map for the estimated MSM population in your collection area was about 5 percent of the whole population.

DR. AUBUCHON: Correct. It's slightly higher in Seattle than Portland. But yeah, that's approximately correct.

DR. LEWIS: How does that 5 percent potential

increase in the population -- knowing that the population doesn't necessarily translate to the fraction that are enthusiastic about becoming platelet donors, how does that 5 percent compare to the potential loss in units associated with this additional safety procedure?

DR. AUBUCHON: I don't have enough experience in collecting platelets for the INTERCEPT process to be able to answer that question. I would hope that we would get good enough so that we would come out ahead in that equation -- good enough in terms of collecting the right volume and the right platelet content. But I don't have the experience to answer that yet.

DR. LEWIS: Okay. Thank you.

DR. BASAVARAJU: Do you plan on asking MSM donors potentially about their use as PrEP? Because that may cause false negative NAT results.

DR. AUBUCHON: We were not planning on asking platelet MSM donors about PrEP. Because, although PrEP may cause a false negative because of very low viremia, that would be no different than the situation of

someone being in the window period and being missed by current NAT testing. And that level of viremia would be well taken care of through the INTERCEPT process. We were anticipating asking questions about PrEP for those donors who wish to participate in the FDA study, but that's a different, separate issue.

DR. KAUFMAN: Dr. Ortel?

DR. ORTEL: Yeah. This might be a question more for the FDA. If this is a request for approval for variance, I'm just curious, what kind of oversight or what kind of supervision does this get approved with? Or is it -- what's the next steps, for example?

DR. AUBUCHON: I'm very interested in the answer to that question also.

DR. ILLOH: This is Orieji Illoh from DBCD. I think, generally, when we receive variance requests, like Dr. Villa mentioned, we look at the supporting data to ensure that whatever changes will maintain the safety, purity, and buoyancy of the product. So, we will be taking away the discussions from today and any available data to consider that decision.

DR. ORTEL: But is there -- do you, then, come back with a plan that you want to see a certain follow-up data in 6 months? Or is there something that's developed with the applicant?

DR. ILLOH: So, depending on the request, there are times that we might request for additional data. Sometimes we grant what we call time-limited variances or we put some conditions with the variance to say you have to do this study or follow up with some data for us to reconsider our variance approval.

DR. KAUFMAN: Dr. Stapleton?

DR. STAPLETON: So, this may reflect my ignorance of the technology, but are there internal controls to document the inactivation? And what sorts of QA, CLIA type things are set up for -- since this system isn't used many places?

DR. AUBUCHON: I'm not understanding the question completely. Are you talking about the use of the INTERCEPT system?

DR. STAPLETON: Yes.

DR. AUBUCHON: Ah, okay. Perhaps I should

defer to Dr. Benjamin on that.

DR. BENJAMIN: Yes, Richard Benjamin, Cerus Corporation. They process controls in the way that -- the process of doing the inactivation, where you scan the product into the machine; you scan them out. Time and length of elimination is recorded. And that's kept in the BECS system as a permanent record of elimination. So, yeah, there are process controls for every step. We do start off by sterile docking your platelet onto the product, and there are usually ways of documenting that so it's an input and an output at the end. So, yes. You use your BECS system to document the process.

DR. BLOCH: Is there a failure rate?

DR. BENJAMIN: Is there a failure rate?

DR. BLOCH: Yeah.

DR. BENJAMIN: I'm not sure what you mean by failure rate.

DR. BLOCH: How frequently does it fail?

DR. BENJAMIN: I'm not understanding what you mean by fail.

DR. BLOCH: If there's an assay that -- there are always cases which are going to escape detection because of whatever reason.

DR. BENJAMIN: We have discussed the relative pathogens that might be resistant to the pathogen inactivation process already. Since this is a manual process where you take a platelet manually through a sterile docking elimination, the whole process, as in any manufacturing environment, things are apparent that your sterile docking may not work. There may be leaks in the bag, there may be defects, et cetera. And the staff are, like any process, trained to look for those. It's no different to any other blood banking process that is currently used today.

DR. AUBUCHON: Please correct me if I'm wrong, Richard. But if, for example, the ultraviolet source did not turn on during the presumed elimination period, then the eliminator would identify that as a failed run.

DR. BENJAMIN: So, I think -- yes. Absolutely, there is a sensor for the elimination. The

way the bag is designed, you're guaranteed to add the Amotosalen. You cannot fail to add the Amotosalen since it's a flow-through system where the platelet runs through a bag containing the Amotosalen into the first bag. So, you are guaranteed to have added the Amotosalen as a control for the actual elimination occurring. There's a control for placing the product into the eliminator and taking it out of the eliminator. So, yes, there's process control, like everything we do in blood banking.

DR. STAPLETON: And I'm sure there are UV light source requirements that are maintained, that sort of thing; as far as duration. Yeah.

DR. BENJAMIN: Absolutely. These lamps have lifespans, and there's a counter and number of times it's been used. The maintenance requirements, et cetera, are all documented and inspected and maintained.

DR. AUBUCHON: I appreciate Dr. Benjamin's assistance in responding to your questions. I should also make it known to the committee that neither I nor

Bloodworks are receiving any monetary support, and we are not engaged in any research studies with Cerus. This is imperially on our own volition.

DR. KAUFMAN: All right. Dr. Bryant?

DR. BRYANT: The variance will be for MSM. Will it be for men who have had -- deferred for 12 months from the most recent contact with a female who had sex during the past 12 months with a man who had sex with another man in the 12 months?

DR. AUBUCHON: Yes.

DR. BRYANT: That will happen as well? Okay. And are you looking at, possibly, any other high-risk groups?

DR. AUBUCHON: We have also submitted a variance request to allow to take donors who are currently deferred for malaria. We have many tens of thousands of Asian and South Asian immigrants in the Seattle area who frequently -- well, they have been in the U.S. for longer than three years, often. But they came from a malarial area and they go home to visit friends and relatives and keep getting deferred.

We would love to have them as blood donors -- as platelet donors in the same kind of approach. And it would be easy to adapt the same process controls that we would use with MSM for those individuals.

DR. BRYANT: Are you looking at possible tattoos, ear piercing, body piercing, or needle sticks? Just curious.

DR. AUBUCHON: We don't lose many donors for tattooing in Washington and Oregon because tattoo establishments are licensed by the state, and we allow those individuals to donate. Our main problem is making the young adult population aware that, after they have been tattooed in one of these establishments, they can still donate blood. So, that's our challenge there rather than the actual deferrals.

DR. KAUFMAN: All right. So, if there are no other questions from the committee, thank you very much. We're going to take a short break. We'll take a 10-minute break and come back at ten to.

BREAK

OPEN PUBLIC HEARING

DR. KAUFMAN: All right. Well, welcome back, everyone. We're going to continue now with the open public hearing. So, I'm going to, again, read the required document.

Welcome to the open public hearing session. Please state your name and your affiliation if relevant to this meeting. Both the 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 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 interest 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.

So, we have one person on the list from this morning, Dr. Richard Benjamin.

DR. BENJAMIN: Good afternoon again. Dr. Richard Benjamin, chief medical officer from Cerus Corporation. I am an employee and a stockholder in the company. Really a pleasure to present in support of Dr. AuBuchon's variance application. I want to reiterate what he said was that we were pleasantly surprised to see that his variance request was being considered by BPAC and, really, there was no collusion. We had let it known in our own talks that we thought this was a possibility, but we did not encourage him to submit the variance application. We're very glad that he did.

Okay. So, what I thought I'd do is just to run through the submission that Cerus made in 2016 to the FDA's request for comments at that time around

blood donor deferral policy for reducing the risk of HIV virus transmission by blood and blood products. Because, in November of that year, we submitted -- and that submission is in the committee's review packet and available outside on the table for anyone who wants to see it.

In that submission, we pointed out that -- in our executive summary -- that the availability of pathogen reduction using the FDA-approved INTERCEPT Blood System for platelets and plasma provides an additional layer of safety to help protect patients from transfusion-transmitted infections. For blood collectors to use pathogen reduction, individual behavioral risk assessment independent of sexual orientation could be implemented immediately for platelet and plasma donors, addressing the major concerns of the regulatory agencies of possible increase for recipient risk.

Any resulting change in the donor population could be assessed by the means of terms and rights to studies in anticipation of the availability of approved

systems for red cells that might allow universal pathogen behavior-based deferrals. So, it's good to see, now, two and a half years later, that we're discussing it in public.

You have already seen this table of claims. Let's see. This is the one table that refers to viral reduction and there's another that refers to bacterial reduction capacity of the system. And I pointed out earlier that the greater than or equal to signs do mean that we inactivated to the limit of detection and that the clinical isolates of HIV really could not be grown above 2 to 3 logs, and that's the limitation there.

We have every reason to believe that they would've cured at least 5.4 or 5.6 logs, if not more. And it's our belief that the combination of mini-pool NAT and pathogen reduction actually makes a very powerful multilayer safety system for blood products, and believe that, actually, we will continue to perform NAT testing even one day when we have universal pathogen reduction available.

Why do I believe this? Well, a good case,

which is impressed today in transfusion, online early, illustrating the capacity of intercept system. This is a French case report that just got published. In France, they introduced individual donor nucleic acid testing in 2010. And the residual risk of HIV is two to three times lower than it is in the U.S., at 1 in 6 million.

Nevertheless, they recalled, back in September 2017, a repeat whole blood donor who seroconverted, was HIV antibody and NAT positive. When they did a look back to four months earlier to his prior donation that had tested antibody and NAT negative -- I.D. NAT negative -- they had his sample on hand and were able to detect very low levels of viremia in that donation, less than 34 CP per mil.

So, they looked at the recipients of those blood products. The plasma had gone to fractionation and could not be traced further. The red cells had been given to a patient who died within six days, and so they had no follow-up on that patient. But the platelet, which was a platelet in pass, had been

transfused to a patient. They did do a follow-up six months after transfusion, and the patient remained seronegative for HIV, to everyone's relief.

The good news is that that platelet had been INTERCEPT treatment. France introduced universal INTERCEPT platelet pathogen reduction in November 2017. This was in about May 2017. So, they were on the ramp-up phase of introducing INTERCEPT at the time. And actually, this particular platelet had been pathogen reduced. We don't know that the low levels of virus in that platelet would have been infectious, but I'm certain that everyone was very reassured that, in fact, it had been.

So, then, the landscape for removing the MSM deferral question and the one-year deferral -- apheresis platelets are a particularly attractive population to lead this change, because there is a robust pathogen reduction process available and in use, there is outpatient reimbursement in place today in the U.S., and platelets are always in short supply. Red cells, it may have been a decline of 30 percent over

the last 10 years in use. But platelet use continues to be stable or increasing year to year. And because of the 5-day shelf life, there are always local shortages of platelets. So, an increase in donors and supplier is needed for platelets.

Finally, the apheresis collection process lends itself to this question. It encourages repeat donation over time, allows longitudinal assessment of individual risks over time, and tends, in the fixed-site setting, to be separate in some way from whole blood donation. So, if you're going to have a different process, apheresis platelet donation is a good place to do it because it's not happening out on the drives and you can do it in a controlled environment. The requirements would include the use of routine donor screening, conventional testing, pathogen reduction, and adequate BECS controls to deploy.

This could be done, as Dr. AuBuchon suggested, at the individual donation level. And you could use the "yes" answer to the MSM question as it triggers to track and treat that donation. An alternative way of

doing it might be to do it either at the donation center level, blood center level, and maybe one day at the universal pathogen reduction level for the whole country. Because, then, you would cover things like noncompliant donors -- donors who don't admit -- say yes to the MSM question. In fact, I would suggest that you can, then, remove the question completely and start to ask questions around behavioral deferrals.

So, in that setting, the current deferral could possibly be removed and you could start to ask behavioral questions in the setting of pathogen reduction plus nucleic acid testing. And I would venture that we really need to be asking both heterosexual and MSM behavioral risk factors, and things like substance abuse and alcohol abuse and sex with alcohol.

Questions that are asked today when they look at HIV vaccines for risk factors; we should look at those questions and ask whether they would apply to blood donation. Of course, now we've heard that we already have systems in place to track the incidence

and prevalence of viral markers through TTIMS REDS-IV. We have the mechanisms to actually look at changes in the donor population over time with pathogen reduction.

Now, this is an important question: is it feasible? We heard the comment that only 50 percent could meet the guard bands. I venture that that's completely incorrect -- that, today, you could treat 100 percent of collections from these donors. How can I say that? Well, today, 100 percent of collections in France -- 330 thousand per year, that's quite a large number -- are treated. 70 thousand collections in Belgium, 30 thousand donations in Switzerland; all 100 percent treated.

So, how do you get there? Simply, today, in apheresis collections, you set your machines for the volume and concentration of platelets you want to collect. There are settings today that you could set to collect double or single, triple platelet collections to make sure that they are 100 percent treatable. Remember that these are all additional collections. You're not taking somebody who gives a

triple and moving them down to a double. These are all additional new collections. You can aim for double collections and make sure they're 100 percent treatable.

Alternatively, you could collect your triples. But, then, you would need to manipulate the product after collection. Split a triple into a single and a double, and treat them separately. The other alternative, with time, is Cerus is working on a triple collection set which is licensed and approved today in Europe. So, we have every confidence that we will get that process available in the U.S. There's a process we have to go through to finally get FDA approvals, and we are highly engaged in moving that forward.

So, while today, blood centers struggle to get to 100 percent or even 75 percent compatibility, that's with the constraint that they do not want to change their split rates. Right? If the focus of blood centers today is to maximize and improve their platelet split rates for economical reasons, if they are prepared to put safety -- as in the MSM situation,

where you'd put safety first, you can get to 100 percent today.

Moving on. One day, when we actually have universal pathogen reduction, we actually have the opportunity to study over a million platelet donations from both heterosexual and MSM donors in the U.S. I would venture that, if we're going to do behavioral questionnaires, you actually want to look at a population that wants to give platelets or wants to give blood. And this is probably the best way to do it, because they've already shown the interest and eagerness to give blood donation. They're in the chair. And they're probably the best population to study.

So, finally, I think we're all on the same page. Every patient deserves safe platelets. This committee has discussed bacterial contamination in great depth, and the top photographs are related to bacteria. But pathogen reduction does provide a comprehensive solution, not only for HIV, but also bacteria, virus and emerging pathogens, parasites, T-

cell contamination, and does provide an opportunity to reduce discrimination and to provide social equity while enhancing patient safety. So, with that, thank you and I'd be happy to take any questions.

Maybe I can just stress one thing before I -- and 7-day platelets came up in discussion. There are two things about 7-day platelets. One, are they that safe from bacteria? And I think pathogen inactivation or pathogen reduction provides the safety you need to get to seven days. And two, are the 7-day-old platelets viable and active and effective? For that second part, the agency requires recovery and survival studies to be performed.

Cerus is in the process of performing those studies to meet the FDA's requirements. So, we know today that in Switzerland and some other countries, they use 7-day platelets routinely. And the hemovigilance data we get from those countries shows, quite convincingly, that those platelets are effective and, in fact, do not require more platelets per patient in use. So, we're confident that we will get there in

the U.S. Thank you.

DR. KAUFMAN: All right. Thank you, Dr. Benjamin. Do we have any other representatives from the public that would like to make a comment? Please.

DR. HERSHMAN: Good afternoon. My name is Dr. Janet Hershman, and I'm the medical director for BioLife Plasma. We are part of Takeda. And I would like to speak on behalf of the PPTA, our industry representative. PPTA is the Plasma Protein Therapeutics Association. We would like to speak on topics 3A and B related to this MSM donation. We are the international trade association and we set the standard for the major producers of plasma-derived and recombinant analog therapies. We produce about 80 percent of the world's needs for source plasma and 60 percent for plasma protein therapies.

As you know, these are for individuals with clotting disorders, immunoglobulins, for those who are immune deficient, some people with neurologic disorders as well as patients with Alpha-1 antitrypsin deficiencies. We also produce albumin, which is used

in emergency rooms and for individuals with shock. Of course, our goal is to produce safe and available medically needed therapies which are plasma-derived.

The PPTA does agree with the FDA's overall stated concept of looking at these policies, monitoring the effective policies and evaluating future policy alternative, including the MSM deferral. Although we agree with the overall changes, we do wish to address a few points that were provided in the FDA's issue summary. The first one is with respect to topic 3A. As you know, PPTA -- our companies operate about 760 U.S.-licensed plasma collection centers in the U.S. And in 2018, we collected 48 million donations of source plasma.

As PPA [sic] stated to the BPAC in 2014, at which time the committee considered the change in deferral policy from a lifelong deferral to the current 12-month deferral, source plasma is marketed globally. And we have to adhere not only to the FDA standards, but to policies beyond the FDA, some of which do not conform with what the FDA's current policies are with

respect to the 12-month deferral. Notwithstanding these changes in the donor policies, are they [00:19:54] generally applied broadly in both donations of blood and plasma.

Without the plasma industry's participation and the design of this study that was discussed this morning, incorporating an additional donor history questionnaire for donors that may be at higher risk of HIV -- which, again, that was discussed this morning -- it is unknown whether the results of such a study could be transferred to source plasma as our collection does differ in several methods from, for example, whole blood. We only have fixed locations. We don't have mobile locations. We have a much higher degree of automation and donor selection and monitoring that could affect the operational applicability to the source plasma industry.

With respect to topic 3B, certainly the PPTA is committed to providing safe and effective therapies. Our patients who receive our therapies made from plasma, as we mentioned, have very chronic and life-

threatening illnesses. Donor selection is certainly one of our layers of safety. We acknowledge that we do have a robust manufacturing processes and a lot of dedicated manufacturing steps. We have complex purification processes in viral removal as well as viral inactivation.

We can tell you that, over the past two decades, there have been no documented transmissions of HIV or hepatitis B or C. Almost all products imply two orthogonal methods for pathogen reduction. The log reduction is generally higher than those achieved with the methods being used for pathogen reduction in transfusable products, and this addresses both enveloped and nonenveloped viruses.

Despite the remarkable safety for final plasma protein therapies, the PPTA members have retained donor selection and donation testing as key quality management tools within our construct, again, of layers of safety. The FDA regulations include the assessment of behaviors associated with the relevant transfusion-transmitted infection and deferral of donors with

behavioral risk factors. PPTA opposes an ad hoc variance approval that includes a specific set of risk factors in a specific indication -- for example, pathogen reduced apheresis platelets.

PPTA and its member companies welcome a broader discussion of the value of behavioral risk assessments and other current requirements in the face of robust pathogen reduction processes. Thank you.

DR. KAUFMAN: Thank you. Is there anyone else from the public that wishes to speak? All right. Thank you. So, I'd like to ask the committee if you have any questions or comments related to what we've just heard during the open public hearing. Dr. Lewis?

DR. LEWIS: Referring back to one of the early slides presented by Cerus, it talked about the desire to move to a place where we could individualize risk assessments of the donor to avoid painting people with overly broad brushes -- for example, based simply on sexual preference. And yet, this seems a teeny bit different to me from the request for the variance, which is to eliminate completely an entire set of

behavioral risk assessments that have to do with behavior.

So, I'm wondering if someone can sort of address how we got from the original text from 2016, which seemed circumspect, and it's asked to something that seems quite a bit more extreme.

DR. BENJAMIN: Maybe I can talk to my slide. That slide was aspirational. It definitely is where we think we could get to. I don't think it's necessarily where we are at the moment. And it's certainly not the request that's on the table for variance from Dr. AuBuchon, which is a more limiting scope. So, I think we could get there.

DR. LEWIS: So, I may have spoken unclearly or we're seeing things quite a bit differently. If we could show your slide -- I'm not sure if it was the second slide. It showed -- it was full of text. It had to do with your 2016 submission, if I understand correctly. While we're waiting for that, where I'm trying to get to is I can see very strong arguments for using a different additional information that we have

available to us, based on epidemiology and other sources, to try to be as discriminating as possible in identifying the probability that an individual donor is likely to be in the window.

I interpreted the phrase “individual behavioral risk assessment independent of sexual orientation” as moving away from simply asking whether there has been MSM behavior over the last 12 months or some period to one of asking whether or not the behaviors, regardless of sexual orientation, are behaviors that we know, epidemiologically, are associated with risk of recent transmission. In fact, I tried, in one of the breaks, to look up to see if I could find a current questionnaire that’s used to identify patients eligible for HIV vaccine trials because that really is attempts to find the exact same population.

In that case, you’re trying to recruit a population at risk for acquisition. And here, we’re trying to avoid a population at risk for being in the window associated with acquisition. I was unable to

find something. But, to me, those are very analogous things. But there, you talk about individual behavioral risk assessment and yet the variance request said no risk assessment associated with MSM behavior, that those -- that entire line of questioning would be removed. And those seem quite a bit different -- qualitatively different.

DR. BENJAMIN: Indeed. The way it could is aspirational -- could be implemented or you could do this. In prior discussions, both in this BPAC and at the Advisory Committee for Blood Tissue Safety and Availability, the voice has been patrolled by the MSM groups that their aspiration is to do away with the question completely and to look at both heterosexual and MSM risk factors. I think, in this 2016 submission, that's what we were attempting to address.

DR. LEWIS: And when you say "do away with the question completely", which question are you referring to?

DR. BENJAMIN: Are you a male that has had sex with a man? Right now, it's for 12 months. At the

time -- three years ago, I can't remember if this was before or after it changed to 12 months. But certainly, it was indefinite at one point. It used to say "since 1977".

OPEN COMMITTEE DISCUSSION/QUESTIONS FOR THE COMMITTEE

DR. KAUFMAN: Okay. Thank you. All right. So why don't we move on to the open committee discussion? And maybe we can have the question up for the group. Issues for discussion -- we want to discuss the use of pathogen reduction of apheresis platelets as an alternative to the current MSM deferral policy and discuss any associated risks and possible mitigations. So, let me open this up to the committee. Sridhar?

DR. BASAVARAJU: So, it seemed to me that much of the risk reduction in blood safety actually occurs because of the donor deferral process. So, by the time a donor is deemed to be eligible to donate blood, it's because they are at lower risk. And I think that's evidenced by the fact that the proportion of total donors who are found to be HIV positive during blood

donor screenings is substantially lower than the population prevalence.

So, if you take that out and then you introduce a population who is known to have the highest, I guess, risk of having incident HIV infection, it would seem that you would have window period cases that are tested and found to be negative even though they could be infected. And then, you would apply a technology that's pathogen reduction. It's not pathogen elimination.

So, presumably, there's still at least some risk. So, it would seem that this -- I think the idea of saying, could we talk about reducing the 12-month period or something like that, I think that's reasonable. But, to say we're going to just stop asking at all, that seems a little extreme.

DR. KAUFMAN: Dr. DeMaria?

DR. DEMARIA: My question would be, is pathogen reduction more or less reliable than the history that we're getting from the donor? Because the deferral depends on the history we're getting from the

donor. And presumably, the residual risk is in people who are not providing an accurate description of what their risk is and, therefore, turn out to be positive. So, it is a balance between that history and the pathogen reduction addition to the safety, it seems to me.

DR. KAUFMAN: Dr. Shapiro?

DR. SHAPIRO: From a standpoint of patients with bleeding disorders who utilize plasma-based products, we, as providers, look at the products. What we want from them is we want donor testing, and we want two viral inactivation methods to assure that the products are likely safe. Now, again, those are larger pool products and it's different than this, but -- and I think this technology's wonderful. I think that I view it as your using of the donor testing and a viral inactivation process, which will help make the blood supply safer to the recipients.

The total elimination of risk questions seems a little premature in light of the discussion when you're considering going from one-year deferral to a

shorter period of time and being totally reliant upon one inactivation technology. And it's not just the risk of what we know; it's the risk of what can appear. This doesn't get every virus.

DR. KAUFMAN: Dr. Bloch?

DR. BLOCH: So, you know, I totally agree with you. I'm really struggling with this because, on the one hand, really, are proponents of pathogen reduction which I see as transformative because it's protecting against emerging, remerging, as well as established pathogens. I also agree with what has been said in terms of the platelet inventory, particularly HLA-compatible products. There's really -- while red cell utilization has gone down, I think that there definitely is a need for platelets.

But the premise for this seems to be -- there seems to be a disconnect. Because we're arguing for eliminating something which we know potentially has established benefit in favor of pathogen reduction because of the bacterial benefit. It's just, in a way, kind of comparing apples with oranges. Is this a real

need to abandon -- we've singled out the highest risk factor, almost arbitrarily. There's no need to abandon the risk factor just to bring in pathogen reduction.

DR. KAUFMAN: I think that -- if I've interpreted Dr. AuBuchon's presentation correctly, I think the bacterial benefit is more of a side thing and not at all the focus to this. And I would like to keep the discussion really focused around HIV for this.

DR. BLOCH: Again, it's kind of selective -- we're arguing selectively. I think that the real benefit is actually the bacterial protection. And then -- because no -- I'm just trying to understand why one would abandon the donor inquiry when we know that that's potentially offering benefits.

So, in terms of precedent with laboratory testing as we mentioned this morning -- well, actually, yesterday -- the only test which have -- where they've given something up was where they had something which improved upon it, whereas this is not really -- it definitely offers a completely different layer of safety. But it's not necessarily in line. It's not --

we didn't go from p24 antigen to NAT testing. They're two different sources of benefit.

DR. KAUFMAN: I think I don't exactly agree. Well -- so what I would say is that it's not possible to get rid of the window. So, we can kind of hammer down the risk by shrinking the window with incredibly sensitive tests. And we may be about as -- where we can be. Maybe there's a way to get it down another couple of days. I don't know. And there's probably a period immediately after infection where something's not infectious; there's not enough virus. But I think that that risk continues to exist that is -- if you're relying on testing and whatever else you do, I think that risk exists.

Pathogen reduction, essentially, can take care of that residual risk which is, again, really what we're talking about. So, even though, yes, I agree with your point that you're actually actively inviting donors who, as a group, have -- at least at the group level, have a higher risk of HIV. That's not debatable. But you're still using NAT with this very

small window. So, what's left is still really quite a low risk.

And then, I think you can essentially, with a -- what could only be a recent infection and a very low level of viremia, I think you're really talking about a zero risk essentially, with pathogen reduction in that setting.

DR. BASAVARAJU: I don't think it'd be zero, right? I mean, I don't -- I think that none of the mitigation strategy is at zero. Even PRT, I don't think -- even Dr. Benjamin wasn't claiming it's zero. So I think you -- I mean, you have a lower pathogen load, by virtue of it being subjected to PRT, but if you're having more people who are acutely infected, then you would presume that some of those people would be potentially not.

DR. KAUFMAN: Dr. Stapleton.

DR. STAPLETON: I think, theoretically, it is zero. Because if you're talking about missing it on NAT testing that has a very high sensitivity -- so the amount of virus in that product is less than a few

copies per mil, and the volume is less than two liters and you've got five logs of reduction, you've gotten rid of every -- you've inactivated every virus in there. So, theoretically -- nothing is zero. But, theoretically, it's zero.

DR. STRAMER: May I say something?

DR. KAUFMAN: Yes, Sue.

DR. STRAMER: So the combination of testing and donor selection obviously doesn't work perfectly, because we have positive donors for all markers we test for. The FDA authority allowed pathogen inactivation to serve as a substitute for bacterial mitigation for Zika and in the plasma industry for many other markers that they don't test for that we do. The pools that we do for NAT in whole blood -- for instance, in the plasma industry -- are much smaller. The donor demographics are very different.

So, I would position pathogen inactivation as an indiscriminate method of the eliminating pathogens. Perhaps not all pathogens, but certainly those envelope pathogens that we're very familiar with in MSM and

other individuals with sexual risk factors. So, I think, if we're trying to compare one-year deferral or two, three-month deferral or donor retest, it's really -- as others have said, it's an unfair comparison because pathogen inactivation is much more robust. It may not be zero, but it's certainly more robust than the other technologies we talked about earlier today.

DR. KAUFMAN: Thank you, Sue. Dr. Lewis?

DR. LEWIS: I, perhaps, like Dr. Bloch -- I'm really disturbed about the structure of the argument. I don't see any connection between reduction of bacterial contamination risk and the question about the deferral question.

Because if, in fact, our concern was about the safety of the platelet supply with respect to the most common pathogens which are bacterial, then we would be discussing widespread use of this pathogen reduction technology along with concomitant strategies to increase the donor pool broadly since it's a very small fraction of the population that donates platelets. These things have nothing to do with each other, and

I'm personally bothered by the attempt to link them and defend that linkage. That's the first point.

The second point is that -- was, I've been going to my logarithmic math in my head, as Dr. Stapleton has as well, and I agree with you that it is likely that the risk is very, very, very close to zero. There's actually no data provided to us or the agency regarding the incidence of folks in the window that would be associated with reduction of those screening questions.

Unlike some things where you have to replace one technology with another technology -- and for some reason, they're mutually incompatible -- in this case, there's nothing that says you can't ask some questions and then also treat the platelet with pathogen reduction. Again, it's a false choice. So, I believe that Dr. Stapleton's math is probably correct. I believe there's no data to support it other than just sort of conjecture about what we believe about the population.

I think that the linkage of questions that

should not be linked is something that we should call out, and that it is perfectly reasonable to recommend that one pathogen reduction technology be used because it does increase the safety of the platelet supply; that broad approaches to increasing the population that provides platelets to the nation's platelet supply be pursued because it will be some loss of efficiency that's the cost of that additional safety; and that the real issue with the MSM question is that it paints an overly broad brush that is, therefore, offensive because people know it is not sexual orientation or it is not a monogamous relationship that places you at risk.

And the question, now, inappropriately captures that. What we should focus on is trying to figure out what the questions are that capture the risk so that we don't appear discriminatory as we try to distinguish levels of risk.

DR. STAPLETON: I agree with that. And I think that the participation in the study and at the time of screening is very appropriate.

DR. BAKER: A general lending of support to Dr. Lewis' statements.

DR. KAUFMAN: Mr. Templin.

MR. TEMPLIN: Personally, I think the whole question entered needs to be revisited. And maybe more people should be deferred in other risk categories. But, because of the short shelf life of these platelets, I would think if there's at all a possibility that this technology could harm -- because it could let something go through that isn't being inactivated other than HIV -- these folks that are receiving these platelets would be in more danger.

Going to listen to what PPTA says, their product is held in inventory for a long while. It's not just used within a few days. So, I just wanted to add that.

DR. KAUFMAN: I think those are -- well, a couple of different points. Obviously, the consideration for a donation in testing and then to come back and retest the donor strategy truly can only be applied for products with longer storage. So, for

platelets, at least as they're currently collected, it's just completely not viable. I do think that from a -- strictly from a pathogen -- from the potential for a platelet unit to transmit any pathogen, a pathogen reduced unit is considered to be the safest that is available.

So, it's -- one of the things that we were kind of talking about a little bit today, a little bit more in the morning, is, well, when you ask questions, do people understand them? Do they answer accurately? Do they remember? Do they not remember? You know? And then, ultimately, you're left with, okay, so, now we think we have someone who's incredibly low risk; they're in a monogamous relationship. And the truth is, you can never be 100 percent sure about monogamy. There's just no way around that.

One of the, I think, attractions of an approach like pathogen reduction is, because it's completely different, none of that matters. So, while you may, as part of a multilayered approach, be able to drive risk down, it does allow to cover up for

potential limitations for some of these other approaches, like risk questions.

DR. TEMPLIN: I think if, with this technology, you get rid of bacteria, that's great and it should probably be used for that purpose. But I would rather have a product that was solvent/detergent treated that have filtered in a multiple-step approach. I also think, too -- I know, personally, people who have told me they lied on the questionnaire for whatever reason they did.

It's heartbreaking because I would want that person to have a unit of whatever that was perfectly clean at any time. Everybody should have the right to have safe blood or any kind of medication period. So, it is sad when people say they would only donate now because they can't. But if they had the opportunity to donate, they would. So, it is just sad to hear.

DR. KAUFMAN: Well, and with respect to the other products -- plasma drive clotting factors, for example. So, here, we're talking about acellular products that can be more intensively processed and

that sort of thing.

DR. SHAPIRO: Right. So, cellular products.

DR. KAUFMAN: Right. For cellular products, it is different. I will say, again -- and I have no financial conflict of any sorts, but I will say that one of the advantages that we've seen with pathogen reduction is, even with these large pools, these approaches, somewhat different -- solvent/detergent, ultrafiltration, and so on -- were applied to factory products, for example. So, when West Nile Virus, for example, came to the U.S., it was a nonproblem. It is sort of already had been taken care of.

Anyway, so, it's another argument for a pathogen reduction approach versus a, "Did you travel somewhere where there's West Nile?" or that sort of thing.

DR. SHAPIRO: I wasn't arguing against pathogen reduction; I was arguing for it for these products, just not necessarily elimination of assessment of risk through questionnaires.

DR. KAUFMAN: Dr. Demaria?

DR. DEMARIA: I think -- well, you know, to get back at why we're here discussing this is that the -- and people may or may not agree, but the reason we are discussing this is because there's a perception that the way we do it now is not equitable or just in terms of eliminating people purely on their sexual orientation, not what they actually do or do not do that may put them at risk or not put them at risk. And there are ways to address that.

I like the Bloodworks Northwest approach; I feel that it's a safe approach and that it's preferable to the approach of quarantining plasma, which we don't really need the plasma. It's just being done as a concession to make up for the fact that we have this policy in place whereas the platelets are really needed, and it could enhance overall health by providing more platelet products for people who really need them.

So, I think, looking at it from that standpoint, there's not one solution to all of this. But there is an exploration of various solutions. And

I still think, if you can find that technological fix that gets around the fact that people many not always tell you what behavior they're participating in, that is preferable to depending on that kind of history.

DR. CHITLUR: This is Meera. Can I ask a question?

DR. KAUFMAN: Yes. Please go ahead.

DR. CHITLUR: The Bloodworks Northwest approach of considering doing a PRT for all platelet donations coming from MSMs -- did I understand that right? Is that what they were saying, that they will consider PRT for those units?

DR. KAUFMAN: I'm going to try to say this correctly. So, their approach will be, if, in the course of a routine screening, an individual answers yes to one of the MSM questions, they would automatically be restricted just to donating apheresis platelets. Those apheresis platelets would be automatically restricted to be pathogen reduced, and then have to meet the guard bands on sort of manufacturing steps necessary to ensure inactivation of

the units.

The donors would be tested by the usual nucleic acid test, and the product at the end would be essentially considered to be equivalent as any of their pathogen reduced apheresis platelets currently in inventory.

DR. CHITLUR: Is there any reason to think that -- I don't know if this is even right. But if -- considering that we have some information, does the recipient have to somehow -- I know at the end, I guess, they're all equivalent. Am I right? So, it does not -- that information up front that we got does not necessarily have to reach the consumer at the end.

DR. KAUFMAN: Yes, that's correct. The label of the product would be exactly the same, and there would be nothing different from the hospital that got this. From their perspective, it would be the same as every other platelet. And really, that's, I guess, one of the questions the group is being asked to contemplate is, does that sound reasonable? That is, could the product be considered as safe as every other

product? I personally think that the answer to that question is yes.

Sorry. Dr. DeVan? Dr. Bryant?

DR. BRYANT: I agree with you, Dr. Kaufman. I look at this and think, okay, what could go wrong? A donor comes in; answers a question yes for MSM. Then, they'd be tested anyway for infectious disease, right? So, worst case scenario, in a window period or maybe on PrEP, and viral load's really low and not getting picked up. But then you're going to go through pathogen reduction. So, you're going to be covered with that.

I think that's a safe alternative to our current policy. As long as there's -- have all the stopgaps to make sure that you're not going to have a problem with the eliminator being turned on or the Amotosalen being added. And those are things that are built into the system that that wouldn't pass; I mean, there would be a big flag that's -- that product would not get through the processing. As long as a computer system's picking this up and flags the patient that

this unit of platelets would need to go and be -- we could only collect platelets and it would, then, become pathogen reduced.

So, I think, if everything is in place, it would make sense. And it actually would probably be a better product than possibly a three-month deferral or maybe even a year. I mean, I don't know. Especially since we've got the added PrEP in place. We don't know what that means. Is that going to delay the window for how many weeks? So, pathogen reduction, I think, is a good option.

DR. KAUFMAN: Yeah. And just a couple of points; I think, what you talked about at the end -- would everything work right? I think that is really kind of the risk. On the other hand, those are the sorts of risks that blood centers have to deal with continuously. Did you get the correct result matched to the correct donor? And was the NAT test done properly? All I can say is it's a industry that deals with risk. And I forget who said it; maybe it was Dr. Goldman earlier, like, "Standardization is next to

godliness."

So that is a question, but that is a practical logistical question for Dr. AuBuchon and the blood center. I thought the way that he laid it out in his presentation, where, sure, it's a different pathway; they have some different products in their inventory. But the pathway that he laid out wasn't radically different from how they're making other PRT platelets. In the absence of a computer system to handle a lot of the sorting of a product, I would be much more concerned about the logistics. But for the same reason that, for example -- I don't know -- electric crossmatch works, that sort of thing, to me, it seems okay is my feeling.

Dr. DeVan?

DR. DEVAN: This -- along the same lines of your thinking "what could go wrong?", I was wondering about, during the process, the phlebotomy of a donor that comes in the phlebotomy -- the removal of the unit before it's gone through the Amotosalen processing. Does that increase any risk if we do accept donors from

a higher risk pool? And does -- should that play any role? Does that play a role or should that play any role? A patient that comes in from a higher risk population and the phlebotomy, the removal of the unit itself before it's gone through the inactivation process.

DR. STAPLETON: I don't know if you're talking about transmission or to the donor.

DR. DEVAN: I'm thinking of a potential risk to the phlebotomist.

DR. STAPLETON: I have a number of patients with hemochromatosis and HIV, and before they were on HIV meds, we sent them for a phlebotomy. And that's not considered a dangerous procedure other than -- more so than using universal precautions. So, I would not think so, but others could argue with me if they want.

DR. STRAMER: This is Sue Stramer. I mean, that risk exists today when we collect from any -- from a donor who may be in the window period as HIV positive and before we even know the test results. So, those risks occur now with HIV positive. 62 percent, as we

heard earlier, come from donors who have MSM.

The real question today is, you have two choices for platelets. One are platelets the way they are today, with the 12-month deferral for MSM, accepting a 7 to 10-day window period, knowing that our residual risks for HIV are somewhere in the 1 to 2, to 1 to 3 million range -- probably lower for platelets because they're so pedigreed -- versus accepting the same testing that we do today and substituting the MSM question with its flaws, the noncompliance, and other issues we've talked about. But the technology that especially, within the window period, is fairly robust.

And for those viruses that may present an MSM, we know they're very susceptible to pathogen reduction. The agents that Dr. Benjamin mentioned of bacterial spores, bacillus, or HIV or HAV possibly, but those are not the agents you would expect today to be in a presenting MSM donor.

DR. KAUFMAN: Dr. Lewis?

DR. LEWIS: But I think there is a third option. I think we get different answers depending on

-- for each of us, we can pick two options and make a choice between them, but we all get to pick which two we want to choose between. The third option that the previous speaker didn't mention is the option of adding the pathogen reduction, which everybody is unanimous about its merits, but retaining some level of behavioral risk stratification as well.

And I just don't see why we tie the addition of this additional layer of safety necessarily with elimination of a different layer of safety about whose removal we've actually been seeing no data in terms of what it does to, I guess, the prevalence of donors being in the window. And I agree with everybody's math that the risks here are very, very low. But we should structure our argument accurately.

DR. KAUFMAN: Oh, sorry. Mr. Templin?

MR. TEMPLIN: I'm all for the safety of blood supply, I don't want anybody to be discriminated. I want social justice, everybody to be happy. Yes, the industry takes risks, but also the recipient of the products take risk. And I get some infected products

and nobody compensates me because there is no compensation. The blood share laws protect these products.

So, maybe a Vaccine Injury Act for blood would be something that should be created because, if I get a vaccine and something happens, somebody takes care of me. I'm all for the industry taking risks, but if I need some sort of product, I'm taking a risk too. Unfortunately, some people have to take more risk than others.

DR. KAUFMAN: I think you're at one of the most risk-adverse places in the country. That is, I think that, truly, we -- I'm very proud of the fact that blood has gotten so safe. I don't think anyone could've imagined blood could be this safe in the 1980s. It's gotten amazingly safe relative to how it used to be, even before there was HIV in the U.S. Again, we've kind of -- I've kind of said this before, but I think that the general theme is we want to try to maintain that safety. That is the primary mission. That is not something that I don't think anyone is

talking about compromising.

So, having that as a first and immutable goal, the next question is, can we meet that in different ways that might allow more people to donate? And I think that's kind of the crux of it. So, I guess I don't frame it as, well, let's pick a flyer on this approach or that. And I think Dr. Marks said it as well. And again, the FDA, in this instance, after much deliberation, went from a permanent deferral for MSM to 12-month, and that's where it's staying for the time being without further data. He made that very clear.

And then, I think the question is sort of one -- truly an exploratory effort that we talked about this morning is a study that may or may not lead to further changes, and then this other approach, which -- frankly, because it offers a completely different way of making blood safe, you end up discussing some -- I don't know -- different sorts of possibilities, is what I would say.

Dr. Stapleton?

DR. STAPLETON: Dr. Schreiber may not have

appreciated my taking his comments this morning, but I thought his comments about, “What was the evidence for going to 12 months as opposed to 3 months or 2 years?” The exclusion doesn’t apply to heterosexuals who don’t answer the questionnaire honestly either. So, there is that social justice issue. And those at-risk people will still be donating, and they’ll be excluded from the PRT. So, if they get platelets, actually, those units will still be there.

I think, on balance, there is a more biological support for this approach, even dropping the three-month window, than there is for -- well, than there would be for the blood supply. And the other thing that will happen is we will collect -- we should generate good evidence and data on this group of people over the next few years that will help us in understanding about blood transfusion.

DR. KAUFMAN: Sridhar?

DR. BASAVARAJU: So, we haven’t seen any data here, right? So, we don’t know how many MSM will show up to donate apheresis platelets. We don’t know how

many of those would be acutely infected. And we don't know how many of those would be acutely infected on PrEP, let's say. Then, let's say that there are those people we don't know necessarily how much of this will be eliminated by PRT, right? We haven't seen data on that because I don't think that they have that data. But we're going to give it to recipients without telling the recipients we don't know any of this information. Right?

DR. STAPLETON: I don't -- we do that with heterosexual people who have risk as well, who lie on the questionnaire.

DR. KAUFMAN: And I will say there is a lot of published data over many years, both in vitro and in vivo related to PRT. It was not presented today. I think that's fair.

DR. SHAPIRO: I mean, you're right that we do that with heterosexual people who do not tell the truth on the questionnaire, but not knowingly.

DR. STAPLETON: So, I guess you could argue, how do you knowingly know that a homosexual man is

lying on the questionnaire versus a heterosexual? And so --

DR. SHAPIRO: No, you don't. I mean, both groups lie a certain percent. I mean --

DR. STAPLETON: So, the beauty of the PRT is that it takes away that.

DR. SHAPIRO: I'm not arguing against PRT. I'm talking about dropping of risk questions on the questionnaire and not informing the recipients of those products that you've dropped a level of what was considered safety by the public.

DR. STAPLETON: Would -- I guess it would be publicized that this was happening in Seattle. I would assume it.

DR. SHAPIRO: I wouldn't guess. I would ask.

DR. STAPLETON: Yeah. That's -- yeah. I would -- yeah.

DR. KAUFMAN: I don't know, maybe Dr. AuBuchon can -- if you -- maybe you want to comment a little bit about that, because that's something we haven't talked about. How would the hospitals feel about it? How

would the public feel about it?

DR. AUBUCHON: I can assure you that, if this variance is granted and the program begins, it will be front page news in the Seattle Times. And it will be well-known across the community. It is our opinion that -- well, it's not my opinion. It is the data that any donor who tests negative in NAT will have any HIV or hepatitis B or C inactivated through the INTERCEPT process. The data are well established, by orders of magnitude, for that safety.

Therefore, we feel there is no reason to raise unnecessary concern in the recipient population that these products are somehow less safe. That is just not true. In fact, were there a requirement misguided, in my opinion, that we get informed consent, this program has zero chance of ever getting off the ground. Because the assumption will be, from the recipient, that it is a less safe unit and they will not want it. I do not believe the data supports that assertion.

DR. KAUFMAN: Dr. Marks?

DR. MARKS: Can I just formally, for the

record, just make sure that we understand -- because I seem to be thinking there's some question here. The remainder of the donor questionnaire questions will be asked for these units, so it's -- the only question that is not in play here is the one by definition, because it's the MSM question, right? All the other questions are being asked. Is that correct?

DR. AUBUCHON: That's correct.

DR. MARKS: Okay. Thank you.

DR. LEWIS: So -- I'm sorry. That's different than how I interpreted one of your slides. And I think this is a --

DR. MARKS: That's why I was a little worried. I was worried that's -- with some of the questioning, that's why we were worried.

DR. LEWIS: Yeah. So, in one of your -- the slides, it was presented early on. It says -- when you're going through what is being requested, it said, eliminate all then something questions. And maybe you could explain that to make sure that we're at least debating the same issue, the same request.

DR. AUBUCHON: This variance request applies only to two questions on the donor history questionnaire. Actually, one question per donor because one question would be asked of women; the other of men. But it pertains to whether or not a man has had sex with another man in the last 12 months -- that's the male question -- or whether a woman has had sex, within the last 12 months, with a man who's had sex with a man in 12 months. So, that's the only question that would still be asked, but would not lead to an immediate deferral and asking the donor to leave.

DR. LEWIS: And then, for the sake of completeness, could you just go through the other questions that would be asked about recent sexual practices that would remain on the questionnaire?

DR. AUBUCHON: There are no questions, at the moment, that are asked of donors about particular sexual practices. There are those in the gay community who feel we should be asking heterosexuals the same kinds of questions about sexual activities leading to increased risk that is presumed to occur in the MSM

population. But, at the moment, there are no such questions.

DR. STAPLETON: There is a paying for sex question. Correct?

DR. AUBUCHON: Oh, I'm sorry. That is -- there is a prostitution question. You are correct. Thank you. That would still be asked and would still lead to a deferral.

DR. LEWIS: And no questions about multiple partners or new partners?

DR. AUBUCHON: No. There are no questions about numbers of partners or new partners. There's a question about having recently been incarcerated, but that would still stand.

DR. LEWIS: As I said, question --

DR. AUBUCHON: Yes, and there's still a question regarding syphilis and gonorrhea. Thank you. I don't have all the questions in front of me. But all other questions would stand. It's just the MSM question.

DR. KAUFMAN: Dr. Bloch.

DR. BLOCH: Just to clarify something.

DR. VERDUN: Sorry.

DR. KAUFMAN: Oh, sorry.

DR. VERDUN: No, while you're there, can you comment on the part of the question that someone asked about what the hospitals think or any conversations you've had?

DR. AUBUCHON: Our hospitals have only recently been informed of our interest in this approach. We have not had detailed discussions with them. Informal discussions with some transfusion medicine physicians in the community has yielded no concern whatsoever. We'll obviously be having more conversations with them as this process proceeds.

DR. SHAPIRO: So, could I ask one question? Would you accept, as a donor, an individual who was on PrEP because they were in a relationship with someone who was HIV-infected?

DR. AUBUCHON: There is already a question in the questionnaire whether or not you have had sex with anyone who has HIV. That would still be a deferral

criterion.

DR. KAUFMAN: Dr. Bloch?

DR. BLOCH: So -- not to revisit this again and again, but this is where I'm completely torn in that I actually think that the risk is really -- I can't say negligible, but it really is theoretical. So, by putting in that layer of safety when really -- when it's achieving, really, a safe product.

The problem is the approach where, if this was sold as -- one wanted to increase the inventory of safe platelets or increase the access to platelets, and then it was kind of a broad-based approach where one looked at all the risk factors together and, essentially, it's just kept them all out. But it's really so selective. One went to one and one -- one actually went to the highest risk first, which doesn't make any sense.

So, on the one hand, it doesn't really matter because that's kind of academic. Because, if your product is safe when achieved, achieve that anywhere. But I just -- the whole sell. This doesn't make any sense to me.

DR. KAUFMAN: Dr. Baker?

DR. BAKER: Thank you. Following up with that point, if it doesn't make sense to some of us around the table and we have these questions, I wish to go back and ask what proactive steps are being taken to have structured communications now with the leaders of the hemophilia -- you know, the platelet community, the people who are end users, to discuss this in a proactive fashion. Because they will begin to get questions if it, indeed, gets on the headlines of the Seattle news.

DR. AUBUCHON: We intend to have those discussions as we proceed through this process toward implementing the variance, if granted. We haven't completed that process obviously. We have a long ways to go. So, if the agency is taking additional months to consider our request, we will be putting that to good use. The hemophilia community, rightly, is very concerned about the safety of transfusion in general, but they're particularly focused on the products they receive. And, for the most part, those are not

platelets.

That's why we have been attempting to pull together a group to get input from patients so that we can structure our media releases, structure our public education campaigns, as we move toward implementation to address concerns that they may have. Admittedly, we are working from a belief that this proposal is safe. If we did not believe that, we would not have presented it to you for consideration. We feel, with appropriate information, that a reasonable person will come to the same conclusion.

However, we haven't tested the exact messages that we will be using yet, but we do intend to do that. We will continue to have discussions with our hospitals because those hospitals that depend on their own physicians and their own transfusion service to lead the patient care in their institution will have to field those questions first, likely. And we want to make sure that those people are informed and are also comfortable with our approach.

But again, we've got time before we roll that

out. We have not rolled that out. We didn't put that at the front of our process because we are anxious, not to create undue desire in the MSM community to donate; it's not that we're keeping it quiet in order to do something nefarious. We just feel that we don't want to make this a public discussion on the front page of the newspaper before we actually have a process that we can offer those donors who would be affected.

DR. KAUFMAN: All right. Well, why don't we just go around -- I'm sorry. Dr. Bryant?

DR. BRYANT: I have a billing question. I don't know if this is appropriate. But I -- I just want to throw this out there. If you have an apheresis donor who's answered all the questions correctly and is not an MSM, and then you decide to pathogen reduce that platelet, them that platelet is sold to the community as a apheresis platelet and there's a charge for the fact that it's pathogen-activated.

On the other hand, if it's an MSM -- and for you to get that platelet to market, you've got to pathogen-reduce it. Is that cost of pathogen reduction

-- will that be passed on to the consumer? Because it's what the blood center has to take on to get it to be marketable. I'm just kind of curious; will that set up a -- will you have double population of billing of these products, or will you just treat them all the same?

DR. AUBUCHON: All units with the same product code would be charged out similarly. And the units that would come from donors previously deferred under MSM deferral criteria would not be distinguished in any way. But the same token, however, we would not attempt to recover the additional costs associated with opening up donation to MSM donors.

For example, all of the hours -- and there are hundreds of hours that have already gone into thinking about this -- the additional cost of recruiting an entirely new donor population, the pre-testing involved to make sure that the donors will be appropriate for a donation -- none of that would be charged out. So, as I said at the beginning, every unit would be handled the same way. And the source of the donation would not

distinguish it at any manner.

DR. KAUFMAN: So, I thought we can just go around to kind of wrap this up, and I'm going to -- not that -- well, I am going to put everybody on the spot slightly and just ask if you have any final -- what your final thoughts are on the experience. So, I'll start with Dr. Schreiber and we'll just go around.

DR. SCHREIBER: Based on my knowledge of what we've seen today and prior knowledge, I think that this is -- I think, to me, again, the most important thing is patient safety. I think this proposal meets the criteria for patient safety. I think there's concern about continuing asking appropriate questions. I think those questions should be continued to be answered. I don't think that this should change that at all, because I think that that process is also important. I think that -- it's very nice that this is being done with platelets, but I think that this technology is also proof for plasma.

And, in the future, I'd like to see a plasma involved with this. We're all saying that there's not

a plasma problem, but on any given day there could be a plasma problem. If there's mass causalities, other events could occur. So, it'd be nice to see this also generalized to the use of plasma. There's essentially a unit of plasma in a unit of platelets anyway. Those are my comments.

DR. KAUFMAN: Thank you. Dr. Baker?

DR. BAKER: Thank you. Agreed that patient safety comes first. I would love to see this also apply to plasma. I just don't see that we have the data to suggest that this should be an alternative to the current MSM deferral policy. I think those MSM questions should be asked.

DR. KAUFMAN: Thank you. Dr. Bloch?

DR. BLOCH: I agree with both. I think that pathogen reduction (inaudible) is an additional layer of benefits. I think the risk is so minuscule that I don't think it's going to -- it makes a difference. I think that's -- I would support the variance.

DR. KAUFMAN: All right. Dr. Stapleton?

DR. STAPLETON: So, I would like to mention

Dr. Baker's comment. I think the questions are still asked; it's just they're overridden for those two. Have you had sex with a man who's had sex with a man? Or have you had sex with a man? So, the questions are still asked.

I think this is an ideal way to move MSM into the general donor pool, because the risk is low to start with. And with the vaccine reduction, I think it becomes as low as humanly possible to transmit HIV or hep C from this -- hep B from these platelet units. It gives us an opportunity to obtain data that we won't get very easily otherwise from, potentially, a large number of MSM. So, I'm very much in favor of this.

DR. KAUFMAN: Thank you. Dr. Bryant?

DR. BRYANT: I believe patient safety is at most of importance. And I do believe that pathogen reduction as an alternative to MSM is an acceptable procedure. So, I support this variance.

DR. KAUFMAN: Thank you. Mr. Templin.

MR. TEMPLIN: I think, if the technology could make the product safer, that's a good thing and it

should probably be used. But I also think there needs to be some sort of study, and this issue needs to be followed closely by the folks behind me and all the other alphabet soup that goes along with making the blood safe in this country. Because I want to make sure it's safe for me and my children and my wife if we need it.

DR. KAUFMAN: Thank you. Dr. DeVan?

DR. DEVAN: I agree. I think it's -- I think the data support this is an acceptable variance. And I think it expands the donor pool, which is something that I think is critical. I can't transfuse the platelets that haven't been collected.

DR. KAUFMAN: Dr. Shapiro?

DR. SHAPIRO: I'm a little conflicted. I'm having a little trouble with this. I support the pathogen inactivation. I understand the questions you're still being asked in an alternative route, being created for some individuals. I think that we need to look at refining the questions to pick out individuals, not just MSM but other individuals, who could be at

risk to transmit viral infections, either known or unknown, to the population so that we're not using one set of questions to adversely affect one group, but that we get a better set of questions that affect -- that could put other patients at risk.

That being said, I'm a little concerned about individuals who are on PrEP being allowed to donate. They are a subpopulation of the population of MSM or other individuals, even IV drug users, that could be a high-risk group and could stress the technology in some way or create a failure if there were some mechanical failure within the system.

DR. KAUFMAN: All right. I would note that the IV drug use question would still be asked.

DR. SHAPIRO: Right. But, if someone's on PrEP, they've self-selected themselves as a subpopulation who is probably of higher risk. Either refusal to use protection, some other risk factor.

DR. KAUFMAN: Dr. Ortel?

DR. ORTEL: I feel that the variance, as proposed, where the questions are still asked, the

baseline precautions are still in place, that there is this variance on the one question that is perfectly appropriate and expands the potential pool. I think that continued ongoing research does need to be done to try to figure out if there's ways to refine the questions or improve the questions, and that can replace things later down the line. But that's a different question.

DR. KAUFMAN: Thank you. Dr. Lewis?

DR. LEWIS: So, first of all, I agree completely with the previous comments about the value of pathogen reduction in a broad sense, and that anything we can do to increase the use of that or similarly effective technologies to make the platelet supply safer is a good thing. On slide 6 of the Bloodworks presentation, I found the phrase that, I think, caused some confusion. It says, "accept as apheresis platelet donor; MSM, regardless of sexual activity, full stop." And that's, I think, not -- in retrospect -- what was intended. I think it means, except for all those other questions, we're still going

to ask. And that's an important qualitative difference.

The previous speakers have commented about the importance of figuring out what the right other questions are. The right questions may never mention sexual orientation, but they should inquire about practices that, based on sound epidemiologic data, place people at higher risk of new acquisition of transmissible agents. And anything that can be done to bring nonjudgmental science to bear on the refinement of those questions, I think, is a good thing. So, with my renewed understanding that the slide didn't say what I thought it said or it said what you didn't mean, I support the variance.

DR. KAUFMAN: Thank you. Dr. Basavaraju?

DR. BASAVARAJU: So, I think that -- I definitely see the advantages and benefits of PRT. I also see the benefits and advantages of nucleic acid testing. And I think the FDA's effort to try to identify whether there's subgroups within the MSM population that may be at lower risk is a good one. I

think, in the absence of figuring that out, I would not support -- just -- no donor deferral based on that.

DR. KAUFMAN: Thank you. Dr. Chitlur?

DR. CHITLUR: Okay. So, I agree with a lot of what has been said so far. I think PRT is definitely going to add to the safety of the product that is being infused. I definitely think this is new technology and needs to be followed. Research or just data collection should continue. But the questions should stay. I think they still need to ask, because I'm not convinced yet that we can afford to not ask the questions anymore.

If sexual orientation has been shown to be the highest risk factor for transmission of these blood retroviruses, then I don't know that not asking that question at this point of time is okay. I think, in view of the fact that all of us agree that patient safety comes first, I don't feel that not having a deferral policy is okay at this point.

DR. KAUFMAN: And just for clarity, all the questions that are currently asked will be asked.

Really, truly, the only difference -- the difference with respect to the questionnaire is that, whereas answering yes to the question, “Are you a man that’s had sex with a man?” would typically lead to a deferral, it would not under this variance, given that the product would be a pathogen inactivated -- sorry, pathogen reduced apheresis platelet.

But thank you for your comments. Dr. Stramer?

DR. STRAMER: Yes. I think industry is supportive of the variance and broadening the use of pathogen inactivation. I think, as noted, Dr. AuBuchon and Bloodworks still have some challenges ahead in planning for the variance, if it’s granted; and pathogen inactivation towards anywhere above a 50 percent yield, whether they do splits or not.

DR. KAUFMAN: And finally, I support the variances described. I think that some of the -- there will be some logistical challenges to work out. I’m optimistic that that can be done. It will -- well, we’ll see what happens in terms of reaction from the community and from the hospitals. I think that the

reality is, I think the platelet products that we're talking about are incredibly safe and, likely, a little bit safer than a typical platelet that we would have on the shelf at my hospital today which are not pathogen reduced.

Anyway, I think it's a logical approach and I support it. Dr. Schreiber?

DR. SCHREIBER: I've been sitting here, as we all have, all day and I've been thinking about this MSM. We talked about the social issues. It is a very pointed, directed group of people that were -- you know, that are being identified. As I think about this, I would think -- there may be a better way to say this that is more socially acceptable, such as, people who practice high-risk sexual practices. It doesn't fit a nice three-letter MSM, but there's other risk factors involved. We talked about prostitution, females who have sex with men who have HIV. These are all people who are practicing high-risk sexual activity.

I think that's a less directed way and more

socially acceptable way to discuss it. And I would just ask the FDA to consider changing this MSM terminology, which, I think, is very pointed and really is kind of a social message focusing on one segment of society, when really, it doesn't have to be that one segment that's at risk here.

DR. KAUFMAN: I'm actually not sure of the origin of that term. I don't believe it's an FDA-coined expression. All right. So, anyway, I think I'd like to close the meeting then. I thought it was a really interesting discussion. I want to thank everybody for your input. It's really great to have a variety of different opinions. Anyway, I thank you all for your time and for your presentations.

DR. VERDUN: And I just wanted to, on behalf of the FDA, thank everyone for a very robust and extremely helpful discussion over these past two days. We're very appreciative of your time and thank you.

MEETING ADJOURNED