U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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U.S. PUBLIC HEALTH SERVICE

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ADVISORY COMMITTEE ON BLOOD SAFETY AND AVAILABILITY

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THIRTY-SEVENTH MEETING

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THURSDAY,
NOVEMBER 19, 2009

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The Advisory Committee convened at 8:30 a.m. in the Potomac and Rockville Rooms at The Universities at Shady Grove, located at 9630 Gudelsky Drive, Rockville, Maryland, Arthur W. Bracey, M.D., Chairman, presiding.

PUBLIC MEMBERS (VOTING) PRESENT:

ARTHUR W. BRACEY, M.D., Chairman
JOHN H. ARNOLD, M.D.
ANN MARIE BENZINGER
CHARLES E. HALEY, M.D., M.S.
PETER KOUIDES, M.D.
ILEANA LOPEZ-PLAZA, M.D.
GREGORY J. POMPER, M.D.
RAVINDRA SARODE, M.D.

REPRESENTATIVE (VOTING) MEMBERS PRESENT:

DARRELL J. TRIULZI, M.D.
American Association of Blood Banks

FREDERICK B. AXELROD, M.D.
America's Blood Centers

JULIE A. BIRKOFER
Plasma Protein Therapeutics Association

KLAUS NETHER
The Joint Commission

MICHAEL G. ISON, M.D., M.S.
United Network for Organ Sharing

LAURENCE CORASH, M.D.
Manufacturer

NON-VOTING EX OFFICIO MEMBERS PRESENT:

CAPT MATTHEW J. KUEHNERT, M.D., FACP
U.S. Public Health Service
Centers for Disease Control and Prevention

ALAN E. WILLIAMS, Ph.D.
(filling in for JAY S. EPSTEIN, M.D.)
Food and Drug Administration

CDR MONIQUE HOLLIS-PERRY, M.D.
Department of Defense

LCDR LAURA ST. MARTIN, M.D., M.P.H.
U.S. Public Health Service
Food and Drug Administration

JAMES BOWMAN, III, M.D., M.S.M., FACS
Health Resources and Services Administration

EXECUTIVE SECRETARY:

JERRY A. HOLMBERG, Ph.D.

TABLE OF CONTENTS

Page

Call to Order
Arthur W. Bracey, M.D. 5

Roll Call/Conflict of Interest
Jerry A. Holmberg, Ph.D. 6

Assistant Secretary for Health's Charge to the Committee
Jerry A. Holmberg, Ph.D. 24

HISTORICAL OVERVIEW OF TRANSPLANTATION SAFETY: "The Evolution of Organ and Tissue Regulations, Oversight and Standards"

Evolution of Organ Oversight and Role of the OPTN HRSA Role
Walter Graham, Executive Director, UNOS..... 30

HRSA Oversight and Organ Transplantation Related Serious Adverse Events
Elizabeth Ortiz-Rios Division of Transplantation HRSA. 61

FDA Role in Tissue Safety and Update on Adverse Events
Ellen Lazarus, M.D. Office of Cellular Tissue, and Gene Therapies CBER, FDA..... 90

The Joint Commission
Kelly Fugate, N.D., R.N. The Joint Commission..... 132

American Association of Tissue Banks
Scott Brubaker, Chief Policy Officer, AATB..... 154

TABLE OF CONTENTS (Continued)

Page

Eye Bank Association of America
Mr. David Korroch, Executive Director Lions Medical Eye Bank & Research Center of Eastern Virginia..... 183

U.S. BIOVIGALENCE: EFFORTS TO BRIDGE A CRITICAL GAP IN PATIENT SAFETY AND DONOR HEALTH. A work product of the Public Health Service (PHS) Biovigilance Task Group in Response to Recommendations of the ACBSA

Public Health Service (PHS) Biovigilance Task Group
Matthew Kuehnert, M.D..... 200

Human Cell, Tissue, and Cellular and Tissue-Based Product (HCT/P) White Paper Discussion
Laura St. Martin, M.D.
Office of Cellular Tissue, and Gene Therapies
CBER, FDA..... 210

Organ White Paper Discussion
James Bowman, M.D.
Division of Transplantation HRSA.. 265

Open Public Comment
AABB 296
Red Cross Working Committee for Blood Safety..... 302

Committee Discussion on "White Paper". 313

Meeting Adjournment..... 392

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

(8:37 a.m.)

CHAIR BRACEY: Good morning. I had expected that actually perhaps the last meeting would have been my last but I am very happy to be back for an extended duty, tour of duty I should say.

As you know in previous meetings we have dedicated a fair amount of time towards the discussion of biovigilance. And in this meeting, we will continue to have a focus and a discussion on this important endeavor.

There was a White Paper that was circulated, distributed to committee members in advance of the meeting and we will be hearing presentations from several department members who have contributed to this work. I really look forward to continued discussion of this, along with issues specifically related to also a broader topic, transplantation safety so that we, in essence, encompass all of the safety considerations that we have been

charged with.

So with that, why don't we go ahead with the roll call?

DR. HOLMBERG: Very good. You will notice that the AV person turned all the microphones on. So, if you will turn your microphones off, I think that that will help take away some of the extra noise in the room. But please when you use the microphone or when you are speaking, please push the button down for the green light.

Let me first say welcome. And as somebody has already mentioned, we are starting to grow to like this place as a meeting hall. I know that there is some inconvenience as far as distance from the airport and also using the shuttle bus but economically it is very much of a cost savings for us to be here and the availability of these spaces are quite nice.

As you know, we have gone through a lot of changes at Health and Human Services.

And after the roll call, I will be commenting on some of those changes. But one of the things that we were not able to do and that was to be able to get an appointee for the chair position and also another position on the committee here. And so what we have done, according to our charter , was to ask Dr. Bracey if he would come back for one more time. I guess that means, though, I will have to give you another plaque.

CHAIR BRACEY: A little one.

DR. HOLMBERG: A little one.

I have to just recognize Dr. Bracey. In fact when I was talking to people within the Department I said, you know, he has been fantastic to work with and he has just really taken the committee to new levels. He has helped keep the conversations, the discussions going, has had great input into the agenda. I want to thank you personally for all that you have done for us and it has not gone unnoticed within the Department. We have

really appreciated that.

Before we get too far, let me go through first of all and do a roll call. Dr. Bracey?

CHAIR BRACEY: Present.

DR. HOLMBERG: Dr. Arnold.

DR. ARNOLD: Present

DR. HOLMBERG: Ann Marie Benzinger. And Ann Marie, would you please tell us where you have been for the last committee meeting? Because Ann Marie is always to every committee meeting but she had an important distraction this last time.

MS. BENZINGER: Last timed I got called for my transplant. So I was in a coma for the meeting and I failed to tell my family to contact Jerry. But I think Dave Cavanaugh may have told you, anyway to get the word out. But I got a real taste of not only transplantation again because this was my second transplant, but in blood transfusions. I ended up with over 50 units of blood and

blood products. So I got the first-hand experience going with it.

DR. HOLMBERG: Very good. Well, you are looking great and you are definitely a patient advocate that we can count on for comments.

Anne Marie Finley will not be with us today.

Dr. Haley?

DR. HALEY: Here -- present.

DR. HOLMBERG: Dr. James will not be able to be with us.

Dr. Kouides?

DR. KOUIDES: Present.

DR. HOLMBERG: Dr. Lopez?

DR. LOPEZ-PLAZA: Present.

DR. HOLMBERG: Dr. Pierce will not be able to be with us today.

Dr. Pomper?

DR. POMPER: Present.

DR. HOLMBERG: Dr. Sarode?

DR. SARODE: Present.

DR. HOLMBERG: Dr. Shander will not be able to be with us today.

Ms. Wade will not be able to be with us today.

Dr. Yomtovian informed me late yesterday afternoon she will not be able to be with us today.

CHAIR BRACEY: Do we have a quorum?

DR. HOLMBERG: I will do a count in just a minute. Okay?

Dr. Triulzi?

DR. TRIULZI: Here.

DR. HOLMBERG: Dr. Axelrod?

DR. AXELROD: Here.

DR. HOLMBERG: Julie Birkofer?

MS. BIRKOFER: Present.

DR. HOLMBERG: Klaus Nether?

MR. NETHER: Present.

DR. HOLMBERG: Dr. Ison?

DR. ISON: Present.

DR. HOLMBERG: Dr. Corash?

DR. CORASH: Present.

DR. HOLMBERG: Dr. Kuehnert?

DR. KUEHNERT: Present.

DR. HOLMBERG: Dr. Epstein is not able to be with us today but we do have sitting in for him is. Alan Williams.

Dr. Harvey Klein will not be able to be with us today either.

Commander Hollis-Perry?

CDR HOLLIS-PERRY: Present.

DR. HOLMBERG: CMS, our new representative is Dr. Sheila Roman could not be with us today. She sends her regrets. She has been assigned to us for the last maybe six months and had other responsibilities put on her the last minute and she will not be able to join us.

Dr. St. Martin?

DR. ST. MARTIN: Here.

DR. HOLMBERG: Dr. Bowman?

DR. BOWMAN: Here.

DR. HOLMBERG: Okay. Mr. Chairman, we have 13 voting members, which is a quorum.

CHAIR BRACEY: Okay, thank you. Let's proceed then with the discussions for this morning.

Okay, we will have a reading of the conflict of interest statement.

DR. HOLMBERG: The Department of Health and Human Services is convening the November 19th and 20th 2009 meeting of the Advisory Committee of Blood Safety and Availability under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of industry representation, all participants of the Committee are special government employees or regular federal employees. Let me just clarify that point. Dr. Yomtovian is employed by the VA System and under our Charter, is a regular government employee versus the ad hoc government employees that are represented by FDA, HRSA, CMS, and NIH.

Federal employees of various operating divisions of the Department, are

subject to the federal conflict of interest laws and regulations. The federal employees are non-voting members of the committee.

The Secretary is responsible under Section 301, 351, 361 of the Public Health Service Act as amended and various provisions under the Food and Drug Administration, Food and Drug Cosmetic Act for issuing and enforcing regulations concerning the collection, preparation, and distribution of blood and blood products, human tissues, and human organs, for issuing and enforcing regulations related to the transmission of communicable diseases and for carrying out research and health fields, including diseases involving these products.

The Advisory Committee on Blood Safety and Availability shall advise, assist, and consult with and make policy recommendations to the Secretary and the Assistant Secretary for Health, regarding these broad responsibilities.

The Department has determined that all members of the Advisory Committee are in compliance with the Federal Ethics and Conflict of Interest laws. We would like to remind members and participants, including those that speak during the public forum that if there is a personal or financial interest in a topic being discussed, the conflict of interest should be disclosed.

I am also going to take a few minutes to sit in for Dr. Koh. On the original agenda, Dr. Koh was to be with us this morning. Unfortunately, he has been called to the White House and he will not be with us today or tomorrow. Tomorrow actually he is having the ceremony of his appointment as Assistant Secretary for Health. He has already been confirmed. He has already taken the oath but the ceremony is actually tomorrow. And Dr. Koh is a Korean American. And as he said yesterday, there will literally be people from around the world coming to this

ceremony tomorrow. And I sent my regrets that our office could not be participating in that ceremony.

I did want to go through a little bit about Dr. Koh. At one point I hope that Dr. Koh will be able to join us at the next meeting but Dr. Koh is the fourteenth Assistant Secretary for Health. And by the way during the ceremony tomorrow, there will also be an opportunity for all former Assistant Secretaries, including Dr. Lee and some of the others, including the Surgeon Generals will also be meeting, former Surgeon Generals.

Dr. Koh is a Harvey Fineberg Professor of the Practice of Public Health at the Harvard School of Public Health and he also was the Commission of Public Health in the Commonwealth of Massachusetts from 1997 to 2003.

Dr. Koh has, in the last four or five months, been able to really take a lot of

our concerns and move some of them forward. And he does have a strong background in hematology and dermatology, as well as public health. And so we look forward to the future years of working with Dr. Koh.

Some of the other changes that have taken place over the last couple of weeks has been that Dr. Regina Benjamin has just been confirmed as the Surgeon General and she will be joining the staff very soon.

There has also been some changes within the Office of Public Health which the Blood Safety and Availability Office sits in and that is that Dr. Wanda Jones, who has a long history within the federal government is the Principal Deputy Assistant Secretary for Health.

Dr. Jones has worked in areas such as CDC, HIV, and also women's health.

Dr. Don Wright was the Principal Deputy Assistant Secretary and he has addressed this Committee many times. He is

now taking over a new office within OPHS to coordinate the Department's efforts on healthcare quality. And this is in regards to the healthcare associated infections. And so there is quite an emphasis on that.

I also wanted to give just a little highlight of some of the things to crystallize some of the thoughts in today's discussion as far as the White Paper and biovigilance. Really when we start looking at biovigilance we look at biovigilance, at least I do, in a Venn diagram as far as my office and some of the responsibilities that we have and where the federal agencies really overlap each other.

And so for policy, there is an aspect of biovigilance that affects the policies that will be made and you can see that within the Assistant Secretary for Health, OPHS is the office and the department and we are coordinating with staff divisions and also operating divisions.

But we also have the regulatory aspect, once a policy is made and also oversight. And you are going to hear a little bit today about not only the regulation part of enforcing policy but also the oversight, such as HRSA has in organs.

And then we also have the research aspect, healthcare research and quality. And they are also taking a very prominent lead in that new office of healthcare quality, NIH, FDA, and CDC, and their research aspects. And then also surveillance, which CDC has the bulk of surveillance responsibilities but also when we start talking about phase four and post-marketing surveillance, FDA has a responsibility there.

And so when we look at the various agencies that are within the department, you can see their logos down below. And where the Venn really intersects is really where we need to be coordinating a lot of activities so that there is great interoperability and

coordination of biovigilance.

When I look at the biovigilance, I look at the structure of collaboration and interoperability. I am sorry that the slide sort of changed on me. I don't know if that is a result of going from Microsoft 2003 to the most recent version, but as you can see, the basis of what we do is really the interoperability, that is our foundation, and surveillance and sentinel detection and traceability are really supporting the collaboration that must ultimately happen in a biovigilance type of program.

So when we look at the key features of a biovigilance program and the capabilities we need, surveillance sentinel identification traceability, but most importantly, we need the interoperability. And then at least within the federal government and also within the private sector, we need to be able to interact and have collaboration on the findings that are presented and also analysis

of the findings.

All of you have seen this document come to you both electronically and by mail. You should have a hard copy in your presence. This was actually a labor that took three years to complete. Dr. Kuehnert will be talking more about this later and it came out of a recommendation of the Advisory Committee on Blood Safety and Availability for PHS to look within the government and to look at some of the gaps and what we are currently doing.

So Dr. Koh signed this out on October 4th. Many of you have -- well you all have a copy of this. It has, because it is in your presence, it is really a public document at this point in time and we have refrained from posting it on the website until we could have discussion at this meeting.

As we will go through and Dr. Kuehnert will spend more time on this, we did identify the gaps in blood tissue and organs and there will be discussions today on the

White Paper.

The other activities that have taken place over the last couple of months of Dr. Koh's administration is that Dr. Koh did formalize a pathogen reduction technology task force within the federal government. And this came out on October 26th requesting the Department Task Force to explore your recommendations and possible paths forward.

And also we have reorganized the internal Blood Safety Committee within the federal government so that it is a senior executive council and it now has a charter.

Also, later in this meeting we will go over some of the H1N1 guidances and we were very pleased that the efforts between FDA and CDC were coordinated in such that both of these documents for blood and plasma centers came out at the same time and are referenced in each other's documents. The FDA, Alan will be addressing that as draft guidance on H1N1.

And then also I just want to, I

really had this labeled as emerging infectious diseases and I want to speak to one emerging infectious disease specifically but for recognition of the Arbovirus Workshop, I want all of you to be aware of the December 14th and 15th workshop that will be taking place and this will be a two day workshop and some of you in the room are participants in that discussion.

I also want to just let you know as a committee and it is very important as we talk about biovigilance and as we talk about organ and tissue safety, that we have become aware in the last month of another emerging infectious disease. It is emerging in the sense that we are finding more about this virus and the virus you actually do have papers in your handout is called XMRV and this is xenotropic murine leukemia related virus. This was identified a few years ago to be associated with individuals with prostate cancer. And on October 8th there was a report

in Science that the virus was also detected in individuals that had chronic fatigue syndrome.

So I don't want to spend a lot of time. I just want you to be aware of this. That within the Department I have presented at the Chronic Fatigue Syndrome advisory committee to explain a little bit about what we are doing to monitor this and also to investigate some of the findings. And the Department is taking this very seriously and looking at, first of all, standardizing the tests that the researchers have used to detect this virus and then also potentially we will be looking at our recipients and donor repositories to investigate not only the prevalence but also if this virus can be transmitted by blood products.

So I just wanted to throw that article in your pile of information so that you have this and you will be aware of this. But at the present time, we will not be taking discussion on that. In fact, it is very

premature in collection of the data but I wanted to make sure that you were all aware of that.

If you will turn to the question sheet, this is very similar to the question that was presented at the April and May Committee meeting. And I realize that many times we talk about blood issues and strictly it seems like our focus tends to be blood safety but the charge that we have is to also discuss transfusion and transplantation safety.

And so I will go through this. The questions have changed just a little bit. At the April/May meeting we discussed primarily how policy is generated for blood safety and there was a lot of discussion, a lot of great recommendations that came out of that. We, within the Department have refrained from responding back to the committee on your letter, Dr. Bracey, primarily because what we wanted to do was we wanted to wait until we

heard back from this committee meeting, so that we could handle both transfusion and transplantation safety at one time and give you a response back at that.

So let me read this for the record, as far as the question in the background.

The quality of the government decision making on safety policies of blood organ cells and tissues is a matter of great significance to the public health and to public confidence in the medical system. President Obama commented on transparency and the government's decision-making process on January 21, 2009. As he said, "Our commitment to openness means more than simply informing the American people about how decisions are made. It means recognizing that government does not have all the answers and that the public officials need to draw on what citizens know. And that is why as of today, I am directing members of my administration to find new ways of tapping the knowledge and

experience of ordinary Americans, scientists and civic leaders, educators and entrepreneurs because the way to solve the problems of our time is the way to solve the problems of our time as one nation is by involving the American people in shaping the policies that affect their lives."

Within the United States, blood organ cells and tissues are supplied by non-governmental organizations that operate under government oversight. In general terms, practices and policies related to safety of these human-derived resources, have been established under federal statute and through agency regulations. However, the authority and decision-making process vary from setting to setting and are not always comprehensive compared to current practice.

Additionally, there is not a straight-forward linkage between policy-making and funding of incremental safety measures. In this context, and at the time of transition

in leadership at HHS and the Public Health Service agencies, it is timely to ask whether the decision-making processes currently in place are meeting the challenges inherent in addressing new technology opportunities and new safety threats. In particular, the Committee is asked at this meeting to consider whether greater or more orderly use of formal tools of policy analysis such as risk assessment and cost-effectiveness, cost utility modeling would be of value to enhance the current decision-making process of new safety measures.

Implementation of a new safety strategy is often initiated in the face of scientific uncertainties, with limited information due to a crisis, without adequate evaluation of comprehensive effectiveness of new safety strategies against the value of intervention or alternate interventions, without considering the prioritization strategy and lacking a process to decide under

what circumstance a safety strategy should be continued, modified, or discontinued after implementation.

The question then arises whether these limitations can be mitigated through a more standardized policy-making process that incorporates use of formal assessment tools.

The goal of this meeting of the ACBSA is to ask the Committee to comment on the elements that would characterize a more robust and transparent decision-making process for organ and tissue transplantation safety policy. In particular, please comment on mechanisms to identify and address information gaps. For example, how might the federal government leverage the resources of its agencies, industry, and healthcare sector partners to gather data on infectious disease risk of organs and tissues. What approaches may be used to gauge and encourage willingness of industry and healthcare sector partners to participate in data collection and research

projects within the federal government?

Please comment on the types of tools of policy analysis that may be used to enhance the current decision-making process, such as risk assessment and cost-effectiveness, cost utility modeling and how they might be integrated into the current system.

What next steps, if any, does the committee recommend to enhance the quality and transparency of federal decision-making for organ and tissue transplantation safety policy? Thank you, Mr. Chairman.

CHAIR BRACEY: Thank you, Executive Secretary. With that, I think the charge is clear.

And at this point in time, I would like to introduce our first speaker today --

MS. BIRKOFER: Dr. Bracey, excuse me.

CHAIR BRACEY: Yes?

MS. BIRKOFER: To what Dr. Holmberg

just read, is the emphasis of this Committee going to be on cost effectiveness and not clinical effectiveness?

CHAIR BRACEY: No. I think cost effectiveness is just on element of the consideration but it is one of the elements. That is not the only element.

Let's then begin with the presentations. The first presentation is by Walter Graham. Walter Graham is the Executive Direction of UNOS, United Network of Organ Sharing, and he will present on the evolution of organ oversight and the role of the OPTN, as well as HRSA's role.

MR. GRAHAM: Thank you Mr. Chairman and I appreciate this opportunity to talk with you this morning about the general framework of oversight for the Organ Transplantation Network.

Can you hear me? Is the sound turned up?

I understand that the documents

that were given to you were a copy of a paper presented in the American Journal of Transplantation. By way of background, that presents in fairly detail of how you perceive oversight. What I would like to do is give you the general framework by which that occurs.

So again, we have got the legislative and regulatory background. The National Organ Transplant Act of 1984 governs everything that we do in organ transplantation. That Act in many ways is important for our purposes. It calls for the creation of the Organ Procurement and Transplantation Network, or OPTN, I will generally refer to it as that.

The law specifies that every clinic be a private non-profit entity and be operated by contract with HHS. In fact the first part of that section of the law says the Secretary shall by contract provide for the establishment and operation of the OPTN. And

so that is a unique relationship whereby legislators work with the private sector and then contract with HHS.

The National Organ Transplant Act also stipulated that oversight by the federal government would occur within the Public Health Service. It specified that the OPTN would have a national policy board that would establish membership criteria for the network and medical criteria for allocating organs. So that is a primary function of the OPTN.

It is stipulated also to be a national policy, a system would be a nationwide system and there is a nationwide organized system -- and it also created a modern organization system that is in operation now. You may know that there were 58 OPTNs throughout the country. Prior to the passage of this law, there was an index of 150 at one time. This was the standards by which OPTNs are to be certified.

Now in 1987, Congress passed an

1 additional law that made a -- much more
2 binding on transplant centers. In the Omnibus
3 Reconciliation Act, Congress added a section
4 to the Social Security Act that requires OPOs
5 and hospitals that perform transplants to
6 belong to and abide by the rules and
7 requirements of the Act. They must do this in
8 order to receive Medicare and Medicaid
9 funding.
10 So the effect of this particular
11 provision is that if a hospital that performs
12 organ transplantation does not abide by the
13 rules of the OPTN, it may not qualify to
14 receive any federal funds under the Medicare
15 or Medicaid programs whatsoever, not just for
16 transplantation. An enormous penalty can be
17 assessed to the transplant centers or --.
18 Well after that was published in
19 1989 the HCFA issued a notice in the Federal
20 Register saying that that provision of the law
21 would not be enforced by HCFA until HHS had
22 published regulations defining what that

means.

What does it mean to follow the rules and requirements of the OPTN? And that was particularly important because the law had established that the OPTN is a private non-profit facility. So there was the prospect of a private entity establishing rules and requirements that would cause someone to perhaps not be eligible for the federal Medicare program. And so HCFA, of course, did not allow that to occur and so they issued this notice.

In 1994, regulations were adopted and promulgated by HHS. It is known in the field as the Final Rule.

The scope of the national network is this. It includes all patients who need organ transplants. Organ has been defined in the Final Rule as liver, heart, lungs, pancreas and intestines. HRSA is now considering whether to add other organs to that list, such as faces or hands but that is

a decision that they haven't made.

OPTN covers this area. Not all the tissue transplant section or organ transplantation is in this area. However, it does involve all patients who are waiting for such transplants.

It involves all living and deceased organ donors, all deceased organ donors and candidate matches, so that any match between a donor and recipient is made by the OPTN. All those transplants are covered by this network. All OPOs and all transplant centers must belong to it, according to the Social Security Act. So you see this in a comprehensive scope of jurisdiction for the OPTN.

This slide shows you who the members of network are. There are only 250 hospitals in this country that do organ transplants. There are 58 OPOs, 58 histocompatibility laboratories, and then several other organizations, primarily the public and scientific organizations that do

organ donation and advance the science. But the top three institutional members are the primary members of the OPTN.

Now I mentioned that there was a Final Rule passed in 2000. And we operate the OPTN under the auspices of this Final Rule. So we have got almost everything that is not in organ transplantation. It applies not only to the network itself but also to all the network members.

The Final Rule contains a section on organization requirements for membership, it stipulates the corporate status of the OPTN being a private, non-profit entity. It describes who can sit on the Board of Directors. It has requirements about policies and how we are to develop the policies that govern the network, policies regarding how persons are listed on a waiting list, how organs are being procured, how matches between donors and recipients are to occur.

The Final Rule also lists policy

criteria as well as performance goals for those policies. There is a concept called designated programs. Within the 250 organ transplant hospitals, there may be multiple programs. So there may be a program for heart transplantation, one for kidney, and so forth. Each of those programs must meet criteria established by the OPTN under the Final Rule in order to be able to receive organs through the network. If they are not designated as such, they may not be able to receive organs through the transplant network.

There are unit evaluation requirements for the OPTN to review activities of the federal disciplines. There are requirements for enforcement by HHS of the requirements of the Final Rule and the requirements for records and record keeping among the participants of the networks and reporting requirements.

An important requirement there is that all transplant centers and investigators

are required to send data to the OPTN. If they fail to submit that data, then they may be in jeopardy of losing their Medicare certification.

And it calls for the creation of an Advisory Committee on Transplantation. The acronym for that we call it ACOT. ACOT has been meeting since a little after 2000 to provide advice to the Secretary about the field of organ transplantation.

In the Final Rule, to give you a little bit more detail about the requirements or stipulations there, the OPTN is responsible for developing policies, according to the Final Rule and it must do so in these areas. It must develop policies regarding the equitable allocation of deceased donor organs, donor testing to prevent the spread of infectious diseases, and you will hear more from some of our staff during these two days about how go about doing that.

Also to develop policies to reduce

socioeconomic inequities, requirements of transplant surgeons and physicians in the designated programs that do transplants, and any other policy that the Secretary may direct OPTN to adopt.

In the Final Rule itself there are very specific criteria that these rules must follow. There are specific performance codes and performance criteria to establish them.

So in the process of developing policy, the Board of Directors must seek public comment. They need to do that for every policy to be passed that has any sort of any major consequence to the community. We tend to do so in the same manner that the federal government seeks public comment.

Those policies are being made enforceable under the Social Security Act that I described in my second slide. The Secretary must approve those policies as federal regulations. And in doing so, the Secretary must publish those policies and refer them to

the ACOT. They refer them to others and then they regularly begin to change the policies that the Secretary feels are inconsistence with the National Transparency Act or taking any action that is necessary. And in the end, it is important to deal with the secretary. So you can see the risks, I hope.

The Final Rule establishes a very strong level of federal oversight of the OPTN. Even though the OPTN is a private entity, it is employed both by contract and by regulation through the Final Rule.

Now although they have organizations and relationships, this shows the important relationship for the OPTN. The green boxes down the middle show the direct reporting relationship. The Department of Health and Human Services and there is, over to the left, the Advisory Committee on Organ Transplantation. Under HHS, of course, is HRSA. Within HRSA is the Healthcare Systems Bureau and the actual addition of

transplantation, which outweighs several different aspects of transplantation, including the OPTN contract. We hold the contract that is for analysis of the scientific registry of organ transplant recipients that sold out all the research.

And then the C.W. Bill Young Cellular Transplantation Program, which is the bone marrow and cellular transplantation, has a second contract unrelated to what we are doing but I want to show that there as a division of transplantation.

So you see that here we are in the Public Health Service, not related to the ITB CMS or seen this as this set of policies and regulations regarding those hospitals that would qualify as Medicare programs to receive Medicare funding for transplantation. So that is the relationship that we have to the government agencies.

Then the OPTN itself, the National Hall of Records, includes 44 individuals.

Two of those are non-voting ex-officio members which is some within the Division of Transplantation. The other 42 are in the field of transplantation and they include transplant surgeons, transplant physicians, OPO representatives, various other healthcare experts, as well as organ transplantation recipients, organ donors, and family members from deceased donors. In fact that last group of public members, includes about one-third of donors. So it is a very interesting mix. We have a very big difference. Once again the policies. That is specified by the Final Rule.

Under that then we have the executive director, staff. There are 320 of us. We are located in West Virginia. And we have external operations, and internal operations, a large information technology department.

We divided the country of members into 12 regions. And actually let me just

talk about there is not 12, there is 11 regions, and those 11 regions have within them review boards of practicing transplant experts. So those review boards are available to review unusual cases. So that there is a policy that provides a scoring mechanism for how a person is to be ranked on the waiting list for organs where the condition is such that it doesn't exactly match the criteria, that this review board can have the authority to review the case and make recommendations for individual consideration.

We also have 21 national committees that comprise the representatives from the transplant community. Each of the regions has someone on each of the committees and we have representatives on those committees as well. They develop policy recommendations that ultimately go to the Board of Directors.

The relationship we have with the government, as I said before, it is a about contracts. So UNOS is charitable organization

incorporated in the state of Virginia and we hold a contract with HHS to operate the OPTN. We like to say that UNOS is acting as the OPTN. If someone else would hold the contract, that contract would step into the role acting as the OPTN. Other research then has contractors who analyze the data in the Scientific Registry and make recommendations to our committees and board without the scientific merits of the policy proposals.

The contract that we have is currently a two-year contract with five one-year renewals. UNOS has been the only contractor for the OPTN since its inception in 1986. Primarily, it is a mechanism to ensure that the contractor continues to do this work and that there is constant oversight and renewals by HRSA.

It is cautionary arrangements, currently average 8.6 percent of the federal appropriated funds that had historically been capped by law, it seems like a year. It is

now up to seven million a year in the law but the current amount of our contract is 2.5 million. The remainder comes from fees that we charge to the hospitals when they list patients on the waiting list. So a fee of about $600 charged to a hospital each time a patient is registered for a transplant. That makes up the most money that the OPTN receives.

Our annual budget for the network is 30 million dollars. The contract itself has several specific tasks and deliverables that is in the contract but this gives you an idea of the scope of the contract activity, whether it is we are required to have the board and committees that I showed you. We are required also to develop membership criteria and policies governing the network.

We monitor the compliance with those policies and take actions if someone wanted to bring someone into compliance if they have not complied with our policies.

There is actually a very elaborate compliance monitoring provision that is described in this part.

We maintain the national waiting list of all patients waiting for organ receipts and we execute every match for ever organ that is donated. We assist with the placement of those organs. We collect and provide data, extensive data on all transplant recipients, including the annual follow-up information for each recipient, going back to 1987. So, some very extensive data. There is a sense of security, as you can imagine. We really want someone in the system changing the way he lives or how to manage with life threatening consequences.

We have been tasked to work with HRSA collaboratively, that has done a fantastic job in increasing the supply of organs in this country. We also got tasked to communicate with group membership and the national and strategic goal setting.

This graphic shows on the areas of emphasis in the OPTN going back to 1986. I wanted to include this slide so that you could see how over time the OPTN mandate and early development has increased. Originally, the OPTN was established primarily for organ allocation purposes, because the network did not exist prior to that and there were many more patients needing transplants than there were organs available. So how do allocate organs among those patients. That has been our primary job and still is today.

Increasing supply has been a primary function and continues. Establishing standards, and promulgation of standards. Going back to the very beginning of the network, those three have always been our primary functions.

In 1987 we began employing the data for the national registry. In 2000, following the passage of the Final Rule, as we became much more involved in compliance monitoring

and enforcement of our policies. Prior to that time, all the OPTN policies were stated as being voluntary. And so that our members could comply with them or not. Once the Final Rule was passed, there was a mechanism for enforcement in place and that allowed us to pair up where we have a fairly elaborate compliance mechanism.

We also have moved into the area of monitoring patient safety and we worry about that especially in the area of disease transmission.

And then most recently, three years ago, we were given the mandate to become involved in living donor transplantation. That was something new. The original contract did not include us getting involved in that area at all.

So that is the current body of work that we are working on and that concludes this presentation. Mr. Chairman, I would be happy to answer any questions.

CHAIR BRACEY: Well thank you for that very nice presentation. May I ask perhaps an initial question and that is, that as the organization acquires information on outcomes specifically, are data with respect to infectious diseases, are those data collected and is that reported in a direct manner to the government?

MR. GRAHAM: Yes. We do collect data and we do report to the government. We are relatively young in that area and actually Dr. Ison has been involved in helping us in that regard. We are just now beginning to make those data available more to the transplant community and to the public. But any data that we collect as a contractor is available to HHS and we make them available to the databases.

CHAIR BRACEY: Actually, I was just wondering in terms of, rather than available, is there an automatic transfer of the data?

MR. GRAHAM: Yes. As a matter of

fact, we transfer all the data we collect in our scientific registry to the scientific registry contractor that I have described, as well as to CMS. And so the data are widespread and available.

CHAIR BRACEY: Questions? Dr. Triulzi.

DR. TRIULZI: Thank you for the presentation. A question about the living related, which appears to have come in late in the process. Does that mean since it was not part of the original Final Rule that anything is voluntary as far as the testing, what is reported, adverse event reporting, how those organs are used? You know, we read about the tandem transplants that are done. Can you describe what actually applies to the living related donor setting?

MR. GRAHAM: Yes, I can. And generally in 2006, HRSA published a notice in the Federal Register that the Secretary directed the OPTN to adopt policies governing

living donor organ donors and the transplants and to have them have the same consequences as those for deceased donor organs. So that put it in the same realm.

And so members are required to follow those policies, once those policies have been adopted. We have adopted several standards for who can do living donor transplants, what transplant centers must comply with those. And then some policies in that area, we are currently in deep negotiation and discussion, not negotiation, discussion with HRSA about what further we need in that area to increase patient safety. So this is an evolving area but we do have authority as expressed in that Federal Register notice.

CHAIR BRACEY: Dr. Ison?

DR. ISON: So a couple of questions and this may be directed both to Walter and Jim Bowman.

So we heard about ACOT. Has ACOT

ever had a meeting that has been focused on organ safety and disease transmission?

And then the follow-up question is to maybe Jerry. I didn't see anywhere ACBSA on any of those slides, but how do our recommendations impact on this process?

MR. GRAHAM: I can't recall --

DR. CORASH: Dr. Ison that is a great question. Traditionally in the past, the charge to the Advisory Committee on Organ Transplantation from the Secretary has primarily focused on organ donation and increasing organ donation and increasing the safety of those donated organs as it relates to increasing organ donation.

The focus and the charge has never specifically been directed at what the topic is today of this deliberation. It isn't clear how that would in the future be expanded, given the current expansion of this committee's charge. And we certainly don't want too many cooks in the kitchen and so that

is actually under review right now at HRSA and the Department.

CHAIR BRACEY: Dr. Holmberg?

DR. HOLMBERG: Excuse me. Let me jump in and answer that question or complete the question that you had.

One of the reasons why the charter was changed, and you can see that the emphasis started around 2000 on safety issues, and that was primarily within the Department there was a void as far as safety. And we realized that many of the infectious diseases that are identified in blood are also identified in organs. And so what we have done is in 2006, the charter got changed to include the safety.

Now how do the recommendations interact back and forth? Personally, we do not have within the Office of Public Health and Science, we have no input into the recommendations coming out of the advisory committee on transplantation. Recommendations that come out of this Committee are

distributed within the agencies, including HRSA, and they are then discussed at the new charter Internal Safety Committee, which is the Blood, Organ, and Tissue Senior Executive Council. Now that is new but the plan is that all the recommendations will come into there so that the senior executives can make a decision on how do we handle those recommendations.

So there is a mechanism that, at least for this Committee, things would be circled back through not only FDA but also HRSA and NIH.

CHAIR BRACEY: Dr. Kuehnert?

DR. KUEHNERT: Thank you for the presentation. CDC clearly supports an emphasis on organ transplant safety. So we are glad to see that UNOS agrees with that.

What I wanted to ask in follow-up to some of the questions here about organ transplant safety is which entity at UNOS has primary responsibility for organ transplant

safety? And I understand that the Disease Transmission Advisory Committee handles the disease transmission aspect but oftentimes processes are found that may be flawed and represent a risk to safety that goes beyond disease transmission.

I am wondering if there is entity at UNOS that primarily has responsibility for that.

MR. GRAHAM: We have several things. One, I will say first off, I showed you the list of primary tasks in the contract. And patient safety itself is not specified in the contract, nor is it specified in the Final Rule, other than to say the Secretary would require us to go on site if there appears to be an imminent threat to patient health or public safety. And so that hasn't been a major part of our charter. However, we began leaning in that area, as I described in my slide in 2000.

A couple of things. One, we have

an Operations Committee that they actually came to be after the very unfortunate case at Duke several years ago when there was a blood typing problem that led to the death of a little girl. And we looked at the system then and wanted to increase the safety of the system. So we began making changes in our policies for that very specific purpose, something that the OPTN and HRSA began working together on to establish. So that committee looks at systematic ways that we might improve safety.

There is an OPO committee that also makes recommendations about OPO testing that would be done for that. Now the Disease Transmission Committee itself actually came out of that Operations Committee that I mentioned before. At one time was simply an advisory group to that committee it is now its own, it has its own status as a committee reporting to the Board of Directors.

So over time, there has been an

increasing emphasis on safety itself.

CHAIR BRACEY: Dr. Holmberg? Okay, Ms. Birkofer, then.

MS. BIRKOFER: Just a quick question, Mr. Graham. You said your operating budget was 30 million and of that 30 million, approximately what percentage goes to staffing, admin, and your computer security?

MR. GRAHAM: Probably about 80 percent. I mean it is almost all. It is a staff-heavy organization. That is primarily what we do is to provide staff. We pay for transportation for the volunteers to come to the committee meetings but they volunteer their time for that. The remainder are expenses we incur operating the staff.

CHAIR BRACEY: To stay on track, we are probably going to move ahead but Dr. Holmberg?

DR. HOLMBERG: Yes, I just wanted to ask another question. Actually maybe it will come out into two questions. But Mr.

Graham thank you for your presentation.

I made a note early in your discussion about the performance goals. And one of the big questions I had was safety. So it clarifies the question I had regarding safety not being part of the contract. That is something that really stood out to me.

The other thing that stood out to me was your comment on the Scientific Research Organization and some of its functions to provide you with data for your policies. If you are not collecting safety data, or are you? Are you collecting outcome data?

MR. GRAHAM: Yes.

DR. HOLMBERG: You are collecting outcome data.

MR. GRAHAM: Yes.

DR. HOLMBERG: How does this Scientific Research Group interact into your policy process?

MR. GRAHAM: Well each of the committees that developed the policies has a

representative from that contractor that meets with the committee. And the committee will request certain data and analyses from them. We also have staff who are Ph.D., biostatisticians who also attend the meeting and also can provide research to them.

The research being done by the SR contractor is primarily a multivariate analysis, where you get into some of the heavy statistics. We may be providing some univariate analysis for the committees. But there are multiple ways that they get data.

And also I want to emphasize when I said that data are available widely, anyone in the world can get a full data set from us, absent patient and center identifiers. And so we make the data available to a wide range of folks. So, the scientists themselves often will come to the meeting having done their own evaluation of our data.

DR. HOLMBERG: Okay but at the present time, the committee that you are

talking about is that ACOT or your board?

MR. GRAHAM: Our internal committees.

DR. HOLMBERG: Okay.

CHAIR BRACEY: Thank you very much. Let's move on then to the next presenter and that is Dr. Elizabeth Ortiz-Rios.

Dr. Ortiz-Rios is from the Division of Transplantation of HRSA and she will present HRSA oversight and organ transplantation-related serious adverse events. Thank you.

DR. ORTIZ-RIOS: Good morning. Thank you, Mr. Chairman. And it will seem in my talk it is going to be a little but redundant in many of the areas that Mr. Graham already covered. I will talk about HRSA oversight on organ transplantation related to adverse events but mostly in the process of collecting this information.

The Organ Procurement and Transplantation Network, Walter already

covered all of this area. So I just wanted to mention the primary goals of the OPTN is to increase effectiveness and efficiency in organ sharing and equity in the national system of organ allocation and to increase the supply of donated organs available for transplantation.

The Final Rule which was implemented by HHS in 2000 provided a regulatory framework for the operations of the OPTN and the objective is to make allocation policies more strongly based on objective and measurable medical criteria and it provided responsibilities. HRSA has the regulatory oversight, OPTN, as Mr. Graham described, as the responsibility of development of policies and data collection. This SRTR has the responsibility of doing a statistical analysis on the OPTN data and providing center-specific performance reports on the volume of transplants occurring at the transplant centers and providing outcome data on the one and three-year patient and graft survival

rate.

OPTN has a secure online database UNet for the collection, storage, analysis, and publication of all OPTN data related to waiting list, organ matching, and transplants. It is used by all transplant programs, OPOs and histocompatibility labs and it is a secure means of communication between OPTN members to disseminate information on policy changes, technology, updates, or training events.

Limitations of the OPTN database. There is no data collected about serious viral, bacterial, fungal, or parasitic infections other than if there is patient death or allograft, loss of the allograft. That information is collected and we could get what are the causes for the patient death or the loss of the graft but when viral or fungal or parasitic infections occur, that data is not collected. I will describe the DTAC Committee later that is providing, is helping in collecting this information.

The donor-related malignancy data are collected but are limited compared to recipient immunosuppressive malignancy data in the recipients.

I want to describe a little bit of the HRSA-CMS Memorandum of Understanding. Dr. Bowman will probably go into more detail during the meeting. This was signed in July 2008, to establish an interagency agreement outlining the criteria and procedures for sharing information regarding organ transplant programs and organ procurement organizations. It provides for interagency conference calls and data sharing on transplant centers and OPOs.

The process of their sharing between the two agencies is categorized into three general areas. Incidents that pose an immediate threat to the public and safety, or the MPSC actions related to a potential OPTN policy or bylaw violation, or CMS deficient Conditions of Participation deficiencies.

There is also an area of just routine information-sharing that increases the accuracy of information and coordination between the agencies.

Regarding the Condition of Participation for transplant Centers on data submission, clinical experience, and outcomes requirements, to renew the Medicare approval, the transplant program must submit required data to the OPTN within a specified time frame; the adult heart, liver, lung, intestine, and kidney transplant programs must perform an average of ten transplants per year; and the heart, liver, lung, and kidney transplant programs must have an acceptable patient and graft survival rate. And they have criteria to determine the acceptable survival rates.

The CMS will review the graft and patient survival outcomes at one and three years for all transplants performed at a center, including outcomes for living donor

transplants, if applicable. And except for lung transplants, CMS will review the adult and pediatric outcomes separately when a center requests Medicare approval to perform both adult and pediatric transplants.

HRSA's goals are to optimize organs available for transplantation, decrease death on the waitlist and protect the recipients.

The OPTN/UNOS Policy 4.0 focuses on reporting infectious disease transmission or other medical conditions that are thought to be donor-related.

In 2004, the UNOS Board of Directors approved the revised UNOS Policy 4.0, which created a list of diseases and medical conditions that must be communicated to the transplant center, if known to be present in the donor and establish requirements for reporting of cases, of potential transmission of diseases or medical conditions of donor origin detected by the transplant center or the OPO.

To describe quickly the responsibilities of each, when a transplant program is informed that an organ recipient at that program is confirmed positive for or has died from a transmissible disease or medical condition that could be of donor origin, the program must notify the OPO as soon as possible, not to exceed one working day and send all laboratories that they have available to the OPO.

The OPO, in turn, communicates the test results and diagnosis to any transplant center or tissue bank that received an organ or a tissue from that donor and manages the investigation, determines whether the donor was diagnosed with potentially transmissible disease, and notifies the OPTN as soon as possible. The OPO must also submit to OPTN a final written report within 45 days.

The OPTN, in turn, assists the procuring OPO in identifying all transplant programs and recipients who receive an organ

or a tissue from that donor, and monitor the notification process, request that any additional diagnostic tests be forwarded to the OPO and OPTN, and forward a copy of the OPO's final report to the recipient transplant centers and to HRSA.

To quickly describe the Disease Transmission Advisory Committee which Dr. Ison will probably go into much more detail later during the meeting, this was, as Mr. Graham described, it was an advisory group from the operations committee initially. Then in 2008, he became a committee. It was established to review each case report reported to the electronic Patient Safety System. And the electronic Patient Safety System was established because there have been some notable reports on donor-related transmissions like rabies, HIV, West Nile Virus, Chagas, during previous years.

HRSA and CDC are ex-officio members. And the committee reviews current

disease transmission reporting policies and recommends revisions to the OPTN. It also the goal of the DTAC is to review all of these cases that are reported to the Patient Safety System and try to assess the risk, to determine the risk of donor-related transmission.

To quickly describe the DTAC workflow, a report is made to UNOS. The UNOS personnel prepare a summary of the event, redacts the patient, OPO and Transplant Center identifiers and uploads these materials to a secure SharePoint Server and alert the DTAC members by e-mail of this case. The members review the data and respond within 24 to 48 hours and have questions or provide recommendations of what other laboratories should be performed. And this is an ongoing electronic discussion.

That is all I will say about DTAC. Dr. Ison will go into more detail.

Now I am just going to describe

what I have mentioned previously but do a summary of what are we doing to prevent donor disease transmission before donation, during the transplant, and after the transplant.

Before donation, there is a donor history taken, which includes whether the donor is high-risk, as described by the CDC 1994 MMWR guidelines, which are being revised. There is a donor history, which includes whether any elements of cancer transmissions or other factors that are not included in the MMWR guidance are present; a donor physical exam which includes whether track marks, very poor nutrition or hygiene or other risk factors are present in this donor; and laboratory tests recorded include serological tests for transmissible infections always and NAT tests in 60 to 80 percent of the time.

At donation or organ offers or during the transplant, the donor operation allows inspection of internal organs and questionable findings. Masses, lymph nodes

are sent for biopsy. And as the organs are being offered to the transplant centers, the risk factors must be communicated. If the donor was CDC high-risk, OPTN policy requires that all prospective recipients be informed of this. And CMS requires that informed consent for transplantations include donor-specific organ risk factors.

On transplants, if the donor team in preparing the organ findings an abnormality, this is evaluated and often with a biopsy.

After transplantation, complications in recipients are evaluated for the possibility of donor transmission. OPTN policy requires that it be notified of a possible transmission and reportable diseases require a state or CDC notification.

The OPTN Patient Safety Group promptly notifies programs with other recipients from these donors and asks for follow-up information on them to investigate

if a transmission has occurred. The OPTN Disease Transmission Advisory Committee investigates whether there has been a donor. That is where DTAC comes in, at donor transmission. And CDC obtains routine data through the OPTN SharePoint database for all transmission and evaluation of cases and has access to identified data as necessary for the investigation.

With regards to current issues, ongoing issues within HRSA, we are working on defining reporting expectations to OPOs, CDC, and state health authorities to strengthen DTAC interactions for initial determination of donor transmission and strengthen DTAC communications to other potential tissue and organ destinations and to clarify and expedite CDC involvement in the investigation as an event unfolds.

For the future to decrease event occurrence, HRSA will collaborate with CDC on studies to more effectively screen donors

without loss of organs to false positives and will support CDC in the development of updated guidance for screening of potential organ donors and collaborate with CDC on the development of a National Transplantation Sentinel Network. CDC has RFA already out there that Dr. Kuehnert will probably talk about on the development of a National Transplantation Sentinel Network.

Thank you.

CHAIR BRACEY: Thank you. Thank you. Questions from the Committee? Dr. Pomper?

DR. POMPER: Yes. Very interesting presentation. I was curious to ask is there a requirement for say, or is there support for, post-mortem examinations of the donors that goes, say, in a little more detail than just an inspection at the time of harvest?

DR. ORTIZ-RIOS: I am not quite sure how to respond to that but other than what they usually do. I don't think they go

into more details unless they have a finding that they have a biopsy or sent for a violation.

CHAIR BRACEY: I think Dr. Ison has a comment.

DR. ISON: So there is no requirement or mechanism to facilitate autopsies. And I will just say anecdotally sometimes it is a bit of a challenge, particularly if the autopsy is performed by the medical examiner, getting information back in real time that may be useful. We have had a number of disease transmissions in which an autopsy is performed by the medical examiners or even by the hospital pathologists. And because of the period of time that it takes for most autopsies to occur, there may be significant delay in transmitting that information back, in part because the autopsy report itself may take months.

CHAIR BRACEY: Dr. Triulzi?

DR. TRIULZI: Yes, one quick

question.

I saw that you noted 60 to 80 percent of the donors have nucleic acid testing done. And can you comment which tests and are those all done prior to organ distribution or are those tests retroactive, after the organs have been distributed?

DR. ORTIZ-RIOS: There was a survey last year, Dr. Ison might be able to speak more to this, where the OPOs were surveyed to see how many were using that testing and that is where that number but I don't have the specifics.

CHAIR BRACEY: Dr. Kuehnert?

DR. KUEHNERT: Well I could just add that the 1994 guidelines are silent on the issue of nucleic acid testing, as in 1994 that wasn't commonly available and that technology was not available. And that furthermore, the guidelines only apply for HIV, as they were written. Organ procurement organizations choose to expand the use of them beyond that

but they were only really meant for HIV.

And as far as I know, there are no policies in place to recommend that nucleic acid testing be used for organ donor screening but some organ procurement organizations voluntarily do that testing.

And Mike, I don't know if you have exact numbers on how often this is done.

DR. ISON: Yes, I just pulled up the slides. So I think it is careful that the phrasing needs to be, I think, very specific. So 77.6 percent of OPOs conduct any NAT testing and the majority of those, and let me just pull up the right slide, is actually only of high-risk donors and most of the time it is before transplantation. Although, at the time the survey was done, which was a year and a half or so ago, there were a number of OPOs that were doing it retrospectively. I think that most OPOs that are doing it though now are doing it prospectively.

There was also a NAT consensus

conference that was held about a year ago, a little less than a year ago. The summary of those reports are coming out, which will probably help standardize the approach. There is a lot of discussion within the transplant community because kind of that take-home message from this NAT consensus conference was to only recommend NAT testing in "high-risk" donors, those donors that were classified as excluded by the '94 guidelines from the Public Health Services.

And there is a lot of discussion about why not doing testing in all donors. And basically the kind of gist of it is that the number of organs lost through false positive testing, far exceeds the safety benefit in that population. Again, I personally didn't vote for that but that is what the consensus conference moved towards. I think that it is still a point of discussion and debate.

CHAIR BRACEY: A question with

respect to the extent of epidemiologic knowledge that goes into the policy making. What is the state of the epidemiology, the knowledge of the transmission of diseases, borrowed, infectious diseases among transplant recipients? How robustly has that been studied?

DR. ORTIZ-RIOS: We have some data. In 2007 there was a published article recently that the percentage was very low of those reported, which we are assuming that this under-reporting. Right now I don't have it but it is 0.8 or something like that.

DR. ISON: So I will be presenting that data tomorrow. I think that the only thing that I would say is this is only an estimate based on reported cases. There has never been a study done in the United States that has actually looked at this. And the number of patients that have had post-transplant testing for transmissible diseases is exceptionally low and so there may have

been transmissions that aren't recognized.

DR. ORTIZ-RIOS: And in the last couple of years, there have been many more reports, especially when a high profile case comes into the news. But this year I believe that we have had much more reports than the previous years. So people are reporting more and thinking about donor-related transmission more.

CHAIR BRACEY: Okay. We have a question from Ms. Birkofer.

MS. BIRKOFER: Thank you, Dr. Bracey. May I ask a follow-up question to Dr. Ison?

CHAIR BRACEY: Sure.

MS. BIRKOFER: Okay, thank you. If we are supposed to consider risk assessment, cost effectiveness, and cost utility, I would certainly think that NAT testing would mitigate risk. Can you give me a sense or give the Committee a sense of the cost of NAT testing for HIV and what would the cost be if

you expanded that to hepatitis B and C, for example, or other things?

DR. ISON: So there is a couple of things I think in some regards we are getting a little ahead of ourselves because there is going to be a number of presentations that are coming up. I know Debbie is going to present some information, I think, on the NAT yield project, which will give -- maybe not. Oh, sorry. She is not presenting that.

But there are issues related to yield. So the effectiveness side, I think honestly needs further study in this population. From a cost standpoint, the cost is highly variable and I will have to go through and get the actual numbers but a lot of it depends on when the testing is being done, where it is being done and what resources are needed to get the sample to the testing site, unlike blood and tissue where you can use standard methods to transport.

You could take a test that may cost

a couple of hundred dollars but then if you have to courier and rent an airplane to take a sample of blood from some distant site to the central lab, you may actually turn a relatively reasonable cost test into one that costs $20,000.

So that is, I think, one of the challenges. And if you look at the cost ranges, you know, they can be anywhere down in the neighborhood of about $400 to $500 for doing a stat test during routine business hours, when you would normally have your lab employed with the usual employees to a substantially higher amount, if you are having to call techs in at 3:00 a.m. and then you would have a lot of other costs that you would have to adjust into that, any false positive testing. Because you can appreciate that if you have someone that is bleary-eyed at 3:00 a.m. that isn't doing very many of these tests, the likelihood of having a false positive might be higher than if you are

having individuals do the testing during the day.

And if you look at the data, the best information on this comes from Emory. Something like 80 percent of the testing would be done between about midnight and 6:00 a.m. So really the majority of the testing, for organs at least, is being done in these kind of odd hours and many of the samples are having to be sent in from remote sites, particularly if you want to concentrate your NAT testing so that you reduce that false positive rate.

CHAIR BRACEY: Question from Dr. Williams and then Dr. Kuehnert will follow.

DR. WILLIAMS: Yes, thanks. I am trying to think about ways to improve infectious disease risk data capture. What percentage of organs come from donors who have self-identified as being organ donors, for instance, on their driver license, versus those where a family has made the difficult

decision and, I guess, maybe later if there is any breakdown between those two groups of donors in terms of infectious disease risk?

DR. ORTIZ-RIOS: I don't have that information right now but maybe we could get it but right now I can't provide you with that information, that breakdown.

DR. ISON: That is a good idea. We haven't actually specifically looked at that. It is something for us to think about.

CHAIR BRACEY: Dr. Kuehnert?

DR. KUEHNERT: Thanks, Dr. Ortiz-Rios for the presentation. I wanted to point out one bullet that you had that I thought was an important point of emphasis which talks about the limitations of the OPTN database and that there is no data collected about serious viral, bacterial, fungal, or parasitic infections, so that although the government has access to all the data that are collected, if the data aren't collected, then we don't have access to that data that are needed.

The other point I wanted to make is that in the 1994 guidelines, there is a recommendation that if a donor is identified as high risk, that there be testing of the recipient. And I think studies have been done showing that that is rarely done. So concerning what we know versus what more may be out there, I think that there is a lot of uncertainty about the number of infections that might be going undetected.

CHAIR BRACEY: Dr. Holmberg?

DR. HOLMBERG: Yes, I know we are running out of time but I think these questions are very good. And one of the questions that I have is when you talk about the DTAC and the members being notified, does that also include the ad hoc members from HRSA and CDC?

DR. ORTIZ-RIOS: Yes.

DR. HOLMBERG: Are they notified within 24 to 48 hours?

DR. ORTIZ-RIOS: Yes, this is

everyone receives the e-mail at the same times and the ongoing discussion. We all have access the discussion by e-mail and to the SharePoint drive where the data is uploaded. We could go and look at it and have comments back and forth. Yes.

DR. HOLMBERG: Okay. And then my next question really could probably be broken down into two different questions. But I guess the impression I am getting is that there appears to be a lack within the federal government to do research on organ or organ improvement safety aspects and also test development. I think that we have heard in the past couple of months about the HTLV-I and II issue and I know that that is probably going to be discussed later. But I think that what I am hearing is that research and test development is something that is also lacking, as well as what Dr. Kuehnert mentioned about follow-up on a requirement that people, organizations just aren't doing the follow-up.

CHAIR BRACEY: Okay. Two last questions. Mr. Nether?

MR. NETHER: Yes, thank you very much for the presentation. I just had a question with regards to the data that is collected. You mentioned that in terms of death and loss of allograft that is collected and with that, there is a drill-down with root causes. In terms of the analysis, do you look in terms of patterns and trends? And then how is that information disseminated both to the transplant centers and to the OPOs? And then how does that feed into, in terms of creating solutions for improvement?

DR. ORTIZ-RIOS: Well the SRTR provides outcome data related to patient and graft survivals, one year and three year outcome data, for the centers and this is provided to the centers. Leukemia, last year I presented some patient and graft survival data but focusing on the adverse event of death and I was able to look at causes for

these deaths. But they have, I believe I talked to the OPTN its decision and they collect three causes of death. So sometimes they might just report other and you will have to do a more specific analysis to actually find out what is the cause of death per se. But that information is collected. It needs a little bit more detail but it will only be patient death and allograft, loss of the allograft.

CHAIR BRACEY: Dr. Lopez.

DR. LOPEZ-PLAZA: Yes. I have a question. Is like there is some decisions that would come, you know, for a date we can screen for them? There is other decisions that actually we don't know that they are going to happen.

So the question I have right now is how stringent are the requirements to report any suspected infection post-transplant back to UNOS, like a bacterial infection, a fungal infection. What are the rules that we have in

place that the surgeon will be kind of obliged to report back? Do we have anything like that right now?

DR. ORTIZ-RIOS: I think Dr. Ison could respond more to that. But we do initially people were reporting everything, even the expected and the unexpected.

DR. ISON: So the policy as written requires people to report if they recognize or suspect a disease transmission. The real challenge is, many times, is it is not suspected and there aren't any real time. And I think Matt will get into this when he talks about the biovigilance. There is real challenges, having participated in one of the LCMV transmission cases. We had a patient literally dying before our eyes and we had no idea that the exact same thing was happening with the other recipients until someone called after one of the recipients had died.

So really, there is no system in place in the United States to recognize

concurrent presentation of similar diseases. And unfortunately with organs, oftentimes they are either at different hospitals, which was the case in the LCMV and many of the cases, or even if they are at the same hospital, they may be cared for by different teams. If it is a heart and a kidney, they are totally different surgical teams and medicine teams that are caring for those patients. And so the only people that cross that sometimes are the infectious disease experts.

Additionally, I think even with the infectious disease community, our center, and many larger centers are very lucky to have transplant ID experts that are tuned in on this. The reality is is not all transplant centers have that luxury.

CHAIR BRACEY: Good discussion and great comments. I think we need to take a break now to be fair to the Committee members and the public. Thank you. We will reconvene in 15 minutes.

(Whereupon, the foregoing meeting went off the record at 10:09 a.m. and resumed at 10:25 a.m.)

CHAIR BRACEY: We are ready to resume. And again, it has been great discussion and great presentation.

Our next presentation will be on the role of the FDA and tissue safety and an update on adverse events. And that will be Dr. Ellen Lazarus, who is from the Office of Cellular Tissue and Gene Therapies in CBER and the FDA.

DR. LAZARUS: Thank you very much, Dr. Bracey. I am very pleased to be able to be here and give a very brief overview of the way that FDA regulates transplanted tissues and also give you some data that will, I think, help describe the type of information we get about adverse reactions associated with tissue transplant. And I hope that this information will help you later answer the questions that are posed to you about how the

federal agencies can better identify and understand the gaps in our understanding of tissue and organ transplantation risk.

So I am just going to very briefly give you an overview of the history of the tissue regulations and explain what the products are that we call tissues that we are regulating, since not everybody uses those terms the same way, and then I will give you a very brief summary of the regulations themselves.

So many of you are familiar with the history of our current regulatory approach. And as you know, there has been a very long history predating the institution of a regulatory approach of medical use of the so-called conventional tissues like the placement type products and reproductive products. And then over time there were developed innovative methods of manipulating and using the tissues and the Agency recognized that a one-size-fits-all general

approach to tissues probably wasn't sufficient and there was a need to more clearly define criteria for characterizing these different types of products and to try to tailor the regulation a little bit more closely to the nature of those products and their associated risks.

I took a quick look at Scott Brubaker's slides from AATB and he will give you a nice summary of some of the known infectious disease transmissions, all of which, up until the time our tissue rules came into effect, definitely influenced the way we addressed, or the way we applied the regulatory approach to tissues.

And Scott will also give you a little more information than I am going to go into here. The bottom line is this is a rapidly growing industry. We have a registration database which I will explain a little bit later in which over 3,000 establishments are registered and this ranges

from the recovery establishments, the processors, the distributors, and also the testing laboratories and sterilization facilities. There are many, many tissue transplants occurring. And the interesting aspect of transplant for me as a blood banker is the way that so many tissues are obtained for each donor so the considerations for donor risk have to involve our understanding of the widespread distribution of those products.

And also it is important, I think for you all to keep in mind, and many of you know this, that under our regulatory approach, we also consider cell therapy products and there have been over 4,000 unrelated donor progenerative cell transplants facilitated by the NMDP registry last year. So that number is sizeable and some of the risk considerations are very, very different for that living donor population than they are for the conventional tissues.

So very briefly, the interim final

rule on human tissues intended for transplantation was published in 1993 and finalized in 1997. And that was like the first tissue rule and it covered a relatively limited scope of conventional tissues and infectious diseases, namely HIV, HBV, HCV. And the statutory authority on which those regulations were based was Section 361 of the Public Health Service Act, which focuses on prevention of introduction transmission and spread of communicable diseases.

So in 1997, the government published a proposed approach to regulation of human cells and tissues, which again was meant to address the greater complexity of the cells and tissues that were being transplanted at the time. And it was meant to be tiered risk-based approach, where like products would be treated alike from a regulatory standpoint and it had three main goals, one being to prevent the transmission of communicable diseases; another being to prevent

contamination of the tissues during the processing, which is kind of a different issue than donor transmissibility; and then thirdly to ensure that tissues that are highly manipulated, very complex for non-native purposes undergo additional evaluation.

So that approach was implemented by publication of the three tissue rules that composed the 21 Code of Federal Regulations Part 1271, and I will run through them very briefly. These rules became effective May 25, 2005. So any tissues collected, manufactured before that time are considered under the previous 21 CFR Part 1270 regulations.

So the tissue rules are the establishment registration listing rule, which that part of the regulation describes the applicability of the rules. It explains the type of products and the uses of those products that are covered by the tissue regulations and that subpart also gives the actual requirements for the manufacturers to

register and list their products.

The second rule is a donor eligibility rule, which outlines requirements for donor screening and testing for what we call the relevant communicable disease agents and diseases. And I will explain to you what we have addressed, identified communicable diseases as relevant. And then finally the current good tissue practice rule which requires that the manufacturing be performed in such a way to ensure that the tissues do not contain communicable disease agents and also includes reporting and inspectional provisions.

So these three rules form the platform for regulation of all human cells, tissues, and cellular and tissue-based products as we define them. And I will give you that definition.

And what I wanted to convey, which I think is an important point, is that for some of these human cells and tissues, the so-

called 361 HCT/Ps, these tissue rules comprise the sole regulatory requirements. But for others, namely those as I mentioned earlier that are very complex, they are highly manipulated, therefore used in ways that we would consider non-homologous or non-native, they would be subject to additional regulatory requirements, including good manufacturing practices for devices, the quality system regulations, and would require pre-market approval. So the pre-market approval is not required for all HCT/Ps.

In addition to publication of those three rules that are codified in the code of federal regulations, we published a number of guidance documents. This is just a list of three that are very significant, contain a lot of information about safety and safety-related provisions, including the donor-eligibility determination final guidance, a Small Entity Compliance Guide published in August 2007 which we hope we promulgated to help the

smaller establishments understand how the regulations apply to them and it gives some interesting and useful information. I recommend taking a look at it about the number of registration issues, about the way we regard tissue establishments outside the U.S., importing products into the U.S.

And then also there is a draft guidance for industry that was published in January of this year on current good tissue practices.

Okay, so what is an HCT/P? We define them as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient. And examples include musculoskeletal tissues, skin, and ocular tissue which were the sort of conventional tissues that were covered under the previous, the interim rule but also human heart valves, dura mater, reproductive tissues, and cells such as hematopoietic

stem/progenitor cells, and other cell therapy products, and HCT/Ps also include some combination therapies, such as combinations of tissues and devices.

As you have heard earlier, of course, the vascularized human organs fall under HRSA purview and we do not include them under the regulatory approach to HCT/Ps. Also, some bone marrow does not fall under the FDA regulatory purview for HCT/Ps. Xenografts, blood and blood products, secreted or extracted products such as human milk and collagen, ancillary products used in manufacture, in vitro diagnostic products and blood vessels recovered with organs all are not considered HCT/Ps.

So also as you heard earlier, there is some overlap or shared federal responsibility for oversight of some of these tissue transplantation activities, especially here where you heard earlier, HRSA oversees the C. W. Bill Young Cell Transplantation

Program, which would include the unrelated donor, hematopoietic progenitor cell registry and also the national cord blood inventory. And FDA regulates unrelated donor HPCs from peripheral blood and also unrelated and related donor cord blood and cord blood for autologous use. So there is a little bit of overlap in a lot of areas where the federal oversight falls into one administration or the other.

So this is a slide that explains in a little more detail the point I made earlier that some HCT/Ps are regulated solely under Section 361 of the Public Health Service Act but others are also regulated under Section 351 as biologic drug products or possibly devices. And those so-called 351 HCT/Ps require pre-market review and approval.

The 361 HCT/Ps all have to meet four criteria that are described in subpart A of the 1271 regulations, specifically 1271(10) and those criteria are listed here. Those are

products that are minimally manipulated that are for homologous or native use. They are not combined with another article, with some exceptions. And either they don't have a systemic effect or don't depend on the metabolic activity of living cells or if they do, they are for autologous use or use in first or second degree blood relatives.

So if a particular tissue meets all of those criteria, then it is regulated solely under 361 of the Public Health Service Health. Distribution of those tissues begin prior to inspection and compliance of those manufacturers with the regulations is determined at the FDA inspections.

So just a quick overview of the three rules, some of the major points. Any establishment that manufactures HCT/Ps, as we define them, must register with the FDA and submit a list of every HCT/P manufacturer.

So what do we mean by manufacturer? Here we mean any or all steps in the

recovery, processing, storage, labeling, or distribution of any human cell or tissue product and also screening or testing of the HCT/P donor. Those are all considered manufacturing.

I just want to point out this is discussed in the Small Entity Compliance Guide that I mentioned but all foreign establishments importing HCT/Ps to the U.S. must register and list their products.

So the donor eligibility rule, very briefly says that a donor eligibility determination based on donor screening and testing for relevant communicable disease agents and diseases is required for all donors of HCT/Ps with some exceptions, which I will review in a minute. The donor is considered eligible if donor screening indicates that the donor is free from risk factors for and clinical evidence of relevant communicable diseases and also if the donor testing is negative or non-reactive.

The regulation specifies that the HCT/P must not be administered until the donor has been determined to be eligible. However, there are some exceptions here as well to address issues of urgent medical need.

So what is a relevant communicable disease agent or disease? We consider two groups, those that are specifically listed in the published regulation and those that meet certain criteria that are described in the regulation and may be added later through guidance. So those that we list in the regulation are for all HCT/Ps, HIV-1 and 2, hepatitis B, hepatitis C, human transmissible spongiform encephalopathies, including CJD, VCJD, and syphilis.

For the viable leukocyte-rich cells, then HTLV-I and II is also considered a relevant communicable disease agent. And for reproductive cells and tissues, in addition to the entities listed above, chlamydia and Neisseria gonorrhea are considered relevant

communicable disease agents or diseases for which donors have to be screened and tested.

So, how do we determine what emerging infectious disease or other recognized infectious disease, how do we determine that it is relevant? As we have listed in the regulation, there has to be a risk of transmission by the HCT/P and sufficient incidence or prevalence or risk of infection among potential donors. Also there needs to be a significant health risk to the recipient and there need to be appropriate screening measures or screening tests available. And diseases that meet these criteria can be added to our list of relevant communicable disease agents or diseases for which every HCT/P donor has to be screened and tested.

So, in accordance with this process, we listed in the donor eligibility guidance, three additional communicable disease agents or diseases, namely, West Nile

Virus, sepsis and vaccinia.

So I mentioned earlier that there are some exceptions to the requirements for donor eligibility determination. This determination is not required for cells and tissues for autologous use and it is not required for donors of reproductive cells or tissues from sexually intimate partners. And donor eligibility determination is not required for certain cryopreserved reproductive cells or tissues. In those cases, however, there is required labeling as applicable. For example, for the cells and tissues for autologous there must be the statement in the labeling for autologous use only and not evaluated for infectious substances warning, advise recipient of communicable disease risk. And if there is any screening or testing performed that identifies a risk or positive marker for communicable disease, then a biohazard and an additional warning statement must be applied.

So let me briefly give you a very topical overview of the current good tissue practice rule. The general requirements are to prevent the interruption, transmission, or spread of communicable diseases, the manufacturers have to have met these facilities and controls in place. And they have to have requirements for, we have in the rule requirements for process validation, labeling, tracking, complaint files, and adverse reaction reporting, all of which have to be in place.

And you will see that the cGTPs are very broad. They are applicable to a very wide range of HCT/Ps and therefore they are not always entirely prescriptive. Each manufacturing establishment has flexibility to determine how to meet the goals through their SOPs. Another important point is that the GTPs, the good tissue practices, are narrower in scope than the good manufacturing practices. So that establishments that are

manufacturing cell and tissue products that are considered HCT/Ps, if they are following the good manufacturing practices, they are usually, they are following almost all of the good tissue practices.

And the GTPs specify that the manufacturer has to have a quality program to prevent, detect, and correct deficiencies that could increase communicable disease risk.

I wanted to mention one specific provision of the GTPs that is particularly relevant to our discussions today and that is the tracking provisions, where the manufacturer is required to establish and maintain a system to track each HCT/P. And the manufacturer must inform the consignee about the tracking system it has established. And the manufacturer is also required to label the product with a distinct identification code.

A point to make here is that you can see that this regulation only addresses

tracking to the level of the consignee. And one of the current activities within the Agency is to evaluate opportunities under the regulatory approach to address tracking to the level of the recipient, that that is not currently covered under the GTPs. Only to the consignee.

The regulations also include additional requirements but the applicability of those requirements is limited to the HCT/Ps that are regulated solely under Section 361 of the Act, and subpart E which is the adverse reaction reporting, deviation reporting, and some labeling provisions, don't apply to reproductive HCT/Ps.

So this is selecting out a few of these additional provisions because they are particularly relevant to your discussions. The adverse reaction reporting provisions include a definition of what we mean by adverse reaction, where again under the statutory authority of Section 361 of the

Public Health Service Act, these regulations focus on prevention of spread of communicable disease. So an adverse reaction is defined in this regulation as a noxious and unintended response to any HCT/P for which is there is a reasonable possibility that the HCT/P caused the response but the regs say the manufacturer must investigate any adverse reaction involving a communicable disease related to an HCT/P they made available for distribution and the manufacturers report to the FDA adverse reactions involving a communicable disease.

So you can see the definition of the adverse reaction is somewhat broad but what the regulations specify regarding which of those reactions must be reported to the FDA, that relates only to those reactions involving a communicable disease. And of those, only if the reaction is associated with a fatality, is life-threatening, results in permanent damage to the recipient, or necessitates medical or surgical intervention.

And these were reported in MedWatch form.

So I just wanted to give you some data to give you an idea about the numbers of these types of reports that we have received over the years and Scott Brubaker will also discuss this a little bit in his presentation. But as you can see, since 2005 when there was a smaller number of adverse reactions reported, since then the numbers have held fairly steady and the largest numbers of reports are associated with the musculoskeletal tissues, the bone ocular tissues and skin, to some extent corresponding with the relative numbers of such tissues that are transplanted annually.

Of the type of events that get reported, the majority do meet the definition or are considered infectious in nature. But a good third of those that have held steady over the last couple of years, are actually noninfectious adverse events or aren't really adverse events at all but rather maybe

processing deviations or other types of problems that didn't result in any adverse event in the recipient.

And it is important to understand that these numbers here reflect reports that we receive and don't relate necessarily to any actual transmissions of infectious disease. These are reports we receive from individuals who identify infectious complications in recipients that may be associated with the HCT/P.

So it is interesting to see where these reports come from. All these reports get evaluated by a workgroup of the tissue safety team. Each report is evaluated in detail. And you can see from this slightly busy table if you look at, for example, the 2009 column, that the vast majority, 70 percent or so of the reports come from the manufacturer and, as I pointed out earlier, the manufacturer is responsible for reporting to the FDA all adverse reactions related to

products they made available for distribution.

But a sizeable number do come directly from the consignee which may be a transplant center. Some from recipients themselves. So in 2009, that was about 13 percent. And a sizeable number are simultaneously reported both by the manufacturer and by consignees or others.

So, of the adverse reactions reports we have received, the vast majority relate to bacterial-associated reactions with significant numbers also associated with fungi or viruses and prions.

So, in addition to the adverse reaction reporting requirements, we also require that a manufacturer investigate deviations related to products that they have distributed. And the deviations that they report have to be those that relate to what we call core good tissue practices and those would be the good tissue practices that are specifically related to prevention and spread

of communicable disease very directly. And so any deviations in manufacturing practice that relate to any of those provisions must be reported within 45 days of discovery. And the reports also include information on follow-up actions that the manufacturer took.

So some things we are doing now I thought would be interesting for you all to know. One, newer initiative is the development of a relevant communicable disease agents and diseases workgroup, which we are forming to define gaps in current knowledge about transmission of infectious diseases by tissue transplantation, where I think it will become increasingly evident over the rest of the day today and tomorrow. There are significant scientific gaps or gaps in our current scientific knowledge about the specific risks of transmissibility for specific tissues processed in so many different ways and also from tissues from living and non-living donors, for example,

where we really want to focus on refining our understanding of what is known and what is not known about infectious disease transmissibility risks in a more specific ways for tissues.

The group is also developing approaches for leveraging federal agency and industry research resources for filling these gaps. And to some extent, that is the charge to the committee. So we are listening very carefully to hear any suggestions you had about ways to do this. And also we have some specific projects in mind that will relate to developing policies for screening and testing HCT/P donors for emerging infectious diseases, again, following a risk-based and science-based approach.

Another interesting Agency project I thought was relevant to discussion is the CBER Pilot Projects to assess the large medical encounter databases for tissue utilization and safety. And under this pilot,

there is going to be evaluation of the system characteristics of eight potential databases and the focus will be on looking at infections occurring after certain tissue transplants and identifying health information system gaps to enable automated data systems to efficiently monitor infections in recipients. And this is in collaboration with non-governmental resources and CMS.

And this is an example of a project that hopefully can help enhance the data reporting that we get and the passive surveillance systems. And it will be very interesting to see if this type of assessment can result in identification of trends or herald signs of associations between tissue transplantation and certain outcomes that the current systems and the passive surveillance would not be able to identify.

So that is the extent, pretty much, of what I wanted to convey that I thought would be helpful. Thank you very much for

your attention.

CHAIR BRACEY: Thank you. We have several questions. Dr. Sarode?

DR. SARODE: Thank you for your presentation.

Recently, we started keeping tissues in our blood bank and it is a nightmare.

DR. LAZARUS: Sorry to hear that.

DR. SARODE: Is there guidelines for consent for the patients? Because none of our clinicians take any consent from the patients about getting tissues transplants. So we send nerves or skin or is there a specific guideline? Is it required?

DR. LAZARUS: I'm sorry. I hope I am understanding the question. You are talking about informed consent from recipients --

DR. SARODE: Right.

DR. LAZARUS: -- of tissue transplants?

DR. SARODE: Correct.

DR. LAZARUS: The regulations that we promulgate cover donor screening and testing and manufacture of the tissues through the level of distribution to the consignee, the consignee being the transplant center, the dental office. So our regulations don't cover informed consent of the recipient. Informed consent is beyond the scope.

DR. SARODE: And the same is issue with the tracing of these tissues when they are given to the patients. For example, a surgeon will ask for two nerve tissues. We send it. They use maybe the same patient or two different patients and we are not able to track. And again, as I said it is a nightmare. And if you are just relying on manufacturers to report communicable diseases, I don't know how we are able to capture data from actually surgeons who are using in the patients.

DR. LAZARUS: That is a really,

really good important point. I hope Scott Brubaker is going to be addressing some of the activities in which the AATB is engaging to enhance understanding, knowledge, operability of the hospital tissue services to aid in those types of activities that are also required under Joint Commission Standards.

You make a very interesting point about reporting. And as I showed in my slide, a sizeable number of the reports we received about adverse reactions actually originate from consignees. And a point that I guess I have an opportunity to make here is that although we require the manufacturers to do that reporting, anyone can submit a report on a voluntary MedWatch form. And we do receive many such reports and we do evaluate those reports as well.

CHAIR BRACEY: Dr. Kouides?

DR. KOUIDES: Thank you. Could you clarify then or venture to a degree there are under-reporting of adverse events from say

academic centers? And on the flip side, I am curious you just mentioned to what degree have you had, what proportion of the voluntary reports into MedWatch are from academic centers?

DR. LAZARUS: Okay, so the data that I showed you kind of lump the direct reports so that it is not really, I can't, I don't have numbers on how many of those are academic centers versus non-academic.

DR. KOUIDES: Transplant centers.

DR. LAZARUS: Yes, transplant centers versus dental clinics. But I think that is a very important point that not all of these, what we consider consignees, have the same types of systems for tracking. And I think this is an interesting issue that maybe Dr. Kuehnert might address, others might address. But under-reporting, it is what it is.

One of the very important missions for our Agency and our division in particular

is outreach, where we attend meetings, we give a lot of presentations and we receive a lot of inquiries, consumer inquiries, manufacturer's inquiries about adverse reactions, adverse events reporting mechanisms. And so this is a major focus of our office activity to engage in outreach. So we can help the academic centers, the transplant centers improve their systems for tracking, monitoring, and reporting to the manufacturer any problems with those tissues.

CHAIR BRACEY: Dr. Ison and then Dr. St. Martin. Dr. Ison?

DR. ISON: Well a couple of observations. I find it very interesting that the number of reports of these disease or adverse events is actually very close to the number of reports that DTAC has received and yet there is a couple log difference in the number of tissues that are implanted compared to organs. So, I think under-reporting is an even larger problem from the tissue side.

I think that the point that was made about blood bankers being anxious is also a big issue when I gave a presentation of AATB, I basically got jumped at the end of the talk by everyone asking about these questions. So I do think it is an issue that does warrant some attention.

DR. LAZARUS: I'm sorry. Can I just maybe make a clarification? It might be helpful.

DR. ISON: Sure.

DR. LAZARUS: I mean, there are very significant differences in the regulations governing donor screening testing for organs and tissues. So to some extent, I am not sure we can do a direct proportional correlation between the number of adverse reactions and make conclusions about under-reporting. But it is a point well taken. I certainly believe that there is some extent of under-reporting.

DR. ISON: And this gets to the

question, so of those reports, how many were actual transmissions? And have you done, and maybe this is part of those pilot projects, any assessment to see how many patients have had new positive testing for HIV or hepatitis C after receipt of one of these tissues?

DR. LAZARUS: Okay so a zero conversion or development of infection would definitely meet the definition of an adverse reaction that must be reported by the manufacturer. The information I show you relates to reports we receive. There are a variety of, as you know, we have enforcement tools, we have compliance actions that we take. Those that we take related to issues where there have been recalls related to communicable disease transmission are publicly available. Those others are not publicly available. So, to some extent what we explain and describe publicly can't conflict with compliance actions proprietary information.

And Laura, you might help elaborate

on some of these.

CHAIR BRACEY: Dr. St. Martin?

DR. ISON: So how many of those are there?

DR. ST. MARTIN: How many of the?

DR. ISON: How many confirmed transmissions are there?

DR. ST. MARTIN: Okay and what Ellen was trying to say is we have not been -- the ones that are confirmed, you would know about because they would either be published in something like the MMWR or there would be a posting on the FDA website about a recall. So the ones that --

DR. ISON: So what is the number?

DR. LAZARUS: A few.

DR. ST. MARTIN: It is very few. It is very few.

What I did want to explain, you talked about the comparison of the numbers of reporting that there is certainly under-reporting at multiple levels. We only require

manufacturers to report and they can only report things that they know about. So if they are not receiving reports from the clinicians, they have nothing to report.

The other thing is that our adverse reaction definition includes the terms reasonable possibility. And some manufacturers interpret it differently than others. There are some manufacturers that submit almost every adverse reaction report that they receive to the FDA, even if it is not a serious adverse reaction, they just report almost anything. There are other manufacturers that have a higher threshold for reporting and may only report things that they have decided are ready or actionable.

So it is difficult to even compare the relative reporting between different types of manufacturers, different institutions that they may have received reports because there are some different threshold for reporting.

At compliance inspections, the

inspectors can determine if there are reports that a manufacturer received that probably should have been reported to FDA and those will get reported at that time. But it is hard to determine, you know, how many, you know, what the universe of reports is out there. And that is one of the purposes of these pilot projects is to try to figure out are there large databases that we can check to determine what is the tissue utilization rate. Are there automated data systems maybe in the microlab so that if there is a positive micro report it is linked with a tissue recipient? Is the coding of the surgery specific enough that we can determine what type of allograft was implanted? But we are just exploring those avenues right no to figure out how we can better assess what is happening out there.

DR. ISON: And then can I ask one other follow-on?

CHAIR BRACEY: Sure.

DR. ISON: So when these reports

1 come in to you, recognizing that some of the
2 tissue donors are also organ donors, how do
3 you and when do you report that back to UNOS
4 or to the OPO?
5 DR. LAZARUS: Laura can probably
6 give you a good explanation of that.
7 DR. ST. MARTIN: It has been
8 relatively few but we will almost immediately
9 contact HRSA directly and if the tissue bank,
10 tissue establishment has not already done so,
11 we will ask them to contact the OPTN.
12 CHAIR BRACEY: Mr. Nether?
13 MR. NETHER: My question just got
14 answered. Thank you.
15 CHAIR BRACEY: Oh, okay. One
16 question that I had is there is, in terms of
17 parallel universes, so there are infection
18 control officers in all hospitals and then
19 there is the NHSN, if I got the acronym right.
20 Are those entities linked, in terms of this
21 process? Are they looking at this issue?
22 DR. ST. MARTIN: I guess I am

trying to -- when we do our investigations, we will -- oh.

CHAIR BRACEY: Within a hospital environmental, there are surveillance systems for infections. And the question is, is there any linkage to this particular concern?

DR. ST. MARTIN: There may not be directly although we have had a pilot project actually. I believe it is no longer a pilot project. It may be winding down. But we have had a project through the MedSun Device Reporting System where we had some stimulated surveillance by some of the MedSun participating hospitals, where we trained specific reporters within the hospital system to do active reporting, not just passive reporting, but to actively search for infections. So that was one mechanism to try to get the infection control practitioners at the hospital level more involved in some of this active surveillance but it is limited.

CHAIR BRACEY: Dr. Kuehnert?

DR. KUEHNERT: A couple of years ago, AABB surveyed its hospital members concerning use and responsibility for tissue allografts and CDC collaborated on them with that and found that a very small minority of infection control or healthcare epidemiology departments were involved with allografts. Blood banks or transfusions services at the hospital level were more often involved but it was still a very small number compared to the actual surgical department having the primary responsibility.

The bottom line, and I have given presentations at infection control meetings, is that they are sometimes not even aware that the tissues are being implanted in the hospital. It is not something that has risen to the level of being something that is being addressed by healthcare epidemiology.

I also wanted to just make one point, if I could. I don't know that we even know how many tissue allografts are implanted

in the United States. I am always careful with my slides and Dr. Lazarus is too with her slides, as far as how many allografts are collected, how many are distributed. But we do not know even how many allografts are transplanted or implanted. And that has a lot of implications for determining rates, for determining the scope of the problem, trying to make comparisons to organs besides the other obvious issues about the viability of pathogens in a given graft, given the processing that is done. There is a wide spectrum of that across allografts. So there is a lot of complicated issues here but I just wanted to emphasize that we don't even know the basics of what is happening in this field to some extent, particularly at the hospital or facility level, where the regulations do not extend.

CHAIR BRACEY: Thank you. Dr. Holmberg?

DR. HOLMBERG: Yes, just very

quickly because we are running out of time. But thank you, Dr. Lazarus. I have one question and then a comment.

And that is the first question is, you say that your regulations go to the consignee. Does that include the distributor?

DR. LAZARUS: Distributors are actually considered manufacturers. So distributors have to comply with the regulations that are relevant to the activities that they perform. So they register. They list their products. They are subject to the inspectional enforcement provisions. They are not processing but they are performing distribution. There are provisions in the regulations specific for distribution practices to prevent spread of communicable disease. So distributors are manufacturers.

DR. HOLMBERG: Okay. I just thought it was very interesting that there were no reported adverse events coming from

the distributor on some of those slides that you showed.

DR. LAZARUS: I have to go back and actually look at that slide. But to some extent, the distributors are interesting in that they may be receiving tissues from a variety of different tissue banks. And it is unknown or I don't have data on how many distributors distribute tissues for one versus many. So the reporting can come from many different levels. So I don't want to read too much into those data on that slide with regard to whether distributors report or don't report or when. They are manufacturers.

The way the rule is written is important to understand, too. It is written to say that the manufacturers report adverse reactions relating to HCT/Ps they made available for distribution. So to some extent, the reports would likely be coming from the tissue bank, rather than the distributor.

DR. HOLMBERG: Okay. And the other comment that I have for the Committee, I think that Dr. Kuehnert sort of just touched on the subject and that is that the emphasis of the healthcare associated infections and all of the emphasis that is on that at the present time, is really only looking at the 80 percent rule. In other words, all the big procedures. I have even questioned recently about infectious diseases that may be transmitted by blood, organs, and tissues, and it is really not even on their radar screen.

So I think that this is a concern that I have always expressed is that the infectious disease control officer within the hospital doesn't even view this side of the house and only looks at the big procedures indwelling catheters and things like that.

CHAIR BRACEY: Well now we will hear -- thank you, Dr. Lazarus -- from the hospital side. Our next presentation is from The Joint Commission and the presenter will be Ms. Kelly

Fugate from The Joint Commission.

MS. FUGATE: Good morning. You have quite a few slides for me and I don't expect to belabor each one, especially in the interest of time, but you do have those slides in your handout.

The key points that I am going to cover today is what is the role of The Joint Commission in healthcare safety. How do we develop our standards, what that process looks like and then touch on the transfusion and tissue standards and sentinel event data.

We are looking at The Joint Commission's role, very briefly go over our mission and vision. And the culture of safety and the role of high reliability organizations as a supply to healthcare is a big emphasis of The Joint Commission's leadership at this time and then the value of accreditation. That is where the rubber meets the road.

The mission you can read for yourself. Obviously, it is improving

healthcare and we do that through our accreditation process.

The Joint Commission, as some of you know, was founded in 1951 and it is an independent not-for-profit organization whose mission it is to continuously improve the safety and quality of care provided to the public through the provision of healthcare accreditation and related services and we are supporting performance improvement in healthcare organizations.

This is a pretty lofty vision but this is one that Dr. Chassin has given us to share with everyone and it is all people always experience the safest highest quality best value healthcare across all settings. That is a huge bill to fill right there.

I do want to spend a little bit of time talking about our new center for transforming healthcare. It really is introducing a first of its kind approach to not only identify but also create and

implement consistent safety solutions that address quality and safety challenges facing all healthcare organizations. These challenges such as were mentioned today, primarily healthcare associated infections, they threaten lives and increase costs. The center uses Lean, Six Sigma and Change Management Tools and Methods to identify the most pressing safety problems, measure their impact, discover their causes, and develop specific solutions that are targeted to each important cause and then thoroughly test the solutions in real-life situations.

The Center relies on the extensive reach of The Joint Commission to spread the use of these solutions to improve the quality and safety of care at its more than 16,000 accredited healthcare organizations. And we will do this by providing simple assessment tools for organizations that may not have the capability to implement a full robust process improvement strategy. And it is to enable

these organizations to measure their processes, assess their specific causes of failures, and match the interventions to their specific causes within their organization.

The Joint Commission will provide a customized set of solutions targeted to the accredit organization's specific circumstances. And we are doing this at no additional cost.

Then our field staff that goes out onsite on evaluations, the surveyors will offer applicable solutions during the onsite survey or review as part of our consultative and education process. So the surveyors will actually help coach the organizations through this.

A culture of safety is a cornerstone to what the joint commission is trying to do, not only internally with our staff but also with our accredited organizations. Our efforts are to improve the safety in all types of healthcare and they are

based upon a recognition of the need for the organization's leaders and healthcare practitioners to adopt a systems approach to managing risk and keeping inevitable human error from reaching the patients.

And the five key systems that have to be in place to create a culture of safety is using the data. At the break I was talking with a few of the committee members and we were all bemoaning the fact that we are great at collecting the data but we are not always very good at how we analyze and then use that data. Obviously, planning has to be in place. We were just talking about the role of infection control and the infection preventionist. So we have planning, so that there is collaboration; communicating; changing performance; and then what is the staffing. Do we have the adequate resources for healthcare?

So the tie-in with the culture of safety and high reliability organizations is

you have to avoid those catastrophes. And we are not only talking about the sentinel events, or the adverse events themselves, but also those near misses. And obviously is an environment where normal accidents can be expected due to the high risk and complexity.

I am sure most of you have seen the five characteristics of healthcare, of high reliability organizations. You are not looking for a simple cause. You are actually relying on your line staff. Very similar to what we have seen in the airline industry. We want to make healthcare a high reliability industry as well.

You know, some people are picture people and it is getting to be that time like after breakfast, before lunch, so here is a nice picture. And the systems approach requires organizations to establish a just culture in which people feel safe to systematically identify and report the errors and near misses so that these events serve as

important learning experience for the organization and its staff and then other organizations throughout the healthcare industry.

So we at The Joint Commission have our accreditation process. The accreditation process is a risk reduction process. It is designed to assist healthcare organizations in reducing the safety risks that are part of healthcare delivery and then assess the level of the organization's success in addressing their risks. Risks can never be completely removed but organizations can be highly successful in substantially reducing those errors.

Again, here is another picture. Oh, and we have a little error message. I'm not quite sure what to do with this. Let's see if we can't get rid of it. Is that okay? All righty.

The arms aren't showing up very well but it shows our accreditation process

that The Joint Commission has created a framework to enhance patient safety and these are the critical components in achieving lasting improvements in organizational improvements. And I am going to focus on what is in the lower right-hand corner as the standards in particular. But you can see there is much more to our accreditation process, which I don't have the time to cover today.

Oh, and now my little pointer is not working. Let's try this way. Okay.

Our standards and national patient safety goals, as well as our survey process, which is our onsite evaluation process, I will just briefly run through how those standards are developed. Standards describe the successful operation of administrative and other critical systems of the healthcare organization such as infection prevention and control. And our national patient safety goals focus on the specific high-risk process

that directly impacts the quality and safety of care delivered to the patient. So for example, if the standard is infection, prevention, and control, then a specific national patient safety goal would be reducing infections associated with multi-drug resistant organisms.

These requirements are developed in collaboration with experts and key stakeholders and the final review is carried out by a nationwide field engagement. So the potential need is identified in any number of ways. Our onsite field staff, the calls that we get through our standards interpretation group, meetings such as today, feedback, letters, things like that, things that happen in the news. We do our research. We ask, is this evidence based. You know, what is the evidence for this and does it directly tie into safety and quality and what is the value-added piece for our organization?

Consensus among experts. We

convene task force. We engage with our major stakeholders. We put out the field review which is posted so that anyone can comment on the proposed standards. And then it goes through an advisory council and board process. Once they are approved, there is intensive field education, our field staff education as well as the field, and then we have our ongoing evaluation process.

Again for those who like pictures. The role again of The Joint Commission is to help organizations decrease errors through compliance with our standards and national patient safety goals. And they focus on a systems approach to delivering care. So along with the standards development process, we also develop in tandem with that, what is going to be our survey activities when we come out onsite. And these will be picked up through our patient tracer methodology. So for example a patient that has received an organ or tissue or a blood donation, they

would follow them through the process through all of our standards. And then in our leadership session with review of the performance improvement data. So that is how this is all pulled together on our onsite evaluation.

I know the gist of this morning's talk is on transplantation so I will just quickly go through. We do have transfusion standards in our National Patient Safety goals in our performance improvement chapter. And because we use a systems approach, they are actually sprinkled throughout. I think that there is an extra slide in your packet that is not showing up here but for the laboratory programs, there actually is a non-waived testing chapter for blood transfusion service and donor centers.

The transfusion standards are also sprinkled throughout the environment of care, human resources, medical staff, provision of care treatment and services, our universal

protocol, and of course we are following a CMS hospital Conditions of Participation. It also is covered under our sentinel event policy if there is a hemolytic transfusion reaction, we monitor compliance of our organizations that way.

The tissue standards, there is a transplant safety chapter and it covers donating and procuring organs and tissues. And then you can see it, it goes to outlying tissues a little bit further about procedures to acquire, receive, store, and issue tissues, tracing adverse events investigation. And again, this will be picked up on our onsite evaluation when our surveyors are out, through our patient tracer methodology, as well as the review of the organization's performance improvement data.

Besides the transplantation safety chapter, again these requirements are sprinkled throughout. All of the accreditation standards and the infection

control chapter environment of care, provision of care treatment and services.

I just wanted to briefly touch on our sentinel event data of what is reported to the Joint Commission. Again, we can only go by what is reported to us. So we are assuming that there is under-reporting here as well. But of the transfusion and tissue-related events that occurred in this almost three year period, 42 percent of those transfusion and tissue related events that were reported, 42 percent of those were a cross-match error and 34 percent were wrong blood/wrong patient. And then the other percentages fell out to either labeling issues or contaminated products and tissues.

So that was the end of my prepared comments, basically what the Joint Commission's role is, the culture of safety is paramount and everyone is always working toward making healthcare a high reliability industry. Thank you.

CHAIR BRACEY: Thank you, Dr. Fugate. Any questions for the committee and/or comments?

One thing that remains a real challenge, I was in our hospital's quality of care committee meeting recently and we are trying to encourage reporting among physicians. And so much of this is dependent upon developing that culture of safety. So how does The Joint Commission approach that and try to move in that direction?

MS. FUGATE: We take this very seriously. Recently we released within our Leadership Chapter Standards about disruptive behavior. And there has been, you know, we have done much publications in our perspectives, and there was a sentinel event alert about how disruptive behavior, primarily physicians but not solely so, how that affects patient care. So we are taking a very hard line at looking at that within our organizations.

CHAIR BRACEY: Maybe one last question from me and then I will yield to Dr. Holmberg.

And if and when there is an issue related to a tissue that may be a sentinel event, etcetera, that information I would take it is held within The Joint Commission and not available elsewhere.

MS. FUGATE: Correct. The organization where this happened is completely, the name and the identifying information is removed. If we put out a sentinel event alert or some other publication, it is lessons learned in general.

We definitely do not want to point fingers. That is not what a culture of safety is about. It is about, do you have, does the organization have processes in place where first of all the staff feel comfortable bringing this forward so we also want to make sure that they feel comfortable bringing it forward to The Joint Commission as well and we

don't want to be the stern parent with the ruler saying, oh, you did wrong. It is what are the lessons learned. And our Office of Quality monitoring has a very intense process where we work with the organization to look at that and how other organizations can follow and beef up their processes.

CHAIR BRACEY: Dr. Holmberg?

DR. HOLMBERG: Yes, thank you, Dr. Fugate. That was very good.

You know, I like the expression "the culture of safety" and I think that that is sort of a mantra that I think we all need to have. I guess my question for you, you saw, at the end you put the data up there as far as the percentages of errors in transfusion service. But do you have anything on tissues and organs? And I guess following on to that, the question that begs is how effective is The Joint Commission on giving that culture of safety into tissues and organs?

MS. FUGATE: That is a challenge as we have mentioned before. Not all of the infection preventionist or hospital epidemiology is even looking at this.

But to go back to your first question, we struggle all the time with what data do we want reported to The Joint Commission that might already be reported elsewhere because we don't want to turn this into an additional burden that adds administrative costs to our healthcare organizations.

So part of our standards talk about you need to comply with laws and regulation. So therefore since this information is reported to OPO, OPTN, and through HRSA, that is how we work with getting the data that way. So we don't have the data reported directly to us because we have heard very clearly from our customers that that would be a duplication of burden and efforts.

So then what we try to do is work

collaboratively with the community to see how that data is interpreted.

DR. BOWMAN: Dr. Pomper.

DR. POMPER: Thank you. That was very interesting. And the work The Joint Commission does is very excellent work. I think it is very proactive. The question is regarding surveys of behavior or more along the lines of I think there is sometimes a perception of perfection that occurs in both physicians and patients. Do you have any information, have you done any surveys that sort of would get at the question of what is the perceived risk, say of an infectious transmission from a tissue?

So reading one of the testimonials and I think this is fairly relevant and also probably more common than at least I would like to think. It refers to that the physicians were at the understanding that the tissue they were using was a sterile product. And I think that there is a perception that

everything is sterile, not only from the physicians but also from the patients and yet for me it is hard to believe that anything is actually perfectly sterile. There is always a chance that there might be a contamination.

So I think if there is some level of realism, then there is also more of an effort put into checking and acting on that. If everything is okay on the front end, you know, it is not necessary to be very vigilant.

Do you have any data regarding say patient surveys? You know, do you think that your treatment will be perfect or things along those lines?

MS. FUGATE: We don't have survey data because we don't routinely survey the patients in that fashion. When we are out on survey, we do talk to patients and their families about their care and some anecdotal things will come through that way. What The Joint Commission is doing and again not directly but indirectly, we have our speak-up

campaign, where we encourage the patients and their families not only about hand hygiene but things that you can do to prevent infection in general, about asking questions. How do you ask questions when you have a healthcare encounter?

But I think that you raise a good point that I could take that back and that is something that we can look at.

DR. POMPER: How about healthcare providers? Have there been surveys of the hospitals or healthcare providers in general as to levels of say expectation that nothing goes wrong?

MS. FUGATE: Not that I am aware of. Klaus has been at The Joint Commission longer than I. Do you have anything to add?

MR. NETHER: No. Actually, we are not collecting any of that data but it is definitely something that we can take back and talk more of.

With regards Kelly mentioned with

the Center for Transforming Healthcare, that was established in 2009 in response to what we have been hearing from our healthcare organizations with regard to helping them to develop solutions as well as to help them sustain those solutions.

CHAIR BRACEY: Thank you. We will -- oh, sorry. Dr. Kuehnert.

DR. KUEHNERT: I just had one other question which is related to the standards and how they are being applied. I just wondered if there has been any work that has been done by The Joint Commission on how often it is even documented that a tissue was implanted, if there has been any work done on that or that an adverse event has been detected. But I just wanted to start with the basics on just whether it is even documented in the chart.

MS. FUGATE: We have selected a patient in our patient tracer. That is something that they would look at through that entire process. But I don't think that

answers your question because we don't say, we don't sit down and do chart review of all of those patients. You know, it is more of a slice of what is going through. So the answer to your question is yes and no.

DR. KUEHNERT: Thanks.

CHAIR BRACEY: Thank you again. We will now move on to Scott Brubaker. He is the Chief Policy Officer of the American Association of Tissue Banks and thank you for joining us.

MR. BRUBAKER: Thank you for the opportunity to present and I will try to only take ten minutes. I do want to mention I saw I was placed in part of the program to kind of give you an idea of AATB and oversight and I don't really have that on my slides. I thought I would give you more cogent information about what we are doing right now that really is related to filling some gaps and some of the recommendations that were in the White Paper.

I will just mention that the AATB is a voluntary association. We were formed in the mid-1970s. By the mid-1980s, we published our first set of standards. And I actually have our current edition here for you. I brought a few copies for members of the committee. I did give out copies I think about a year and a half ago and some of you were members then. For travel ease, I also have it on disk. And I have about a dozen of these so if you would like one of those, let me know. We also certify personnel. We offer that. We accredit tissue banks and those two operations and functions started in the mid-1980s as well.

A little bit about the standards and the accreditation policies we have related to adverse outcome reporting. We do require that. We do require investigations, everything documented, complaints, determining root cause, and also there is a communication responsibilities that are in that as well.

That was mentioned as a question earlier.

We also have standards for tissue distribution intermediaries and we do have some of those establishments that performed that function solely are accredited by the AATB. And if an accredited bank who processes and distributes to a distributor, they have to audit that distributor to make sure they followed that section of the standards. So there was a certain level of control where our standards actually reach out and affect more folks than those that are just accredited.

So if we move on to really what I think is part of the afternoon discussion here is considerations for conventional tissue allograft component of a biovigilance system. And I noticed that Ellen had described conventional tissues. And what I am talking about is the same types of tissues minus reproductive cells and tissues, which our standards do cover but that is not involved here or hematopoietic progenitor stem cells or

ocular tissue.

And I thought because I only have ten minutes, I thought I would put my summary slide first in the beginning here and I will try to substantiate these as we move through. But as we create a transplant sentinel network, I think it would be good to focus on vigilance and surveillance for certain tissue graft types that are known to post the highest risk. And I will show you why we think that way.

We should develop and widely disseminate best practices to all stakeholders, including clinicians, to optimize recognition, reporting, and investigating tissue recipient adverse reactions.

And at the very beginning, I think we need to improve assessment of donor risk and that is by way of a qualified uniform donor risk assessment interview questionnaire. And we are developing that and I will show

you a little bit about that and we would hope that would actually be required. So let's address what are the highest risk tissues?

We are going to actually publish our survey for 2007 activity very soon. It will probably be a Thanksgiving gift next week. But this is, I notice some of the report attributed to AATB surveys that were in the White Paper were actually misleading and they are incorrect and I think I will send a short report to Dr. Holmberg so that he can distribute to the committee of the three or four things that really are misrepresented in that report.

But this is an adjusted number of grafts reported to be distributed. I think, Matt, you might have made the point that yes, we don't know how many are actually transplanted. There is no requirement or compliance requirement by end-users to report when an allograft is used or register it. We do try to get that information. We send a

tissue implant form, which is part of that White Paper. You can see an example of one Tissue Bank's. And compliance is sketchy. It has gotten better thank you to The Joint Commission's standards, though because they require that implant form be returned.

But you can see the number of grafts and types of grafts that are distributed. And I have gotten highlighted in different colors. And many of these are highly processed and some are not so highly processed. And the soft tissue grafts you can see are a little over 150,000. Cardiac and vascular are much lower numbers, they total less than 10,000. And skin allografts are not provided as a sterile graft and it is not sterile when it is recovered. And you can see the numbers there are a little over 300,000 units that were distributed.

Musculoskeletal is about 1.2 million and tissues devises are those described as demineralized bone mixed with a

carrier product and it is a paste, putty, or gel so that is a tissue devise. Again, highly processed. And some of those are operatives labeled as sterile as well.

Now this one is -- I noticed Ellen had an updated report. I guess she has inside information there. I have information really that is older from earlier this year that FDA reported, I believe at one of our meetings. And it is important understand that asterisk that these are reports. Most reports, as she said, they are really difficult to conclude that it was allograft caused and there is some, I guess, hesitation by end-users to report for different reasons and that could be a discussion topic at some point in the future as well.

But as you look at the soft tissue grafts, and I looked at Ellen's numbers. And for 2008, I have 29 and it ended up being 49 and for bone, instead of nine it is 21, and for cardiac, it turned out to be nine instead

of two. And if you relate that to 2009 data that she had on her information on her slide, it was bone at 17, musculoskeletal soft tissue at 38 and cardiac at 5. So we are still seeing twice as many, a two to one ratio for soft tissue versus bone. So soft tissue is more of a primary concern, I guess but again, these are just reports and there is really no control over how to recognize an allograft-caused infection and follow a guideline for what to report or when to report.

Now from our survey, this is the processing and treatment of musculoskeletal or bone tissue and soft tissue. And you can see that a lot of the grafts are radiated today. E-beam radiation. Most of it is gamma irradiated. I don't have that identified there. But most of them are proprietary methods to reduce the potential for contamination. Viral enactivation, some claims are made to that. A lot of that is related to bacterial removal, removal of

bacterial components that might be there. You can see, I can tell you now that this is now about two years old, this data, but the second graft on the right, there, that will now be higher. This will be the proprietary method used plus radiation, gamma radiation is now actually the highest number. I'm sure in our next survey that might show for 2008 as well.

So the sterility assurance levels and claims that can be made for that, we have a task force working on that. So we will have a guidance document. So all tissue banks are following the same validation protocols and evaluating their sterility assurance levels the same way. And part of that guidance will have a labeling requirement in the end. So when it is labeled sterile, it will have some power behind that in the future.

But it is important, I have a star, antibiotic treated only. And I think those, if you think about it, that is where some of our assurance of uncontaminated graft would be

lower. So to me, that is more of a risk.

And if you look at the breakdown from that table, the musculoskeletal tissues, only five tissue banks offer or distribute allografts that are treated minimally this way; 118,000 grafts in soft tissue; only three tissue banks at under 4,000. So if you add that together, it is 121,000. Add the vascular and cardiac tissues that are cryopreserved and they can pose a risk as well because you can only treat them with antibiotics, you end up with about 130,000 grafts that might actually need a higher risk category.

Dr. Ted Eastlund has done a lot of work in reporting and looking at what has been reported in proving transmissions. And I have a typo on here. It is since 1974. Alan's slide reminded me of that. So if you could single line date and initial your 1984 there and change it, that would be good.

So think about that, 1974. Now I

know vigilance and surveillance is an issue but the ones that have been recognized and reported and proven to be caused by the allograft, you can see fresh, frozen, cryopreserved throughout the many years for all these different viruses and bacteria. So I think that is very interesting and that is something that we can't ignore as we move forward.

Again, CJD, freeze-dried dura mater, that was an outlier, compared to all of the other information there.

We do distribute internationally to over 45 other countries outside the U.S. Canada's importation in studies and surveys they have done, and they have estimated greater than 80 percent of tissue they use is imported from the U.S.

And you can see that over half of the banks who actually distribute tissue that are accredited by us, do send tissue outside the U.S.

So, filling a gap. We recognize the big gap regarding the clinician's participation and how they report. And this is actually, we learned a lot of this from our participation in the TTSN, the Tissue Transplantation Sentinel Network, which we know funding has gone to TSN that we hope continues must get funding and I hope this Advisory Committee supports that. But we realize through surveys with our tissue banks what is happening. And I guess one of the biggest problems was correctly identifying transmission from an allograft. So we are putting together guidelines for that, for the end-users to properly recognize and report those and to participate in the investigation. That was a big gap. You might get a report and then they kind of fall off the face of the earth. They just don't respond. You need more information and you just can't get it. So then we are left with well, what happened, and we hope the patient was fine. And in most

cases, I would think they are.

Also how do tissue banks investigate? Put together best practices for how they investigate. So they follow specific guidelines and everyone is actually basically on the same page. And then best practices for handling recalls and market withdrawals really is at the end but that is all related to this.

Now this is the Table of Contents and I just want to point out basically what it is about. Disease transmission and graft failure will be covered in this, guidelines for both. I don't have the rest of the graft failure Table of Contents there, but it matches basically what is up there for disease transmission.

So it will give guidance for identification and reporting by the clinician in its own section and also investigation by the source tissue bank. And you can see the immediate quarantine and so forth. And again, communication, there is going to be time lines

in both of these sections because these kind of investigations have to move. They can't just sit around and wait for information.

Upon completion, now this is going to be a big part and I think the associations that are represented here will be part of this, we will be asking you to be, is to support this document. We need to have support from all stakeholders that are involved, AAOS, ASOSSM, you know, I can go through a litany of acronyms of the end-users but also other associations and government authorities should be involved with this and support it.

We want to develop specific brochures for clinicians because all of the tissue banking information in here and investigation part may be too overwhelming for them. So just to give them an idea of what we expect.

Now this is a part of the recognition criteria I thought I would show to

you. This is the kind of detail we want to give and direction we want to give. And this was developed by Workgroup C of the TTSN project and I will show you the rationale for all of this. But you can see for infection or a transmission of a disease to be suspected as caused by the allograft, there are two basic criteria that must be met and they are both clinical and laboratory evidence.

And I know that FDA sometimes receives reports when a pre-implantation culture is positive, yet the recipient has no clinical symptoms and that could be in some of that report criteria that they list on their table. What do you do with that information? They actually don't encourage that particular scenario to meet the criteria for reporting but it does happen.

So you can see I won't go through this in detail but you have a handout and you can see the requirements for a bacterial and fungal recognition criteria, as well as

parasitic and viral.

And let me just show this next slide. The rationale behind what is listed there is that these are manageable with a reasonable sensitivity. Reporting of common community-acquired diseases that occur post-op like flu or colds is not desired. This is evidence-based as well and the CDC had a lot of input to the criteria and timelines that are here, such as six months was selected for bacterial and fungal infections because that is from experience. We know that that would be the best time frame to list there.

We do have a year for the viral and parasitic infections that might be caused. Allograft removal has not been a factor that would capture cases. So that is not one of the indicators. And you can see that investigations leading to probable and proven infections show that symptoms were recognized between two and 113 days post-op. Patients were readmitted within a month of surgery and

there was really unexpected organisms from the wound or sight where cultured.

Additionally, we will look at adding other disease transmission criteria for malignancy and human TSE. Graft failure, we haven't really actually started on that section yet but what we are trying to do with this whole project is to harmonize with definitions and with some processes with EUSTITE. And I don't know if this Committee has a report on the EUSTITE project in Europe and what they are doing but we are trying to harmonize this guidance document with work that they have done already.

Now going back to the donor as actually a source of infection and trying to control screening a little bit better. And in our survey you can see that we had, this part of the survey for the very first time, we had participation from 22 not AATB-accredited tissue banks and they were basically OPOs who are not accredited by the AATB but do perform

functions related to recovery. And you can se that almost 30,000 deceased donors and almost 600 living donors were recovered in 2007.

In a separate survey I did of 19 AATB-accredited OPOs who perform recovery, this little survey I did for the first nine months of 2006 showed that 37 percent of all organ donors were also tissue donors. So you can see that kind of activity occurs.

We developed, started a project about two years ago actually thanks to the AABB's similar Task Force they put together in developing a donor history questionnaire but we have one now for organ, tissue, and eyes. It is a project that should end next year and I would like to tell you just a little bit about that.

Basically, the idea is to improve a historian comprehension. And our historians are actually very different because most of them, unless it is a living donor situation,

it is a deceased donor situation. A loved one has died. A close friend has died and it is a very stressful situation. So actually asking the questions in a more succinct way and trying to make sure the comprehension is there when you are getting a history to determine if there are high risks or not, say for organ donation, or to determine eligibility for tissue, we need to really work on that.

We found a lot of the same problems that they did in the blood industry when they started their project, a project in the year 2000 I believe.

But our idea is to reduce complexity of the form being used and the questions being asked. Use non-medical terms, broad capture questions, restrict it to required health information. This will help us gather accurate and relevant info. It will have increased attention by reducing time to complete it by the historian.

Fewer ineligible donors recovered.

1 Fewer eligible donors unnecessarily ruled out
2 and for designation as high-risk for organ
3 donors, this all plays into that.
4 This does cost some money, though.
5 The NCHS, we would like to work with them
6 like the AABB did on their questionnaire to
7 actually qualify the questions regarding
8 comprehension, using focus group evaluations
9 and cognitive interviewing techniques. So I
10 am going to pass the hat around here at the
11 end of my talk so we can get some money
12 towards that $151,000.
13 And as an ending slide, I would
14 like to show you we do collaborate with the
15 EBAA and the AABB. And this is a great little
16 book, handbook that was put out, published
17 last year. You can see some of the contents
18 there. We all wrote sections of it. I think
19 it costs $35. We do cover reporting and
20 investigating adverse outcomes in it, tissue
21 recalls, and some history about transmission
22 of infections and malignancies through tissue

allograft transplant. But it is a great guide for hospitals. I promote this as well The Joint Commission's standards transplant safety chapter on a regular basis. So I hope this information is helpful.

CHAIR BRACEY: Thank you very much.

May I ask one question? And that is one thing that struck me is that so with transfusion practice, there is an accrediting body that not only accredits the places that prepare the blood but also the places that use the blood. And the question I have is about the penetration of AATB into the hospital realm and its influence in sort of creating the standard of care.

MR. BRUBAKER: We do receive a lot of, in fact I get most of the questions that come to us from hospital personnel in regard to handling tissue and interpreting the joint commission standards.

We used to have some tissues services that were accredited by us and we can

still do that but it has kind of really dropped off. We have a section in our standards that they would have to adhere to. It is entitled "Tissue Dispensing Services." We saw that not many hospitals, I think it was used more and that we had more of those services accredited when surgical bone banking was actually active in the U.S. when they were taking discarded femoral heads and using them.

But with the advent of regulations and so forth, the hospitals found they couldn't meet the regulations in screening donors, testing donors, and so forth. And actually cadaver donation and distribution of those tissues really increased over those same years, where they really didn't have to perform that kind of a function to obtain a quality tissue and have safe processed tissue.

So I have presented and I have tried to get on the program the past three years at the ARN Congress meeting and I have been successful in doing that and they have

been very receptive. I have had big crowds of OR folks listening to really ideas to meet The Joint Commission standards, as well as information we can provide on the safety of tissue.

CHAIR BRACEY: Thank you. Dr. Triulzi?

DR. TRIULZI: I had two questions. One if I could just pin you down a little bit more. If you were going to estimate the number of facilities that use tissue in their facility, what proportion of those would AATB accredit? And if you look at what proportion of tissues would be used in an -- that is two different questions. One is proportion facilities and I don't know if we are talking 50 percent or 90 percent or 20 percent.

MR. BRUBAKER: If they meet our criteria for our tissue dispensing service, which any user could, they could become accredited.

DR. TRIULZI: Now, how many are?

MR. BRUBAKER: Actually now --

DR. TRIULZI: Like if you were going to estimate.

MR. BRUBAKER: -- I believe it is none. None are accredited by us. But they rely on the tissue coming from, and some other associations like AAOS and the American Burn Association recommend that their constituents, the tissue they receive is from an AATB accredited facility.

DR. TRIULZI: So the hospitals themselves, virtually none are AATB accredited.

MR. BRUBAKER: Right.

DR. TRIULZI: Okay.

MR. BRUBAKER: Now we have just formed a hospital tissue services committee to try to meet the needs of end-users. It will be a committee of end-users and handlers of tissue in different venues, especially hospitals. So we are continuing what AABB had started in that regard.

DR. TRIULZI: Okay. And my other question is, regarding the recognition criteria that are being proposed for the bacterial, parasitic, viral, --

MR. BRUBAKER: Yes.

DR. TRIULZI: -- what you have is a definition of a wound infection. And basically, if you estimated one percent, which would be a reasonable rate, a half to one percent is the rate of wound infections that occur even in procedures that don't have tissue.

MR. BRUBAKER: Yes.

DR. TRIULZI: So if you take your one million to 1.5 million between the musculoskeletal and soft tissue and you take one percent, that is 10,000 reports. Is the system capable of handling 10,000 reports of wound infections?

MR. BRUBAKER: Well we think those would actually be, it wouldn't be that high a number because other criteria also have to be

met. That is just one of them.

DR. TRIULZI: Well, A and one, two, or three, any of them that is a definition of a wound infection.

MR. BRUBAKER: I think that that one culture has to come from near an operative site, from or near an operative site.

DR. TRIULZI: Right.

MR. BRUBAKER: I thought we had that covered. Matt, you could probably address that better than I can because you were involved in putting that together.

We were trying not to include all of those by having this specific criteria.

DR. TRIULZI: Well, I think you are going to get them all.

DR. KUEHNERT: Yes, I would have to look more at the other. I mean, it would have to be an unusual pathogen that you would not expect in a wound infection to be specific.

DR. TRIULZI: Yes, that might --

DR. KUEHNERT: But from this, I

agree that it would be non-specific for wound infections.

DR. KOUIDES: So staph would be sorted out.

DR. KUEHNERT: Yes, sure, staph aureus would have to be sorted out.

DR. TRIULZI: You have got, you know, 8,000 reports of staff.

CHAIR BRACEY: Dr. Ison.

DR. ISON: I think along those lines you would almost need to do it as a study at least as first. Because one of the challenges, you could have staph aureus contamination and in a study setting you could do genotyping or something that you could show that they were all linked. But I think that is one of the emerging themes that I think is true across these. I think a lot of times people would just say oh, it is just a wound infection. It is just this, it is just that. It is a surgical complication when in fact it actually may be a surgical complication from

donor origin and you would have to define that prospectively and the easiest way to do that would be really as part of a study initially and that could potentially refine definitions down the road.

This is a question that I have that others may be able to answer. So from a tissue standpoint from the hospital user, who is responsible in the hospital? Is it always the blood bank? Is it the OR? Is it procurements? Is it all over?

DR. SARODE: It is all over.

(Laughter.)

CHAIR BRACEY: Yes, I think in the information that we received, I think somewhere around 20 percent or so are blood banks and then it is sort of diffuse after that "surgery."

MR. BRUBAKER: We have got slides we could show you from the reports like the one Matt was talking about and also one that the blood utilization survey kind of supported

the older survey that we have.

CHAIR BRACEY: So there are these transfusion committee activities. You know, a group of individuals that oversee these transactions. Does such a model exist with tissue?

MR. BRUBAKER: We are promoting that, yes. And in that AABB handbook, you will see it addressed in there and then other avenues we are trying to promote that there is a Tissue Safety Committee, yes.

CHAIR BRACEY: Dr. Sarode?

DR. SARODE: Yes, I think most of the blood bank transfusion committees, they are trying to get into tissue at the same time. For example, our board now also oversees tissue transplantation.

CHAIR BRACEY: Dr. Kouides, do you have a question or comment? Okay.

Additional questions or comments? If not, thank you very much.

MR. BRUBAKER: All right. Thank

you for the time. And I do have standards if you would like.

CHAIR BRACEY: Our next presenter is Mr. David Korroch. He is the executive director of the Lions Medical Eye Bank and Research Center of Eastern Virginia and he will present on the Eye Bank Association of America. Thank you.

MR. KORROCH: Thank you very much. This will be actually a read-along. In the interests of time, I am not going to use the slides. The handout has the EBAA logo on the top of it.

First, I would like to recognize and thank Renee for helping me get here in such short notice. I really appreciate all of her help.

Mr. Chairman, members of the committee, on behalf of the 88 U.S. member eye bank organization, the Eye Bank Association of America appreciates the opportunity to present to the Advisory Committee.

The 88 U.S. member eye banks of the EBAA represent 100 percent of the entire not-for-profit U.S. eye banking community and are proud of their history. The first corneal transplant was performed in 1905 and the first eye bank opened in New York in 1944, marking the initial organized attempt to facilitate the transfer of tissue from donor to recipient. This eye banking model was successfully replicated in other communities across the U.S. and following development of the eye banking system, the EBAA was founded in 1961 by the American Academy of Ophthalmology.

I would like to mention as a note that last year in 2008 over 52,000 corneal grafts were transplanted provided by eye bank association membership. It is up five percent for 2007.

All members of the eye bank association are non-for-profit organizations, whose mission is to recover and provide

transplanted human eye tissue for sight restoring transplant procedures, education, and research. Significant gains in ophthalmology in are in part due to donated ocular tissue provided by this nation's eye banks. The EBAA strives to ensure the superior quality of banked human ocular tissue through the adoption and implementation of stringent medical standards that are scientifically based and specific to corneas and sclera for transplant.

Eye banks led the transplant field in the early 1980s with the introduction of an accreditation program and medical standards that continue to provide a model of success in the transplant community. The standards are subject to continued review and revision by a board of medical and lay professionals with expertise in eye banking and cornea transplant. They have been endorsed each year by an American Academy of Ophthalmology. The present system works extremely well, as

1 documented through accreditation records and
2 an online adverse reaction reporting system,
3 first required for accreditation in 1991.
4 Today, the 88 eye banks provide a sufficient
5 amount of tissue safe for transplant to those
6 in need of sight restoring transplants.
7 As a side comment, I will tell you
8 it is one thing. I will tell you it is
9 something the Eye Bank Association is proud of
10 that in the United States, there is no longer
11 a waiting list for corneal tissue. We work on
12 a scheduled surgery basis. If a person needs
13 a cornea, the surgery is scheduled and more
14 than nine times out of ten, there will be
15 corneal tissue there ready for that surgery.
16 To reinforce our mission of
17 providing corneal tissue safe for transplant,
18 the EBAA has worked closely with the FDA since
19 publication of its first interim Final Rule in
20 December of 1993. The purpose of which, as
21 you know, was to prevent the transmission of
22 communicable disease through the tissue

transplant.

In May 2007 at its presentation to this Committee, the EBAA addressed eye banking and corneal transplant as it relates to disease transmissibility. The EBAA then emphasized that there has been no transmission of systemic infectious disease from corneal transplants since 1987 due to strict adherence to EBAA medical standards.

The EBAA continues to work with HHS and the FDA to develop practices that are appropriate for the eye banking community to adequately ensure public health. We believe that balance must be achieved in drafting regulations with the recognition of significant differences between the processing of ocular tissue and leukocyte-rich tissues. We have read and submitted comments on past draft guidance and reiterate our recommendations which include require arbovirus testing of donors of corneal tissue only when science has demonstrated a known

benefit of testing to public safety.

Base guidance on data specific to the properties of the tissue being offered for transplant. FDA has provided this model in its requirement for specific testing for specific types of tissue from reproductive donors because of the disease related only to this type of donation.

Provide a risk-based analysis on the numbers of tissues likely to be discarded versus the number of recipients likely to acquire the disease. This is routinely done by the FDA with the blood model.

Allow use of a testing algorithm with an approved confirmation validation when and if science has demonstrated a significant benefit to the testing.

Employ FDA's tiered risk-based approach to transmission. As an example of this, the "viable leukocyte-rich" HCT/P designation described in the donor eligibility final rule and final guidance.

The EBAA offers these comment sin the spirit of cooperation and collegiality and looks forward to working with the FDA and our other transplant partners to ensure the safety of ocular and other tissues provided for transplant.

And you can read some more there regarding our comments and comments from the committees that I previously met. I am going to skip ahead a little bit in the interest of time.

Not all tissues have the same disease risks or associated infection potential. The EBAA believes that such a risk assessment will produce a safe and more appropriate system of regulation which will apply an epidemiological and statistical analysis of the problems, or lack thereof. This will provide safety without inappropriately constraining transplantation medicine. EBAA strongly urges the FDA to weigh individual tissues and individual

diseases based on the known nature of their risk and likelihood of transmission.

Lastly, I would like to mention that in addition to EBAA's Medical Standards, the association has developed the Online Adverse Reaction Reporting System, also known as OARRS. This system further strengthens our commitment to transplant safety and through it we have provided our feedback in workshops and focus groups in the establishment of the national Transplantation Transmission Sentinel Network (TTSN).

OARRS provides member eye banks with a secure internet-based system that generates unique donor and cornea identifiers and a common notification system for adverse events to help track the disposition of corneal tissue. This has not only helped in the reporting of adverse events but also in the generation of valuable data for research and safety improvements.

The EBAA, again, appreciates the

opportunity to comment to the Committee. We look forward to working with you and furthering transplantation safety.

Thank you very much.

CHAIR BRACEY: Thank you.

Questions or comments from the Committee? Dr. Ison.

DR. ISON: So if you get a report, how do you transmit that if the eye donor was also a tissue or organ donor?

MR. KORROCH: If it was what we commonly call a shared donor, we do have in our standards, it is required that that information be shared with the tissue bank or OPO that was also involved with the donor. And so that is an audit that is performed at the time of accreditation.

DR. ISON: And then one other follow-on question. You said that there have no documented transmissions. How many reports of concern or potential transmission have been made through this system?

MR. KORROCH: Well there have been transmissions and those are documented. I don't think I said there have been no transmissions.

DR. ISON: Well you said since '87. But I am getting more to the issue, you say you have the system in place to make reports.

MR. KORROCH: Yes.

DR. ISON: How many reports have been made that have been proven not to be true?

MR. KORROCH: Well, as far as -- I don't know. How many suspected viral transmissions, systemic transmissions have been made that have been proven not to be true? I am going to say a handful.

The investigation that happens afterward is very thorough and we involve other agencies.

CHAIR BRACEY: You did mention that the availability of corneal transplants is quite good at this point.

MR. KORROCH: Yes.

CHAIR BRACEY: So I guess I was trying to understand a sense that -- do you sense that -- So there is not a limitation on availability but is there an impact on cost? And what is your major concern regarding current testing requirements?

MR. KORROCH: The concern is that we would like to be able to continue providing a high level of service to ophthalmologists and patients to restore sight.

A cornea is not a cornea is not a cornea. Just because we have a cornea available to be transplanted doesn't mean it will be suitable for the patient that needs the transplant. There is age differences. It depends on the indication for the transplant. So and we did a study, the EBAA did a study in 2008 looking at our numbers. It take about 1.4 corneas recovered. It takes the recovery from a donor of 1.4 corneas to make one viable cornea.

So if the donor pool shrinks because of regulation, then the availability will shrink as well. And keep in mind that all eye banks are not-for-profit organizations. They depend quite heavily on volunteerism. They are based at universities and hospitals for the most part and every dollar is very important in a non-profit setting.

CHAIR BRACEY: Thank you. Dr. Holmberg?

DR. HOLMBERG: Just a quick question. Do you export?

MR. KORROCH: Yes. Because of what I just talked about, the number of corneas that is recovered to make a cornea suitable, we have the EBAA last year in 2008 EBAA member eye banks exported about 8,000 corneas overseas. And those are provided, again, this is part of a non-profit mission. Those are provided either gratis or at a greatly reduced processing fee.

DR. ISON: So in those exported organs and I probably should have asked this to the tissue banking, too. If a disease is recognized outside of the United States, how is that information transmitted back and are there robust systems or is it possibly lost in translation?

MR. KORROCH: It is a challenge, I will certainly admit that. The EBAA medical standards require the documented attempt to gather follow-up information six to 12 months after the transplant. And in most cases, I will say in most cases, that we are able to get that because it is something that the EBA requires of the source eye bank. And so if the source eye bank is going to be marked with a deficiency because of that, they are going to tell the overseas recipient, listen, you are not going to get tissue unless you cooperate with us and provide this information. So it is getting better. I can say that.

CHAIR BRACEY: Yes, Dr. Kuehnert.

DR. KUEHNERT: I will say just one anecdotal experience we had was involving LCMV, lymphocytic choriomeningitis virus where there was cornea that was implanted in a developing country. And just in terms of the method of transportation of the corneas and in terms of the lack of paperwork, it was almost impossible to get any follow-up.

CHAIR BRACEY: Dr. Sarode?

DR. SARODE: Now, all these corneas that we have in our blood bank, are they coming from eye banks?

MR. KORROCH: Yes.

DR. SARODE: Okay.

MR. KORROCH: That is one thing that, fortunately, we are in a situation where all of the eye tissue being used in the United States is coming from an EBAA member eye bank. So 100 percent of the eye banks in the United States are members of the Eye Bank Association of America and all but two eye banks are

accredited members.

CHAIR BRACEY: All right. Well, thank you very much and we are now at the break for lunch and we will reconvene at 1:15. We will have an hour for lunch.

(Whereupon, at 12:18 p.m. a lunch recess was taken.)

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

(1:17 p.m.)

CHAIR BRACEY: We do have one person coming in today and at least one of our speakers have already left. But the word is that FAA had problems this morning. And I understand from what I hear from CNN that they are back up on track but you know how that has a ripple effect throughout the day on delays.

So be thankful that you are here and hopefully everything will be okay tomorrow.

DR. ISON: So Jerry, I got some information to answer one of the questions before. So there was a question earlier about serologic testing in patients that were a self-proclaimed donor versus those in which they weren't.

So the data that UNOS has is attained at the time of procurement and asks whether or not there was a documentation of

intent to donate. Many times there is still a secondary approval by a family member in that setting. So a third of the recipients in the last year had a statement of intent of donation. And looking at the zero prevalence for hep C, it was 4.1 percent for those that did and 4.5 that did not. For hepatitis B surface antigen, it was 0.1 percent that did, 0.2 that didn't. For hepatitis B, core antibody 4.8 that did, 5.7 that didn't, and for HTLV-I and II, 0.2 in both groups and I don't see HIV but I believe that it should have been zero for both groups. So really not a significant difference between the two.

But I think it is important to recognize the decision to consent to donation may have been years in the past.

CHAIR BRACEY: Okay. With that then we will proceed with this afternoon's sessions. We have a continuation of reports on biovigilance and we do also have time for an active committee discussion as we have this

morning. It was quite good this morning regarding the issues at hand.

So our first presenter is known to all of you as Dr. Kuehnert and he is going to speak about the Public Health Service Biovigilance Task Group. Matt?

DR. KUEHNERT: Thank you, Dr. Bracey. Okay, what I wanted to do is give a short summary. I know we are behind a little bit of the committee recommendations that led to this summary report, otherwise known as a Biovigilance White Paper and just to give you some ideas for discussion and then others will expand more on the gaps that were identified in the organ and tissue areas.

As far as the title slide here, I just wanted to point out that we have a new center that is proposed for emerging and zoonotic infectious diseases. The National Center for Infectious Diseases a few years ago was split apart and now parts of it are coming back together. So I think this will create

some interesting opportunities in the areas for all interested, particularly in the areas of emerging infectious diseases.

And I am representing the Task Group and not the CDC in this presentation. So I will just clarify that.

So going back to the August 2006 recommendations, of course this is quite a while ago and it has taken a long time to get up to speed on everything that is going on in biovigilance and all the gaps that exist. But the recommendations were that HHS should coordinate federal actions and programs to support and facilitate biovigilance in partnership with private sector initiatives and that HHS should form a Biovigilance Task Group to perform a gap analysis of the current systems and make recommendations for a public-private partnership to create a comprehensive and integrated national patient safety program.

So the report that all of you in

the Committee have is over a one hundred page document, including the appendices. The agencies involved have all looked at the document and agree with its contents. And I think that is important that the federal government is together on this and I just want to go over some of the highlights of the document.

First of all how it is set up, the purpose. So the purpose was to identify the vision, goals and processes to allow HHS to coordinate Federal actions and programs within the U.S. to support and facilitate biovigilance in partnership with private sector objectives. And that is a really important last point is in partnership with private sector objectives. We can't move forward without the private sector in this effort.

And that the analysis and operational report should include a gap analysis, reporting requirements as far as

mandates and scope, database characteristics, coordination with non-U.S. systems, design and feasibility of a suitable pilot, and funding mechanisms for a sustainable system. So these were the points that were brought by the committee that the task group was to address and most of those points were hit in the report.

The methods were to review the current surveillance and adverse event reporting systems through data review and discussion. This included not only national programs but also international programs. And to consider the various role and mission of relevant Public Health Service agencies and program oversight and product regulation.

Just to go over those that were involved in the process and in the task group, the office of Public Health and Science and HHS, CDC, CMS, FDA, HRSA, and NIH.

Here are the individuals who were involved in the Working Group. This was very

much a collaborative effort. We had some individuals who moved from one agency to another during the process, which added further cross-fertilization of ideas and a very productive group.

So just to go over the gaps, I will go through the blood gaps quickly, since this was discussed at the previous Advisory Committee meeting. Number one, that there is a patchwork and sometimes fragmented system of various adverse event reporting. Likely under-reporting of transfusion adverse events. There are challenges with FDA required reporting, a need for accurate recipient denominator data, precise definitions, and training, that there is no national surveillance of serious adverse events, other than for fatalities. There is a need for accurate donor denominator data, precise definitions, and training. There is a need for accurate tracking for all donor infectious diseases, infectious disease test data, and

there is a need for timely analysis of the data that is reported.

For tissue, there were six gaps identified that there is limited information on the potential for tissues to transmit infectious disease, number two, an ability to ascertain that reported infections, that should be infections in HCT/P recipients can be attributed to the tissue is limited.

Three, regulations concerning adverse event reporting do not extend to the level of the healthcare facility or healthcare provider and that has been discussed today already.

Four, current mechanisms for tracking tissue grafts to the level of the recipient are limited.

Five, adverse reaction reporting for tissues regulated solely under Section 361 of the PHS Act is limited to infectious disease.

And finally, information about

adverse reactions in other recipients of tissue from an implicated donor may not be readily available.

On the organ side, two gaps were identified. There is a lot rolled into the first one. That there is a lack of nationwide common organ and tissue, a lack of a nationwide common organ tissue donor network system for real time reporting, data collection, communication, and analysis of donor-transmitted diseases in organ and tissue transplant recipients, including there is a need for a common donor identifier necessary for linkage back to implicated donors of both organs and tissues. And second, that there is no requirement to retain donor and recipient samples.

I would add that there is particular challenge of samples existing on the recipient side, primarily.

So, this is, I should have put my summary. I took pieces from the paper to try

to summarize this in one slide. That biovigilance in the U.S. is a patchwork of activities, not a cohesive national program; the existing patchwork is functional in some respects but also has critical gaps, if the objective is patient safety; and that recommendations on actions to move forward are complicated by the lack of a national policy and a pluralistic approach to the safety and availability of blood, tissue and organs. And this is primarily because the regulation is pluralistic.

So, three ways to move forward. One, and this is all contained in the report. One, an HHS biovigilance strategic plan is a first step to set priorities. Secondly that both voluntary, meaning public health oriented systems and mandatory, meaning regulatory systems are both needed in parallel. And three that integration of both public and private sector support with joint governance of a national biovigilance collaborative is

vital.

For those of you in the Committee who haven't dealt with blood, organ, and tissue safety sort of as a whole, there are some difference when you consider the balance between safety and availability, which is something that the Committee looks at often.

So as many of you are aware for blood, the emphasis is on safety and availability is really a lesser concern, unless there is a large impact on it. For organs, as you have heard today, the emphasis is on availability and safety is a lesser concern. And as we have heard for tissues, it is hard to lump tissues all together. I mean, it is really a spectrum. And of course, you could even make it a larger spectrum that blood is a liquid tissue and organs are tissues also.

So, when you are looking at such a broad spectrum, it is very hard to make any blanket statements but that in talking about

the balance between safety and availability, the balance is somewhere in between what it is for blood and what it is for organs.

So I thought this quote summed things up pretty well in the White Paper, which is that biovigilance, which is something that also has a lot of different definitions and that is something we can discuss as we think about recommendations from the Committee to the Department, that as a component -- but thinking of it as component of Public Health Surveillance, should strive to reduce the inherent risk associated with transfusion and transplantation and ensure the availability of the life saving biologic resource.

So, I am happy to answer any questions but I think really what we need to do is move on to discussion. Thanks.

CHAIR BRACEY: Thank you. Questions or comments for Dr. Kuehnert regarding his presentation? If not, it sounds like we are anxious to get to that discussion

phase.

All right then, our next presenter will be, let me just get my agenda out, Dr. St. Martin, who is going to present on human cell tissue and cellular tissue based product. Again, a component of the White Paper discussion. And Dr. St. Martin, again, is also known to all the Committee members. She is from the Office of Cellular Tissue and Gene Therapies at CBER and the FDA.

Dr. St. Martin.

DR. ST. MARTIN: Just by way of background, Ellen Lazarus covered the definition of what we consider human cell tissues and cellular and tissue-based products. And it is important to keep this in mind. It is fairly broad category of diverse products and it is not intuitive just from this definition what those products would be. They include things like bone, skin, tendons, oocytes, semen, and then the hematopoietic progenitor cell. So it is a fairly diverse

group of products.

And I just wanted to also clarify that when we were conducting this gap analysis, the office of cellular tissue and gene therapies made the decision that we would specifically exclude certain products from this gap analysis. For example, we decided that we would exclude reproductive HCT/Ps. And part of the reason is that these are fairly unique tissues, compared to some of the other tissues that we regulate under this paradigm. They have some very unique uses, some unique concerns about reproductive freedom, reproductive choice, an availability.

Currently our regulations regarding these products are limited to establishment registration, product listing and donor eligibility. So these products currently are not subject to the good tissue practice regulations. And some of that will be, you know, we are looking at that as the regulation evolves and it is still a fairly new

regulation.

We also decide to exclude from the scope of the analysis those HCT/Ps that are subject to pre-market review and licensure. And these are what we would describe of the 351 HCT/Ps. We decided to exclude them because they are subject to additional requirements beyond the 361 regulations. They must demonstrate safety and efficacy so they are held to a higher standard then some of the more conventional tissues. They already are subject to some comprehensive reporting requirements.

This next chart I decided to include because it is very complicated to explain the federal oversight of some of these hematopoietic progenitor cells. As Ellen indicated in her talk, there are some HPCs for which there is sort of shared oversight between HRSA and FDA, particularly regarding different aspects of the safety and availability of these products. But we also

wanted to point out that there are some products for which there are no federal oversight, such as the autologous bone marrow, that it is not manipulated, that it is for homologous use.

Some of the biovigilance overarching concerns that we had were the need for better quantification of the potential risk of transmission based on the effectiveness of disinfecting methods. As Scott Brubaker stated, there are a number of different types of tissue and some of them are subjected to processing methods that may remove certain bacteria, even certain viruses. And some of these processing methods may be validated to ensure that they have removed these particular agents but we have not adjusted or rules to make adjustment for these different processing methods. Part of it is each bank has their own method and we just don't have a good understanding of what the potential risk is for these different types of

tissues and different methods at this point in time.

Also another overarching concern is that there are delays in recognition of donor transmission and there are also delays in the communication of possible transmissions to other establishments. And that is something that we hope to remedy. There is also difficulty with timely tracking of HCT/Ps to the level of the recipient. As has been stated, the regulations currently only apply to the manufacturer. So at the level of the recipient, we sometimes are at a loss because we cannot proceed with our investigation past that stage.

We have had particular difficulty at times with tracking recipients in dental facilities. There appears to be a significant difficulty with identifying which HCT/Ps have gone into particular recipients at some of these dental offices where we have had to investigate infections. Even the reporting

physician sometimes is not sure what HCT/P he is reporting about.

I just wanted to highlight some of the global efforts related to biovigilance. These are just a few of the global initiatives. One is the EUSTITE project that has been briefly touched on and one highlight of it is that it is developing guidance documents for the inspection of tissue facilities. And it also is developing training programs in the inspection of tissue facilities.

They have also developed some very good tools for individuals to use to determine whether a transmission has occurred and to sort of rate whether it is probably, possible, you know, likely transmission of an infection. So these are some fairly useful surveillance tools that we have also been looking at here in the U.S.

The Canada Vigilance Program, they require not only reporting of adverse

reactions but they also require reporting of errors and accidents, which is something that we currently do not require for human tissues. They also encourage voluntary reporting by consumers.

Also the Center for International Blood and Marrow Transplant Research, they do have some contracts with HRSA under the C.W. Bill Young Cell Program but even beyond that, the CIBMTR has a large database of information on a broad scope of cellular transplants, even those are not within the U.S. Federal Government purview. But they do collect some information about autologous transplants.

As far as federal reporting, the FDA requires adverse reaction reporting through the MedWatch system. And as was stated, it is limited to a requirement that manufacturers investigate and report certain adverse reactions.

Within CBER there is a tissue safety team. This is composed of

representatives from multiple offices within CBER. We review every adverse reaction report that is received. There is a coordinated approach to the review of these reports. Sometimes it requires contacting the manufacturer. Sometimes it requires contacting the clinician.

We also have requirements for deviation reporting. These are deviations from manufacturing steps. And I also mentioned the TissueNet project. That is a sub-network of the MedSun project where we have described it as a stimulated surveillance program, where we have individuals in these participating hospitals that are trained to look for and report adverse reactions.

At the non-federal level, The Joint Commission has standards related to tissue storage and issuance that are applicable to the accredited healthcare organizations. AATB has their standards and we actually rely quite

a bit on collaboration with AATB in making sure that tissues are safe.

The Eye Bank Association of America also has standards that the eye bank must follow. They also seek follow-up on all patients that receive eye transplants, transplants of eye tissue. And we also work very closely with the Eye Bank Association.

The Stem Cell Therapeutic Outcomes Database, this was also a result of the legislation that established the C.W. Bill Young cell transplant program and requires submission of data on all allogeneic stem cell transplant recipients. And the National Merit Donor Program, which collects on adverse reactions and also posts a nation's symptoms. So they also cover donor events, as well as recipients.

Now some of the gaps, we have identified several gaps. One of the gaps that we have had concerns about and we are working to address is that we have limited information

on the potential for specific HCT/Ps to transmit infectious diseases. It is not well characterized for all of the known infectious diseases and we have even more difficulty determining whether we should worry about some of these emerging infectious diseases. And then different cell types, different tissue types, may have different potential for transmitting diseases. So we are struggling with how could we be more proactive and better characterize these risks.

There have been some improvements in donor screening and testing methods, improvement and processing methods. But even with that, the risk is not zero.

We also have difficulty ascertaining whether a reported adverse reaction is actually due to the tissue. We know that there is a baseline level of post-operative infections and it is often difficult to distinguish a routine, if you can say so, a routine post-op infection from an infection

that was transmitted by the tissue. We particularly have difficulty when we receive adverse reaction reports of a recipient infection that involves something like coag negative staph. It is just very difficult to determine whether -- it is not speciated to begin with and it is very difficult to determine what to do with that type of report.

Right now our regulations do not extend to the hospital level. They are applicable to the manufacturers. So we do have difficulty. There is no way to enforce compliance on the hospitals and the end-users of these tissues. The manufacturers depend on voluntary reporting by the clinicians. They can't report to FDA what hasn't been reported to us.

Again, the current mechanism for tracking HCT/P grafts to the level of the recipient are limited. At the hospital level, the dentist office level, the private physician level, they often fail to report

back to the tissue establishment the final disposition of the graft. Often the establishment doesn't know if the graft was even used. Was it discarded? Was it implanted and to whom was it implanted? This lack of information hinders our adverse reaction investigations and also hinders allograft recalls in the event that there is something identified where we have a concern and we feel that we need to make sure that all recipients are aware of a potential risk. And this is something that we are trying to address.

And probably the biggest limitation is that the scope of our authority for the regulation of these HCT/Ps is related to communicable disease transmission. We are using Section 361 of the PHS Act. So it is a fairly narrow scope of reporting and regulation.

We do encourage voluntary reports and we do receive a fair number of voluntary

reports. We also encourage reports of events that are not infectious. And we do receive some of those. And we do investigate them as needed and to do some trending to determine are there some safety concerns that we need to address. Is there some education that we need to address? Things like we sometimes get reports of things like placing -- we have learned, you know, they may be placing the tissue package on top of the sterile field, assuming that the inner layer is sterile when the tissue may be triple packaged and you have got to get to the third layer before you have got the sterile package.

So those are some things we can easily address by education. And that is the bulk of the concerns that we have. We are also looking at whether there is a better way to transmit information about potential infections.

I think in the report we mentioned the potential utility of something like the

TTSN in terms of disseminating information about potential infections. A single donor may be processed by a number of tissue establishments. And a single tissue establishment might receive the report. Different tissue establishments have different ways of handling them. Some will automatically and immediately contact any other tissues establishment that are aware may have processed tissues from the same donors. Others will perform their own internal investigations and make an assessment of whether they think it could have been a transmission.

And so there is some variation in when and how much information is communicated. And to some degree, that is understandable if it is about raising an alarm when it is not called for but I see that this is an area where may be need for some clarification.

Some of the policy challenges, you know, the bigger one is that it is the 361

authority is the limited scope of authority. And that the reporting requirements only extend to the level of the manufacturer.

And that was basically the extent of the analysis. You know, one of the big I think issues that we are still struggling with is we don't know the full extent of tissue utilization. We don't have that denominator number and we don't have full reporting of those adverse reactions that may occur, even those that may need our definition of adverse reactions.

Thank you.

CHAIR BRACEY: Thank you, Dr. St. Martin. Question from Dr. Corash.

DR. CORASH: Can you just clarify? Is every product given some type of unique identification number, which ends up in a national database someplace?

DR. ST. MARTIN: The short answer is no. There is no national database for every product. Each establishment has their

own system for coding and it is maintained at the manufacturer's level.

DR. CORASH: And do they submit some type of an annual log of everything that they have prepared to FDA or some other agency?

DR. ST. MARTIN: Not to FDA, no.

DR. CORASH: Not to FDA. Does it go to any agency?

DR. ST. MARTIN: Not to any federal agency. I don't know even at levels AATB, I don't know that they require any type of reporting.

I know AATB does annual surveys but it is not a requirement.

DR. CORASH: There is not a legal requirement that says every product has to have a unique registration number that ends up in a national database.

CHAIR BRACEY: Mr. Brubaker.

MR. BRUBAKER: I can offer a little bit of information. Part of your question

about unique identifiers. And we required our banks to do that since the beginning but it is not a national system.

But our Board did vote to look into ISBT-128 as a coding system that our banks could use about three years ago. And we have a North American tissue technical advisory group, including folks from Canada. Some representatives from Europe as well and we are trying to develop a coding system using ISBT-128. So we see it as something that will happen down the road but to collect that data, we survey and we ask specific questions about how many donors are recovered, what types of tissues are processed and distributed. And we have a report coming out next week for 2007.

DR. CORASH: Well, I am assuming, maybe it is an incorrect assumption that organizations which collect and process tissues operate under some type of regulatory license or is that an incorrect assumption?

DR. ST. MARTIN: It is not

licensing if they are involved in the recovery of tissues or processing or any manufacturing step distribution. They must register with FDA and they must list the products that they are manufacturing and the manufacturing steps that they perform but they are not required to report back the specific products that they actually used or the numbers of products that they actually distributed.

DR. CORASH: So it is not like being a blood center in that sense where you hold an establishment license.

DR. ST. MARTIN: There is inspection. There is no licensing. The 361s HCT/Ps are not subject to licensure. And they are not subject to any pre-market approval. Basically what you do is you register as a tissue establishment and you can begin operations without any inspection or pre-approval. You are given a registration number, an ID number.

DR. CORASH: Was that identified as

a gap in what you think should be corrected to improve the system?

DR. ST. MARTIN: We did not identify that as a gap. That was how this was set up. These are, you know, I think one thing to keep in mind was the regulations were promulgated to address some specific safety concerns related to infectious disease transmission. And these parts that we have allowed to come under just the 361 authorities, for the most part, these were products that had been in widespread use for decades and had sort of a track record of safety and had been accepted by the medical community as efficacious. And there were a lot of public discussions and even some public workshops leading up to the rules.

So the rules were set up that way. It is not something we would identify as a gap. We could, not very easily but we could well have required that they be 351 products subject to licensure but we did not think that

they rose to the level of requiring demonstration of safety and efficacy when we knew that ACL ligament repairs you can -- cadaver tendons work.

CHAIR BRACEY: Dr. Kuehnert.

DR. KUEHNERT: Thank you. I just want to follow-up on that question because I think it is really important. There were two questions in there. One was whether a facility that is registered needs to have unique identification numbers for tissues. And then the other was that whether those numbers are stored in some sort of a national database.

Clearly the answer to the same question is no. But what is the answer to the first question?

DR. ST. MARTIN: Yes. Each product has to have a unique identifier, yes.

DR. KUEHNERT: But that --

DR. ST. MARTIN: But that is not anything that is -- it is not reported back to

FDA.

DR. KUEHNERT: Sorry. So that unique identifier is unique to the facility's tissues but not to other facilities. Is that correct?

DR. ST. MARTIN: Correct. It is not necessarily linked to other facilities.

DR. CORASH: So in other words, it sounds like, I don't know this process very well but it sounds like a tissue could be processed by multiple people out of a single donor, I guess a cadaveric donor.

DR. ST. MARTIN: Yes.

DR. CORASH: And so that donor, in other words, wouldn't have a unique identifier that tracks.

DR. ST. MARTIN: No, it would not but each establishment should be able to track where the process -- the tissues that they process.

DR. CORASH: Yes, but those mechanisms for tracking back don't seem to

exist. That sounds like a problem.

CHAIR BRACEY: Yes, that is I think a problem in terms of traceability.

Let me ask perhaps an analogous question and perhaps I remember this from a murder mystery. When implants that are prosthesis are placed, do those have unique identifiers and are traceable?

DR. ST. MARTIN: Are you --

CHAIR BRACEY: I am talking about metallic prosthesis.

DR. ST. MARTIN: I believe that those do have some type of serial number.

CHAIR BRACEY: Yes, so I find it quite unusual to put a non-tissue that probably has even less risk and would have a unique identifier. But for tissues that have greater risk though, the elevation of the risk is unknown, not to have that requirement just seems like that is a huge gap.

DR. ST. MARTIN: They do have identifiers.

CHAIR BRACEY: But they are not unique identifiers.

DR. ST. MARTIN: It is unique to the tissue. It may not be traceable all the way back to the donor. Each establishment may have their own unique identifier but they can trace it back to the donor from their own establishment records.

DR. ISON: I don't think --

DR. ST. MARTIN: But it is not a unique -- I think I see what you are saying. A unique identifier that every establishment that processes --

CHAIR BRACEY: Well not the establishment but the donor source.

DR. ST. MARTIN: It is not -- it is at the establishment level.

DR. ISON: And to complicate things, if they are an organ donor and a tissue donor, their UNOS number is different from their --

CHAIR BRACEY: Or an eye donor.

DR. ISON: Or an eye donor, exactly.

MR. BRUBAKER: But your concern is still covered by the processes that are in places. You are talking all about traceability of the graft or to the donor and vice-versa. And we can all do that by communicating together. When there is an issue, each establishment can do that job that meets your concern but there is not just one number.

And I think with medical devices, they don't have a national numbering system. So they are actually doing the same thing we are. They are able to track their product by that lot number.

DR. ISON: But it is a little bit different because it is coming from, it would be like manufacturing one prosthetic valve and using it in two different people and giving it a different number if you used in a second person.

MR. BRUBAKER: Yes, but the tracing that you are all worried about, it still happens. It can be done very quickly. Tracing to specific recipients, that is the other piece that I know is a concern, is not highly controlled, as much as it is with the manufacturer of the tissues banks.

CHAIR BRACEY: Right because there is no requirement for recording that -- Correct me if I am wrong but there is no requirement at the hospital level to have a hard-wired recording of that specific unique identifier.

DR. ST. MARTIN: Now, I believe the JC standards cover if it is a JC identifier.

MR. NETHER: Yes, they are supposed to track that all at the hospital level as well, that unique identifier that comes through from the tissue bank. They track all that. So that traceability can go all the way back. So it is bidirectional all the way from the donor to the recipient, recipient back to

the donor.

CHAIR BRACEY: Dr. Lopez-Plaza.

DR. LOPEZ-PLAZA: I just have a question and probably someone can clarify it. My understanding is that you know any tissue that is processed, manufactured, is assigned a unique number that is coming from that donor and that is the number that gets distributed among all sites that are going to use that kind of tissue.

And then once that kind of tissue is given to a patient, then there is something that says that this tissue is given to a patient but that is not a unique identifier of that particular fragment of that tissue to that patient. It is just the same number that came all along from the tissue processing place.

I mean, it is just like a blood concentrate, a factor concentrate. It has a lot number and then you don't change that lot number. You just put that lot number down as

what you use on that patient. Can you please clarify that for me?

DR. ST. MARTIN: That is not what is occurring for tissues. As stated, when you have organ, eye tissues, multiple tissues, the processor assigns their own identifying number.

CHAIR BRACEY: But I think --

DR. ST. MARTIN: And it is unique and they can trace that. They have mechanisms for determining who else receives tissue and organs from that same donor.

DR. LOPEZ-PLAZA: Okay, at the processing site, it gets a unique number. At the hospital it doesn't get a unique number.

DR. ST. MARTIN: No, no. It does not get another number at the hospital.

DR. LOPEZ-PLAZA: But somehow the person that has received that prosthesis or whatever, the name will be linked to that particular product that they used. It shows like to be one of 20 pieces that were

manufactured. Isn't that --

CHAIR BRACEY: Well, I think there is a lot of detail. I think that the key is that traceability is the key and the system should have robust traceability back and forth and however the system is structured, that should be the component. And I guess what I am hearing is that that exists.

DR. ST. MARTIN: It exists at the level of the manufacturer. There have been identified issues at the level of the recipient.

CHAIR BRACEY: Right, right. So what we are saying, I think a general consensus would perhaps be that it would be something to have at the level of the hospital as well.

Dr. Holmberg.

DR. HOLMBERG: I want to expand that thought. And it is something that I brought up earlier when Dr. Lazarus was speaking and that is the distributor. And I

guess that I have become more and more aware of the scope of distributors. And I have heard anecdotal stories of products being held in the trunk of their car in hot temperatures.

What really concerns me is the pedigreed status. I mean, within the pharmaceutical world, there is a real requirement to make sure that you track and have a pedigreed status on products. And so I am really concerned that we talk about the processor but it seems like this link in between which is growing because it becomes a logistical aspect and it becomes the link from the bank into the purchasing department of the hospital that is sort of well, yes, they are registered but who is really watching over them.

DR. ST. MARTIN: Just a comment on that. You know, every year the office of compliance develops a priority list of inspectional priorities. And what they have done, you know, they have worked with us with

whatever concerns we have had. And so one year it may have been recovery organization and it has been the cord blood banks, distributors. The intent is that they will do these targeted inspections of a particular category to determine what the issues are. And we have, over time, sort of fine-tuned what we meant by our definition of distributor and what we have meant by contracts, agreements, and arrangements to try to make it, I should say more difficult for some of these independent distributors to operate within the confines of the regulations. So that is how we are trying to address some of these issues.

So there may not be so much of that happening as may have been occurring when the rules were initially implemented and we were not fully aware of all the players out there. But at this point, there have been some inspections and we are trying to make it clear to individuals what they need to comply with.

You know, whether they can actually -- establishments that have contracts, agreements, or arrangements with these distributors are going to be held, you know, they have some level of responsibility for making sure that these contractors are complying with the regulations.

DR. HOLMBERG: Okay so maybe Scott can sort of clarify this for me because I am having a real difficult time trying to understand this.

The distributors are part of the -- they have to be registered. However, are they an intermediary between the tissue bank and the hospital? And if so, are they also under your standards?

MR. BRUBAKER: If the bank sending the tissue to a tissue distribution intermediary is accredited by the AATB, then Section M of our standards have to be followed by the intermediary, whether they are accredited by us or not because the source

bank who is accredited, it is their responsibility per our standards to audit that intermediary to make sure they are following all of Section M which has traceability, adverse outcome reporting to be frank about it, we have a section in there for the intermediary to follow but it is basically to take that report they might get, which they really shouldn't get but if they get it, they must immediately report it to the source tissue establishment because that is the place that can do the investigation. The intermediary can't. So we have taken responsibility away from an intermediary except when they get a report like that, it goes immediately to the tissue establishment, the source tissue establishment.

DR. HOLMBERG: But the bottom line is that we still do not know what happens to that tissue between the tissue bank and going to the hospital.

MR. BRUBAKER: Yes, you know, the

comments about having tissue in the trunk of a car and that comment was made again at the AABB meeting during a tissue session, and my response to that is if the hospital personnel know that happens, that is their responsibility. I know the tissue bank doesn't want that to happen. I can tell you that. It is their responsibility if a representative from a company, an intermediary has told them they do that. If they have knowledge of it, you know, the hospital personnel need to make sure that, tell them that you can't do that. We don't think that is okay. We won't use you as an intermediary or a distributor from now on. I think that has to be understood, too. There is a certain responsibility by the end-user if you have knowledge of that occurring.

DR. HOLMBERG: Well and I guess then my next question goes to The Joint Commission because now what you are saying is that the end-user has a quality issue of

making sure that they are qualifying their source.

And so does The Joint Commission have any standard concerning that?

MR. NETHER: Well I mean, we have standards with regards to when a tissue is received by the hospital, that they are supposed to check in terms of that was maintained at the temperature. There is nothing wrong with the tissue, etcetera. So they have to check that receipt. As far as with regards to the tissue establishment itself, and that is one of the questions that I had, is there any notification? It seems like we have a database with regards to the tissue establishments once they register. If there are any issues or problems found with that tissue establishment, how is that filtered back down to the hospital organization to find out that there are problems with their tissue bank?

DR. ST. MARTIN: I am not quite

sure -- and they depend on what the issue is. If there is a recall, then they would be informed.

MR. BRUBAKER: To actually get inspection information, it is freedom of information, you would have to submit to FDA to the correct office to get information on an inspection of a registered establishment. So you kind of have to go out of your way a little bit to do that.

CHAIR BRACEY: Dr. Corash, comment.

DR. CORASH: A very simple question. Who is actually the legal who is the supplier of the product? Is it the distributor or is it the tissue bank that actually prepared that product? I am confused.

MR. BRUBAKER: It is the tissue bank.

DR. CORASH: It is the tissue bank.

MR. BRUBAKER: Yes. We call them tissue sources.

DR. CORASH: Right. So it is a bit like when you manufacture a device or even a pharmaceutical. You have a supply chain where somebody has to certify all the steps in that supply chain. But it sounds like --

DR. HOLMBERG: Scott, could you please go to the microphone? Because we did not capture your response to the first question.

MR. BRUBAKER: I forgot what it was about.

I used the term tissue source facility because that is what The Joint Commission standards use often throughout the transplant safety chapter for the tissue section. So that is the tissue establishment. that is the registered place but also the distributors are registered as well and we call them a tissue distribution intermediary.

But again, those intermediaries, I guess they perform a function which is basically sometimes storage but of course

distribution, often storage.

DR. CORASH: But the ultimate responsible party would be the tissue source, in other words.

MR. BRUBAKER: Yes, per our standards, yes actually.

I just want to give you one example of where we realized we have to inspect the intermediaries a little closer.

The BTS recall was the Biomedical Tissue Services recall, I have slides on this but that was the largest recall in history that we have experienced. And the large majority of the grafts that couldn't be found, it was about 1200, if I remember correctly, but a lot of those involved distribution intermediaries. They are the ones that once they were really put to the task of being able to track the tissue to where they sent it, they failed. They had SOPs in place but when it was put to the test, they didn't work. And those were medical devices as well as tissue

devices, many of those and then the paste, putties, and gels. And others were just what we call conventional tissues.

But we identified that that is a problem that when we audit a tissue distribution intermediary. And we are coming up with some guidelines for that, that you actually test their tracking capability. Not just check for SOPs but see if they can track a number of grafts from the tissue bank.

CHAIR BRACEY: Dr. Holmberg?

DR. HOLMBERG: A quick question also for you, Scott.

DR. LAZARUS: Can I just -- I think I can say something that might be helpful, --

CHAIR BRACEY: Okay, Dr. Lazarus, please.

DR. LAZARUS: -- if you remember the question. Because I think I didn't spend enough time to the Committee the regulations regarding tracking. I see that now. And if I could just have half a minute to explain, I

1 think this might be helpful.
2 Distributors, as Dr. Holmberg
3 pointed out, are an interesting important
4 issue from a regulatory standpoint. As I
5 said, they are manufacturers. And as
6 manufacturers, they are required to comply
7 with the good tissue practices applicable to
8 the manufacturing steps they perform.
9 Tracking is a good tissue practice.
10 And I have a little copy of the regs in my
11 hand. I just might mention that the
12 regulation says you, the manufacturer, must
13 establish and maintain a system of HCT/P
14 tracking that enables the tracking of all
15 HCT/Ps from the donor to the consignee or
16 final disposition and back. So that is a
17 regulatory requirement.
18 If any manufacturer, including
19 distributor is not doing that, then the tissue
20 is violative and manufacturers are subject to
21 inspection and enforcement provisions.
22 Tissues that a distributor, a distributor

being a manufacturer, maintains in a way that would increase the risk of communicable disease because proper storage conditions as prescribed in the regulations have not been followed, then that tissue is violative.

So, hopefully that helps answer some of the questions about this sort of intermediary. From an FDA standpoint, that distribution step is a manufacturing step and tracking regulations and storage regulations and other applicable GTP supply.

CHAIR BRACEY: Right. I think the regulations are clear but I guess one question that comes up is the audit function and how robust is the test of compliance.

DR. LAZARUS: Right and that is an interesting point for discussion that I agree isn't entirely answered by what is in the regulations. But I think it is an important point to understand that inspectional provisions apply to distributors.

CHAIR BRACEY: Okay. Dr. Axelrod.

DR. AXELROD: Yes, because one of the things I am trying to get a handle on, is it, I mean, just as we in the blood center have to follow regulations and guidelines for how we handle the product and when it leaves our facility, think of us as the distributor or even if we are an intermediary because we import blood from another blood center. We always have to maintain those products within a certain temperature range, have documentation of that and so on and so forth.

And what I am trying to understand here is help us understand both. It sounds like there are regulations there so this issue of the trunk of the car is a violation. I mean, we could have blood in the trunk of a car and that would be a violation if that wasn't handled correctly.

But the process of regulation and the process of inspection and audit and ensuring that those regulations are followed much in the same way our tracking process is

followed all the way up to when FDA or AABB comes and inspects us. They will often look at our processes and make sure that we have the documentation that this product which was shipped to the hospital was kept between this temperature range, was packed accordingly, and so on and so forth.

Does the tissue bank system mirror that? I know the issue once it gets there is another issue. But does the tissue bank system mirror that for both regulation and inspection or audit?

MR. BRUBAKER: For the temperature requirements, when it is a controlled temperature --

DR. AXELROD: Handling the product, yes. I am using just all handling --

MR. BRUBAKER: Yes.

DR. AXELROD: -- just all handling.

MR. BRUBAKER: We have standards for the tissue establishment to follow that I have to qualify the containers used, validate

the procedures used. You know, how much refrigerant is added is on the outside label, the expiration date and time. That kind of thing. What kind of refrigerant, whether it is dry ice, wet ice, liquid nitrogen, that sort of thing.

So that is all in place and it actually fits in well with The Joint Commission standards because they have to check that at receipt of the tissue and make sure the shipping container is not damaged, the inside packaging is not damaged, that sort of thing.

CHAIR BRACEY: Dr. Ison.

DR. ISON: So, I have a question I think to get at the end.

So in the BTS case or even in some more recent cases, you don't have to give specific examples, I just want numbers. How many patients can you track down and contact and get tested if there is a recall or a problem with a donor?

DR. ST. MARTIN: That information would be at the level of the bank, the tissue establishment. That information is not reported back to FDA. Even the information about final consignee is held at the tissue establishment.

DR. ISON: And in that situation, the source tissue banks, as we want to call them, the processors, offered the testing, worked with I know FDA and CDC on actual wording to put in there but you know, and some of the distributors did that as well. But it really gets down to what does the end-user do? I don't want to call them hospitals. They are not all hospitals.

DR. ISON: Right. And that is what I am getting at. So how many patients, so what proportion of the patients that actually receive that tissue can we even find where they are?

MR. BRUBAKER: Yes, that we don't know.

DR. ST. MARTIN: No.

MR. BRUBAKER: I can actually survey the banks that were involved. There were only six and actually one of them doesn't exist anymore. But I could try to find out that type of information. It is very interesting.

CHAIR BRACEY: But I guess in an ideal world that would not be something that would need to be found out. That would be something that would be an absolute.

Dr. Pomper.

DR. POMPER: Just a clarification. If there is a withdrawal in the blood product and an end-user is notified, we cannot, or one cannot track it back to the donor. We track it back to our distributor, who can track it back to the donor.

So it sounds like the system is mirrored and I guess that is what the real question is. Is there that tracking back process? To clarify, as opposed to say an

inanimate object that could have a serial number on it, there is a concern about donor confidentiality which throws a monkey wrench into these processes but it is an important one. So there is a system to track it back to the original source but there is always an intermediary who carries that information, if that makes sense.

So an end-user does not know who the donor is even for a blood product and they know who gave it to them and the expectation is that that person or that organization can then track it back the next way. I just wanted to --

And I am assuming that that system exists in the tissue --

DR. ST. MARTIN: Yes, even in the absence of an identifier that is used by every single establishment, the difficulty has been at the level of the individual recipient. You know, just in the routine adverse reaction report investigations, we have had no trouble

identifying every establishment that has received tissue from a particular donor. The difficulty comes trying to identify sometimes every recipient of the tissue.

And as I mentioned, one example is even the reporter sometimes, you know, a dental office, may not be sure which tissue he used. He just knows that he used tissue in a patient and the patient had an adverse reaction. So it is at that level which would be outside of JC, where we have had some difficulty.

DR. ISON: But you really need bi-directionality. I mean, you have to be able to trace in both directions from the beginning to the end.

CHAIR BRACEY: Dr. Sarode.

DR. SARODE: I think that is a big issue. You cannot track in both directions. For example, the number you wanted that what happened to this particular incident where you identified infection at the source but how

many end-users that were affected. There is no way to try to trace at this time. I mean, that is a big problem.

CHAIR BRACEY: Dr. Corash.

DR. CORASH: So you know, this analogous in some ways that if you get a platelet component and you may split it into two pediatric doses and one child gets sepsis and the other child doesn't. But you then take that information and you bring it back to -- you may have bought that platelet component from another blood center and you can trace it all the way back and then somebody tracks down the red cells that went from that donation. Right?

DR. SARODE: Right. And that is the reason when you know, tissues are kept in the blood bankers they have nightmares because we are not able to trace back to individual recipient because there is no documentation in the chart that a particular patient received this particular organ or tissue, part of this

nerve or part of that skin. And that is a big challenge in the blood bank right now because clinicians, as end-users, they do not feel that these tissues can transmit in disease. They think that they are safe.

CHAIR BRACEY: So part of the issue is that the regulatory requirement covers the banks, the distributors or whomever but it does not cover the hospitals.

DR. SARODE: That is correct.

MR. NETHER: And that is where The Joint Commission bridges that gap because then the tracing starts from the time the tissue comes in to the healthcare organization to the time it gets implanted or transplanted into the recipient. That unique identifier number has to go through. They are able to bi-directionally trace from the recipient back to if it is the tissue establishment or distributor and from the distributor establishment back to the recipient.

CHAIR BRACEY: Well it sounds like

the system is designed so that they should be able to but there needs to be a more careful monitoring of what actually transpires because the rules are there.

DR. ST. MARTIN: If it is a JC accredited organization, it should work. We do have those facilities that are not operating under JC.

CHAIR BRACEY: Dr. Lopez-Plaza.

DR. LOPEZ-PLAZA: Okay. I mean I want to think, I mean this is a real example. What happened is that you have a surgeon that wants to do some kind of implantation and whoever is the person that holds the tissue they say send me these five different sizes. When that gets released into the surgical room, it doesn't go that those five things have been released to that particular patient and then at the end you get a feedback of which one of those five pieces were used for that patient. They just go out as something that someone asked no specifics. And then

when it comes back, I guess hopefully they will have a track system and they know what really got used and what got returned. Okay, so that is one thing.

The other thing that I have seen is that again you have like from a bone you make 1,000 pieces. This hospital purchased 50 of them. So what is going to happen that whenever you are using any of those 50 pieces, the only way you can track them, that serial number with the recipient is that if somehow there was something in the chart that says that that was put in the patient, the card that is supposed to be returned to the distributor that says that indeed one of, you know, manufactured pieces of bone was used on this particular patient, you are lucky if they return it. That is not controlled.

The Joint Commission is trying to put all those things together but so far I don't know how many of the people that use tissues all the time have been able to comply

because it is something very unstructured.

CHAIR BRACEY: So I think we have identified a point that we can continue to discuss, we are going to get to our point of discussion.

If there aren't any other unique observations or comments, we probably need to move on.

Matt -- Dr. Kuehnert?

DR. KUEHNERT: Let me just make one. We have sort of have captured one part of the universe but another part that we haven't as far as the gap is that remember that the FDA regulations are only for selected infectious disease. In other words, if someone implants a graft and it falls apart, that is not something that is required for a tissue bank to report it.

DR. ST. MARTIN: That's true.

DR. KUEHNERT: And what we have found not only for tissues but also for organs, oftentimes that is a clue that there

is a serious disease associated with that graft. And they may say well you know, there is no infection but clearly it is a proxy for an infection or a malignancy.

MR. BRUBAKER: And Matt, our guidance document is going to address that.

DR. KUEHNERT: Excellent.

CHAIR BRACEY: Okay, last comment, Dr. Corash. And then we will move on.

DR. CORASH: All right. Sorry. So just as a really high level commentary, my understanding is that the pathway for oversight for a blood component versus a tissue component is actually very different. And the question is, why shouldn't it be uniform.

CHAIR BRACEY: Correct. Correct.

Okay then --

DR. LAZARUS: You don't want an answer.

CHAIR BRACEY: Oh, okay. Dr. Lazarus, the ultimate comment.

DR. LAZARUS: No, I just want to say one thing. I tried to convey this in my slides but thank you for giving me an opportunity to make this point. That the 1997 proposed approach is a tiered risk-based approach. And as Dr. St. Martin pointed out, this was discussed in public meetings. There was a lot of public and stakeholder input into this. And the concept was that the less risky tissues would be subject to regulations solely as tissues. And those that are more complex, expanded cord blood, gene therapy products, are subject to pre-market approval. So there is a deliberate tiered risk-based approach to try to acknowledge that a one-size-fits-all regulatory approach might be excessively burdensome and not commensurate with the risk associated with certain categories of products. So that was deliberate.

Where were you back in 1997 when we were having these debates? I am sure that you are aware that rule-making is an interesting

and lengthy process but this all followed that process.

DR. CORASH: My only comment is that it inhibits biovigilance I think. That is the problem that we are struggling with now.

CHAIR BRACEY: Right.

DR. CORASH: It interferes with what we want as a good biovigilance process.

DR. LAZARUS: Let me just say, I mean, this has been a good opportunity to discuss where the regulations, and the accreditation standards, and the government biovigilance programs can all work together. No one part, no one set of regulations will address all the issues. Biovigilance won't address all the safety concerns. In fact, there are significant issues regarding tissue, infectious disease risks that probably can't be addressed under a biovigilance program. But I think what we are all discussing here is where all the different pieces fit together to

address all these myriad issues associated with tissue safety. But your point is well taken. The regulations alone cannot do that.

CHAIR BRACEY: But nevertheless, I mean, there is good tissue practice and there is good medical practice. And being able to know what went into a given patient is simply good medical practice. But that's it.

So, thank you so much for generating all that great discussion.

Our next speaker is again, a very familiar face. Dr. James Bowman and he is going to present the organ White Paper discussion. Dr. Bowman is with the Division of Transplantation for the Health Resources Services Administration, HRSA.

DR. BOWMAN: Thank you, Mr. Chairman. We are about 45 minutes behind and I am going to do my best to catch us up. Okay? Fortunately, a lot of the work has already been done by the colleagues and partners that you have already heard this

morning and you will hear more from a few tomorrow. So I am going to breeze through this fairly quickly. You have already heard that the blood and the tissue and cellular sectors are quite patchworked and fragmented and under various regulatory and oversight purview and solid organs are no different.

My whole purpose right now is just to address some of the background information that formed the Biovigilance Task Force White Paper. And as you can see from the alphabet soup up there, the federal government is involved in a lot of aspects of organ transplant, including regulatory, third-party payers, research and advisory capacities.

I work specifically for health resources and services administration. This is a sister agency of many of the other Department of Health and Human Services agencies and we all have a very similar vision, mission, and goals and comport with the Department's vision, mission, and goals.

Ours is unique in that it is primarily focused on access to vulnerable populations. And for this purpose, the transplant community patients and donors are vulnerable populations.

Specifically you already heard from Mr. Graham and also Dr. Ortiz that the evolutionary historical aspects of how the federal government became involved in the regulatory end oversight of solid organ transplantation. You don't need to take notes on any of this. If you want copies, they will be available and save yourself the time and trouble.

The HRSA also is the actual sponsoring agency for the Department's Advisory Committee on Organ Transplantation, which was alluded to earlier and they have some unique missions and objectives that are not necessarily common to this particular body today and tomorrow.

What we haven't discussed in

1 particular is what is an adverse event. In a
2 few minutes I will project up on the screen
3 the Centers for Medicare Services definition
4 of an adverse event from their Conditions of
5 Participation for the OPOs and the transplant
6 centers. Actually the OPTN I don't believe
7 actually defines an adverse event. In general
8 we have heard also from the FDA what their
9 definition of an adverse event is. And
10 generally, it is unintended, it is unexpected,
11 it is serious, life threatening, and I think
12 it is one of those things where you recognize
13 it if you see it, even though it is sometimes
14 hard to put into words.
15 For solid organ transplantation
16 purposes, generally we are talking about
17 infections and cancers. Not necessarily,
18 though. It could be transmitted contaminants
19 in a preservation fluid and used for organ
20 preservation. So it is not just infectious
21 agents.
22 It is also, adverse events are

transplant complications that occur in and around the operative period of transplant and post-operatively, especially with infections and also allow the complications such as immunosuppressive drugs which in and of themselves had powerful toxic effects on the biological immune system.

There are other non-medical origin adverse events that are somewhat related to things like logistics transporting organs across 3,000 or more miles and also countries between say Canada and the U.S. And these involve things like coordinating information, communications, and data collection. And so that is another source of adverse events.

There are some very unique aspects of solid organ transplant that increase the risk factors for adverse events. One of the key is that the recipient is usually highly immunosuppressed that we consider host immune responses and it makes them extraordinarily susceptible, as you will hear tomorrow from

Dr. Ison not only the usual sort of infectious agents that all of us are susceptible to, but also some very atypical infectious agents that have increased virulence. So that adds an enhanced dimension to adverse events in solid organ transplants.

Probably the other most important aspect about solid organ adverse events is that the solid organ transplanters do not have the luxury of leisurely working up and finding out all of the information available from a potential donor before they have time to retrieve the organs from that donor and transplant those organs.

In general if some person has sustained a massive insult and dies from either brain death or circulatory death, especially in brain death, there is usually less than 48 hours to make the proper arrangements to obtain those organs. And then once those organs are removed to the donor's body, in many instances like heart, lungs, and

liver, you usually have less than six to ten hours to get those organs implanted into the new recipient and that includes transport time, prep time and OR time and that type of thing.

So, the real challenge for the whole transplant community is to balance the goal of zero defects for the organs in terms of quality control perspective, along with avoiding wasting organs, that is good organs that may have a false positive test on a screening test but you don't have time enough to do a confirmatory test to exclude an infectious agent in that donor.

I think it is pretty apparent from discussion data that many different federal agencies are involved in various aspects of trying to minimize adverse events in solid organ transplants. HRSA itself has a role that you have already heard this morning. So in the interest of time, I am going to proceed. Let me just speak very briefly that

the next set of slides is primarily a specific delineation of some of the OPTN policies that have to do with the responsibilities of the host OPO and the transplant center, with respect to transplant safety and adverse events.

As Mr. Graham spoke earlier, the OPTN is composed of transplant hospitals and organ procurement organizations and histocompatibility labs. It is not composed of surgeons. It is not composed the transplant physicians. It is not composed of ICU nurses. It is not composed of OPO coordinators. And it is not composed of lab technicians. There is a lot of pieces the puzzle in solid organ transplantation where everybody has to work together with a certain level of trust and responsibility and professional integrity. And the OPTN can only do so much with the policies that it has available, with the tools it has available to affect the ultimate goal of making transplants

safe.

I don't think it is necessary to dwell on a lot of these particular OPTN policies. They are all designed to make transplants safe, in terms of organ donor evaluation. And the hand-off between the OPO, which is the organ banks and the transplant center and getting those organs to places where they belong in a safe fashion for all the recipients involved.

So there is a host of policies that are related to screening organ donors. This is the one for HIV. It specifically does not mention that NAT is required. It can be used but it isn't always used as we have heard before. There are similar screening policies for other medical conditions, infectious agents, and malignancies. This is a continuation of that and the key here is that the host OPO must take responsibility for informing the OPTN and also the transplant recipient centers involved of any known

conditions that it identifies that could be transmitted via that donor.

There is a policy on post-transplant reporting of potential transmission of disease or medical conditions, including malignancies. You heard about that earlier this morning and you will hear more about that from Dr. Ison tomorrow.

In a nutshell, the transplant program has a responsibility to inform the organ recipient of a confirmed positive transmissible disease that has been identified in a donor and it also has a responsibility to inform the OPO if the transplant center is the one that identified this. Sometimes it is actually the OPO that identifies this on the back end after the organs have been shipped out.

This has just to do with the similar reporting of malignancies that are identified and transplant recipients. I'm sorry. This is for potential transmission of

disease or medical conditions. And if it is a malignancy that is identified, the OPO and the transplant center both have shared responsibilities.

So let's get through some of these. They are useful reading material if you get real bored late tonight and you have already read the newspapers. This has been already addressed also again, it is the OPO responsibility to notify the OPTN contractor, which is UNOS, with a final report after it has investigated the potential for a transmissible infectious agent.

I am going to skip this because this isn't the focus of this discussion but there is an OPTN policy on submitting living donor deaths and organ failure in living donors.

Let me very briefly mention, since CMS is not here today to be represented and I don't want to speak for them. But we have been informed earlier today of the Conditions

of Participation that CMS has for the Medicare program for the OPOs and the transplant programs. A transplant program for CMS purposes is a unique organ transplant program, say a heart transplant program, a lung, or a kidney transplant program. And a transplant hospital may have one or more transplant programs. Each transplant program has to be certified and approved by CMS to participate n the Medicare program to get paid for transplanting Medicare patients/beneficiaries.

So, CMS does have a definition of adverse event and it is not for -- this is for OPOs. And as we discussed earlier and just as you would expect, it is serious. It could cause death or serious injury. And as applied to OPOs, adverse events include but are not limited to transmission of the disease from a donor to recipient, avoidable loss of a medically suitable potential donor for whom the consent for donation has been obtained and delivery to a transplant center of the wrong

organ or the organ whose blood type does not match the blood type of the intended recipient.

I am going to skip over some of these other Conditions of Participation in the interest of time for the OPOs. For the transplant programs, the CMS has a very similar definition of adverse event and they provide some examples of adverse events that would include but are not limited again to serious medical complications or death caused by living donation, unintentional transplant of organs of mismatched blood types, and transplant of organs to unintended recipients, and the last one is particularly important for this session, unintended transmission of infectious diseases to recipient.

As some of your are aware, there are some infectious diseases that you might say are not necessarily intended but they are expected and common in transplant recipients. CMV is the most notable. If you have a CMV

donor who has a positive CMV serology and a recipient, often it is a child, it is a recipient of a heart, lung, liver. That recipient very often will sustain a CMV infection and this is not intended to, an adverse event is not intended to encompass that. That is the reason for that phrase.

There are other conditions on transplant programs that I am going to gloss over right now. The key point of all these CMS policies, I'm sorry, CMS Conditions of Participation, is that the transplant programs have to have policies in place to effectively identify adverse events and take action after a thorough analysis of those adverse events when they are identified and occur to try to make sure that they do not happen again.

And with respect to the Biovigilance Working Group White Paper, there were two gaps that were noted and included. That doesn't mean that just because there were only two that they are not necessarily

significant.

As alluded to earlier, there is a lack of a nationwide common organ tissue donor networking system for real time reporting, data collection, communication, and analysis of donor-transmitted diseases. That is what you all were discussing for about the last 45 minutes, partly. There is no single number that you can look up that identifies the 37 or 40 percent of donors who are common to both solid organs and tissues. Okay? That is something that is different than in the blood community. You don't have to worry about common donors in the blood community. Okay?

So the concerns of trace-back and trace-forward are there also but to try to trace back to a particular donor, it stops at the level of the tissue bank or the organ procurement organization that happened to procure that donor. And then they get on the phone and talk to each other very quickly when something is identified but it is done all

very informally, although I would say effectively.

The second gap is, as was mentioned earlier, there is no requirement by Dr. Kuehnert, there is no requirement to retain donor recipient samples. That doesn't say that the system as it is right now, such as it is, it is not really a system, but organ banks, hospitals, histocompatibility labs, dialysis facilities for potential renal transplantations, all these facilities do keep samples, blood samples. They keep other samples, pathology specimens. But they are for variable lengths of time. There is no uniform consistent policies in place and so you never know exactly what sample is available, when it is available and where it might be available for any particular problem that could arise in trying to identify an elucidate the nature, especially an emerging infectious agent but even the common ones that are seen.

So, in that sense of the word, one goal of the National Biovigilance Program would be to have some consistency and uniformity in a policy that would assist with that.

I believe this is the last slide, if I am not mistaken. As I alluded to earlier, there is a balancing act in the sector of solid organ transplants. People who are waiting for lifesaving solid organs vastly outnumber the availability of those organs in our current, in the United States.

To put it in a nutshell, people are dying on the waiting list every day for livers, kidneys, hearts, lungs, pancreas, and intestines. And because of that, there is a sense of urgency within the community to try to obtain all of the available good, safe organs, possible. On the other hand, that has to be balanced against the risk of allowing a bad bug, so to speak, to slip through.

And I already mentioned the sort of

logistical problems with shelf life of organs and the problem with working on a very limited time frame usually within 48 hours to retrieve organs when a potential donor is identified.

So having said all that, as Dr. Humar and Fishman alluded to in their editorial in 2008, having said all of that and looking at the very effective and successful track record of solid organ transplants in this country over the last really 30 years, in spite of the patchwork and fragmented system, there is room for improvement. And as Doctors Human and Fishman noted, it is primarily in the realm of donor screening and timely detection of adverse events. Not a month later or three months later or whatever but more like real time when it occurs and improving the communication when those events are detected. And then also, using the tools that are available with current technologies and hopefully future evolving technologies and public health investigational tools to rapidly

deploy those measures needed to deal with an isolated event when it does occur, albeit infrequently.

In included some references which I think you have most of the copies. At my particular agency that I work for, we are always available. We cannot solve all the problems that are addressed to us. There is a huge patchwork of providers and as you sometimes hear called intermediaries involved with the complex process of transplanting an organ, which is done over a very short time frame from the moment a potential donor is identified in getting that organ finally into a transplant recipient, usually over the course of about 36 hours. And so it involves a lot of hand-offs, a lot of people, a lot of organizations, and it does have to involve a lot of trust but there is also a lot of accountability.

And there is also a lot of avenues for remedy when people feel like they may have

been wronged or if people feel like there are problems. And so I won't go into all those avenues but we are available. We are open to suggestions. We always take suggestions at both the Department level and our Agency levels.

So, thanks, Mr. Chairman.

CHAIR BRACEY: Thank you, Dr. Bowman. Questions? Comments? Dr. Williams.

DR. WILLIAMS: Jim, how often, if ever, would a transplant go forward when there simply wasn't sufficient time to complete all of the relevant infectious disease testing?

DR. BOWMAN: I can't give you an exact percentage. There is a provision in I believe it is OPTN policies and CMS conditions for certain extraordinary situations with recipients that the transplanting surgeon may still elect to accept a particular organ, knowing that not all of the tests have been done but knowing that the particular recipient is in such dire straits that to forego that

organ may mean that potential recipient is going to die in the next, say week or two or three weeks and another organ won't be available.

And I would have to defer to my OPTN and UNOS colleagues to see whether that is actually in the policy of the OPTN or if I am mixing that up with a CMS Condition of Participation. There are some very special circumstances around that. But at this point, as I alluded to earlier, NAT testing, NAT tests are not required because they are not specifically available in every single area of the country where donors become available. And so that is the concern that has been addressed during the course of probably a year and a half at multiple levels.

DR. ISON: So policy 4.1.3 is what he is referring to.

DR. BOWMAN: It is an OPTN/UNOS policy. Thanks, Mike.

CHAIR BRACEY: Additional questions

or comments?

Dr. Triulzi.

DR. TRIULZI: Does the donor testing have to be done in an FDA licensed laboratory?

DR. BOWMAN: I glossed over the slides. It has to be an FDA licensed donor screening test. And if a donor screening test is not available, if I am not mistaken I believe OPTN policy says that an FDA licensed diagnostic test may be used but it does have to be FDA licensed or approved.

DR. TRIULZI: So I learned from Michael that some of the OPOs do the testing.

DR. ISON: Most of them do.

DR. TRIULZI: Right. And so are they FDA licensed facilities?

DR. BOWMAN: No. The facility itself doesn't have to be licensed. It has to be done --

DR. TRIULZI: Or laboratory.

DR. BOWMAN: Yes, it has to be done

--

DR. TRIULZI: Is there a laboratory? Generally not.

DR. BOWMAN: But it has to be done by a licensed test.

DR. TRIULZI: Well that is a different question. Yes, is the laboratory -- like blood. To screen blood, it has to be done in an FDA licensed laboratory.

DR. BOWMAN: I don't think OPTN policy says the laboratory has to be licensed.

DR. ISON: The policy is silent on the laboratory. Just on the test.

CHAIR BRACEY: I would imagine that CLIA, a CLIA-approved laboratory would be the requirement because of the time crunch, as the minimum.

DR. BOWMAN: But all the OPOs do use sources of tests that are either FDA licensed for screening or diagnosis.

CHAIR BRACEY: Dr. Kuehnert?

DR. BOWMAN: So again, the

standards are very different for organ screening.

CHAIR BRACEY: Right.

DR. KUEHNERT: I wanted to ask about the comment that is often made about organ transplant being different because of the urgent need to recipients. And I am wondering how we sort of understand that as a spectrum because a lot of times I think people see that as all organ transplants when there are organs that are urgently needed, depending on the organ and the recipient, potential recipient status on the waitlist. And then there are those that for instance a patient who is on dialysis receiving a kidney or perhaps the urgency isn't quite the same although the need is very much there. And I am wondering how you would suggest that could be looked at from a risk benefit or safety and availability sort of spectrum.

DR. BOWMAN: Again, that is a good question. It gets back a little to Doctor was

it Williams who asked me a few minutes ago about how often is the test just simply not done. And for NAT testing, I will be honest with you, I am not sure if we have access to that data. Those OPOs that do the NAT testing do them because they have access 24/7 to the standard NAT test methodologies that are out there. All of the organs are tested with serology for HIV, HBV, and HCV. So the serology is not an issue. So what you are really trying to narrow the question I think down to is if you were to implement a policy that NAT testing should be done on all organs, with the exceptions, how would you configure those exceptions.

DR. KUEHNERT: Well the problem is that you can't just say well for all kidneys it needs to be screened. Because of course the organ donors have multiple organs and they are screened according to the donor, not according to the organs. And so it can't really be done that way but really if you

think of it that way, it would seem that there are some organs that should be screened more rigorously from a safety standpoint.

DR. BOWMAN: I think it is safe to say, and my colleagues from UNOS could address this a little bit better than I can, there are situations where for some donors whether or not they exhibit high risk behaviors or there are other aspects involved with that particular donor, the heart surgeon may elect to go ahead and accept that heart for a patient who is maybe a status one that is going to have an expected life expectancy of one week or two weeks.

On the other hand, the kidney surgeon may decide he or she does not want to take the risk of accepting kidneys, knowing that another kidney may come available in the next month or two when the person does have alternative to dialysis. So, again that is a difficult -- but that does happen at the OPO level, where organs are used that have need

for certain recipients but are not used from that same donor because the need of the particular recipients isn't as great.

CHAIR BRACEY: We have three comments or questions and then we will need to move on. I have Dr. Triulzi, Dr. Sarode, and a comment from the floor. You want to go ahead with your comment or question?

DR. METZGER: Yes, I was just going to respond a little bit. This is Dr. Bob Metzger. I am the Medical Director at UNOS.

CHAIR BRACEY: Can you identify yourself, please?

DR. METZGER: Dr. Bob Metzger. I am the Medical Director at UNOS --

CHAIR BRACEY: Okay.

DR. METZGER: -- and also of a couple of other organizations.

In response, usually we will have our serologic testing done within six to ten hours of the consent process. And at that point in time, you can run a match run because

a lot of patients are taken off the waitlist if you have a hepatitis C positive donor or hepatitis B or something like that. So you run the match run then.

And as Dr. Bowman said, you know, you might turn down a kidney on a patient that has a high-risk behavior or a CDC or a Public Health Service high-risk behavior but the heat, lung, and liver may go with that.

When you have a standard donor, though, you can't really delay not taking the kidneys out because the recovery teams all come at the same time. So you are going to take those kidneys out and then your efforts at preventing delayed graft function and the need for further dialysis are based on getting those kidneys as rapidly as you can. So you can't sit around with the kidneys. You could, on a machine or something and wait for further testing to be done but it is rarely done that way.

CHAIR BRACEY: Thank you. Dr.

Triulzi.

DR. TRIULZI: I was just going to make the comment that I think the rate-limiting factor in time for testing is more in the organ preservation as opposed to the unusual circumstance where the clinical situation isn't the time. It is more how long can you hold the kidney, the heart, lung, liver, before it needs to be used. That is the limiting factor. It is rarely that the patient is so ill that they can't wait. That happens but that is not the primary reason that that window is too short to get NAT testing done.

But I think that that should be a hurdle that we can overcome eventually.

DR. BOWMAN: It is important to remember that when somebody has died from a brain death, it is not like the movies where you can just keep that person on machines forever. There is a physiologic process that take effect that has a very rapid downward

spiral over the course of about 48 hours. And sometimes the OPO team is already well into that 48 hours by the time they are able to actually get the family to consent to organ donation and to make the necessary preparations through the UNOS matching system to even identify which transplant teams will be available to retrieve those organs.

So the window becomes very, very short and if it is, as mentioned earlier, in the middle of the night, often in certain parts of our country, the standard NAT testing is just not available like it is pretty much on a daily basis, through the blood banking community.

CHAIR BRACEY: Dr. Sarode, last comment and question.

DR. SARODE: I am hearing there is a concern about false positive test results but isn't that more common with serology than NAT testing?

CHAIR BRACEY: Well yes, I think

that may be part of the problem but again, I think the major problem is the issue of delay and organ preservation. And that is an area for future --

DR. ISON: I think that the other problem is that there is no data. You know, we don't collect any information about NAT testing of organ donor -- you know, we don't even know if it is done or not on a particular donor. It is not part of the data that is collected by UNOS currently and there is no standards that are in place for confirming whether it is a true positive or not.

And that is a bit of a challenge in the organ community because unlike blood where many groups are using the multiplex tests that have a confirmatory step built in, many of the OPO labs are using singlet tests that don't have that confirmatory step built in. And likewise although we report the positive results, there aren't attempts usually to look back and see are the serologies truly positive

or not.

CHAIR BRACEY: Okay. We are at --

DR. SARODE: Well, there is data from the blood donors where you see that serology is more false positive than NAT testing.

CHAIR BRACEY: So we are at the break now. And so we will break for 15 minutes and then reconvene with public comments and then Committee discussion.

(Whereupon, the foregoing meeting went off the record at 3:00 p.m. and resumed at 3:16 p.m.)

CHAIR BRACEY: Now we are at the point of the meeting for public comment. I have three submissions for public comment. Any additional? Oh, sorry, actually two.

So the first is from the American Association of Blood Banks by Dr. Whitaker. And it is on the AABB support of gap analysis and an update on hemovigilance.

DR. WHITAKER: Thank you.

AABB appreciates the opportunity to provide the Advisory Committee on Blood Safety and Availability with a brief update regarding hemovigilance activities and in the broader context, the efforts of the International Organizational Task Force on Biovigilance to establish the US Biovigilance Network. AABB commends the Department of Health and Human Services for its work in preparing a gap analysis of biovigilance activities within the federal government. The paper offers important background and analysis of the existing government programs touching upon blood, organ and tissue safety monitoring. However, because this paper focuses mainly on government activities up to a certain time, it does not provide an entirely complete, up-to-date picture of hemovigilance efforts.

Today, I would like to focus on the considerable progress that the public and private sectors, working together, have made in advancing hemovigilance efforts in the

United States as well as the challenges that remain to realizing a robust system which can best lead to improvements in patient care and donor health.

AABB is extremely pleased that the hemovigilance module of the National Healthcare Safety Network will open to all interested participants beyond its current nine pilot sites in January 2010. Over the past year, AABB has worked closely with CDC to recruit and educate the nine hospitals participating in the pilot and worked to improve the system to address issues raised by the pilot participants.

AABB has also expended considerable effort in promoting the hemovigilance module to hospitals across the country with the intent that significant numbers of hospitals will join the system when it becomes fully operational in January. We have held regional recruitment meetings in 11 cities, spoken at numerous regional blood bank meetings in 2008

and 2009, published articles, hosted audio conferences and offered related programs and educational opportunities during our annual meetings in Montreal and New Orleans. Stemming from these efforts, over 60 hospitals have indicated that they will join once the pilot is completed.

In addition, with the support of HHS and strong participation from the private sector, the donor hemovigilance system has been piloted with small, medium and large blood centers. Preparations are underway for full implementation of this system in early 2010.

While this progress is notable, significant challenges remain before a robust, high quality program can lead to meaningful patient care advancements. In today's economic environment, funding for both public and private sector efforts continues to be uncertain. On the private sector side, AABB and our members, many of whom have already

contributed generously to the initial funding for this initiative, cannot afford to financially support biovigilance to the degree we have to date.

Increased federal funding to support the program, including the essential private sector role, is absolutely critical. AABB would like to highlight for the committee the following areas where committed, sustained funding from the federal government is needed to support the private sector role.

Recruitment. Considerable effort is needed to inform and educate hospitals about the significant value of this program.

Education. As hospitals begin to participate in the hemovigilance module, their staffs will need to be educated about the myriad definitions and issues that might arise, so that standardized reporting is assured.

Quality Control. Funds need to be dedicated to data review to assure that data

reported into the system meet the protocols.

And analysis. Finally, considerable funding will be needed to support the analyses of the data to identify optimum interventions to improve transfusion safety.

We recognize that today the Committee is focused primarily on organ and tissue safety. AABB supports expansion into these important areas for patient safety and notes that a robust and financially sound hemovigilance system is a key first step to expansion into tissues and organs. Without a strong private-public collaborative network, including infrastructure of electronic systems and qualified experts working towards the desired patient safety improvements, there is no solid base to expand into these next arenas.

Therefore, AABB urges the Committee to continue to be vigilant about hemovigilance. Your previous recommendations have led directly to the progress that has

been made to date in advancing blood safety surveillance. AABB hopes that the Committee and HHS will promote increased, sustained funding for both the public and private sector roles to support the ongoing collaboration to advance hemovigilance and improve patient care and blood donor health.

Thank you.

CHAIR BRACEY: Thank you. Questions or comments? If none, then we move on to the presentation of the Red Cross working committee for blood safety. And I am not sure who is going to present but I have two presenters.

MR. FILLER: Good afternoon, Mr. Chairman.

CHAIR BRACEY: Could you introduce yourself, please?

MR. FILLER: Yes. My name is Michael Filler. I am the Associate Director of the Public Services Division of the International Brotherhood of Teamsters. I am

kind of a stand-in. Our lead spokesperson, Ann Converso who is a registered nurse and the head of the nurses' union at AFL-CIO, was scheduled to be here but a member of her family became very ill. So I apologize on her behalf.

So I am here this afternoon to summarize her statement and we are also submitting a more comprehensive written statement in to the record that I know you can't get to at this moment in time. But when you do, we are more than willing to supplement the record to answer any questions that you might have.

But I am here today representing the Red Cross Workers' Committee for Blood Safety, and thousands of frontline Red Cross blood workers from across the country. Our members are key stakeholders in the blood safety and biovigilance community. We place the highest value on improving blood collection procedures that are in the interest

of public health.

Our Committee believes there is a strong correlation between maintaining high standards for blood and donor safety, and employing experienced and well-trained frontline blood drive workers, who perform their critical duties under suitable working conditions. For biovigilance to be effective, blood collection organizations must retain a competent work force that is effectively managed.

Unfortunately Mr. Chairman, based on information we have gathered from Red Cross blood drive workers, these conditions are not being met. We have received recent reports of widespread concerns at Red Cross locations across the country. And allow me to focus on some of the conditions that raise safety concerns and then address how these conditions may detract from biovigilance programs.

The first issue I will address is employee turnover, a long-standing problem at

the Red Cross. A primary contributing factor has been the implementation of a human resource strategy of driving down wages and benefits while increasing the workload.

Work hours are often lengthened, because blood drives are artificially overbooked. The Red Cross account managers have a "bonus system" that provides financial rewards when blood drives exceed the collection goal. This incentivizes account managers to low-ball their estimated goals and overbook drives. Despite reports that turnover at Red Cross is higher than 30 percent annually, management has said it has no plans to address this problem, because they believe people can be recruited under the current wage scale. Such policies, however, result in a high concentration of inexperienced blood drive workers, who are more prone to errors.

Red Cross has also impacted the quality of its staff by eliminating or

reducing the number of licensed nurses who work blood drives. In many regions, the number of licensed nurses have been cut by two-thirds over the past ten years.

Another problem is the quality of supervision. We have received reports about individuals, some of whom were previously employed at fast food restaurants, placing too great an emphasis on collecting blood, while demonstrating too little concern, or lack of understanding, with regard to safety for donors and the blood supply. For example, when a question arises about a donor's travel history, some supervisors are too quick to approve the donor rather than have the collections specialist continue with questioning to sort out gaps or inconsistencies in the donor's travel history.

These critical staffing issues leave Red Cross unprepared to address anticipated personnel shortages resulting from the pandemic H1N1 virus. At least one Red

Cross region is already experiencing staffing problems due to an increase in employees on sick leave with the H1N1 flu.

The issues and practices that have been highlighted affect hemovigilance in a number of ways. While reporting of serious adverse reactions is generally reliable, under-reporting is not uncommon for less serious reactions.

Several practices contribute to under-reporting. First, paperwork does not always follow donors after they complete their donations. Second, under-reporting is more prevalent at large blood drives, where under-staffing exists, because there is not enough time to make sure that reports are completed. Third, we believe that licensed nurses and experienced staff are more likely to report adverse reactions because they are more knowledgeable of the potential ramifications if documentation is overlooked or incomplete. And finally, reporting is more consistent and

thorough when the supervisor responsible for the drive has received the proper medical training.

The Red Cross Workers' Committee for Blood Safety provides an important voice for frontline blood workers. Given our role, we are uniquely positioned to make substantive contributions to blood safety policies and procedures. It is within this context that we seek to establish an ongoing working relationship with the Advisory Committee and its constituent groups. Our recommendations are as follows.

One, we would like the ability to conduct quarterly meetings with the Advisory Committee and our representatives to address concerns raised by frontline workers and to provide our members as a resource to the Committee with an opportunity to solicit our input on policies and procedures that impact blood drive settings.

Second, we would appreciate and

faithfully carry out the responsibilities as a representative of this Advisory Committee and we would welcome the opportunity to be appointed.

Number three, we would like to see our facilities enroll in a number of the upcoming hemovigilance pilot projects, so that you can collect data from our workers.

And lastly, we would like the Committee's assistance in facilitating meetings with other constituent groups, including key professional associations, blood collection organizations, and blood recipient advocacy groups.

And thank you for considering our input today. We are willing, as I said earlier, to supplement the record with written answers to any questions you may have, once you have had an opportunity to review our written testimony.

CHAIR BRACEY: Thank you, Mr. Filler. I think, you know, clearly the

Committee is interested in hemovigilance. And by having a robust system, we will be able to clearly address some of the issues that you have stated.

Any other questions or comments from the Committee? Dr. Williams.

DR. WILLIAMS: Thank you for your report. Your report contains a number of generalized statements. And I am curious, did you conduct an objective survey or some other means of objective data collection to support the statements?

MR. FILLER: We did survey our members, the union members who are represented by both Teamsters and other unions within the AFL-CIO. With me this afternoon is one of our coalition members, Ed Thegan, who can better describe the types of questions that we raised there and the process that was used. But yes, we did collect this information nationally from the people we represent.

CHAIR BRACEY: Yes, Dr. Hollis.

DR. HOLLIS: What kind of process have you identified in the constituents to correct the situation?

MR. FILLER: Well, in each location, we engaged in negotiations when those contracts were opened and that process has been a very difficult one. So we are, in part, here today hoping that we could create a national forum to have some of these problems addressed. We have written to the head of the red cross and we are trying to arrange a meeting there as well because we think some national oversight and assistance is needed to implement these programs and these policy changes at the local level. It is a work in progress.

CHAIR BRACEY: I believe Dr. Holmberg has a comment.

DR. HOLMBERG: Thank you, Mr. Filler. What I would like to say is that we do have a process where we ask for candidates for the Advisory Committee and that is usually

on an annual basis sometime around the June time frame. It is posted in the Federal Registry notice. And we have already posted the names for this year for those individuals that we will the vacancies coming up with. it is a slow process. It takes a lot of review and buy-in from the White House liaisons also.

But I would just encourage you and I will try to make an effort to make sure you are aware of when the Federal Registry notice is as I try to do with some of the other major groups.

MR. FILLER: Thank you.

CHAIR BRACEY: Thank you. We appreciate your comments.

MR. FILLER: I thank the Committee and I wish everyone a Happy Thanksgiving.

CHAIR BRACEY: All right. So we are now at the point to being Committee discussion of what we have heard thus far, recognizing that we have a lot more to hear tomorrow with specific reference to solid

organ transplants.

And one of the things I thought I would do is to go back over the question which I had temporarily misplaced but I know have. And again the question to the Committee relates to comment on elements that would characterize a more robust and transparent decision-making process for organ and tissue transplantation safety policy. In particular, the comments are being sought on mechanisms to identify and address information gaps. Examples are given in terms of federal government using its leverage to leverage the resources of this Agency's industry and health sector partners to data on infectious disease risk of organs and tissues, what approach is maybe used to gauge and encourage willingness of industry and healthcare sector partners to participate in data collection and research projects with federal government.

Then going on, a comment on the types of tools of policy analysis that may be

used to enhance the current decision-making process, such as risk assessment, cost effectiveness, utility modeling, etcetera. And then what steps, if any, does the Committee recommend to enhance the quality and transparency of the federal decision-making process for organ and tissue transplantation.

And I guess I would like to start off by saying I think a point that resonates fairly clearly for me is that there is a lack of information, in terms of the risk. So that absent information related to the risk not only of infectious diseases transmission but all adverse events associated with this procedures, we are sort of, our ability to assess policy and make decisions is impaired so that, I mean, I will just start off with that as a starting point. It seems to me that we need to, as a nation, figure out a better strategy so that we really understand the hazards associated with these life saving interventions so that we can generate sound

policy and recommendations. But I will just start off with that.

Dr. Ison?

DR. ISON: Yes, and I think that that is actually one of the key points. You know, I am in charge of the committee at UNOS that has been charged by the Board to estimate the risk of infectious disease and disease transmission through organ transplantation. That is one of our goals. And the reality is, as I will show you a little bit tomorrow in the presentation and I think as you pointed out, unless we have some numbers, we can't really assess that risk.

And so we are challenged on both sides. And I think that we have heard some things today and we will hear some more tomorrow but donor screening, you know, we don't have robust data on all tests that are being done. At least in the organ field we only collect data on donors in which at least one organ is procured and there is a number of

donors that may not be used for which there is no data collected.

There is no data collected on non-required tests. So there is no NAT test results that are collected in a uniform fashion. There are some OPOs that do things like Chaga testing, West Nile Virus testing, things that aren't required, that aren't collected in any way. And so without that, it is actually hard to even make any inferences as to whether or not those testings should be done in the organ population.

Further, there is limitations to testing post-transplant to the recognition of disease transmission and that is a real problem. Thinking more about what we have heard about today, we really need to get a better sense of a numerator and a denominator. And I think unless we can track who is getting all of the organs, tissues and blood products, we really have a hard time even recognizing who we should be looking at to

assess for risk.

And I think for organs, at least, which is the only group I can personally speak for, I think we know who is receiving which organs and can track those individuals but I am not sure from the data that we have heard today that at least on tissues that we can track all recipients of tissue. And so I am thinking about ways and research to understand how to better track and monitor those patients is the first step, before we even consider doing any additional testing or study of those recipients to see if there is a disease transmission.

CHAIR BRACEY: Dr. Lopez-Plaza.

DR. LOPEZ-PLAZA: One of the impressions I got from all the presentations today is that we are completely dependent on passive reporting to understand or to even capture any adverse events. Maybe perhaps we should be really thinking and this even includes blood. That maybe we should think

about pilot where we could do an active surveillance, maybe a 24 to 72 hour period and see what comes from that. And not only for any what looks like an infection complication but any kind of adverse event and see what things really come out of that because I think we would learn a lot more.

CHAIR BRACEY: One thing that also seemed to also resonate is that the regulatory structure is structured in such a way that the procuring entities are regulated and, to some degree, that translates to the distributors. The place where it happens, the hospitals, while they are, unless I really missed something, they are sort of a dearth of, there is control because there is a requirement from The Joint Commission to follow given procedures and processes. But I guess the thing that bothers me to a degree is that when you hear the conversation about well what happened with certain events, that even though a structure exists, it is not necessarily

being followed.

And so I guess I wonder, is there a way, number one, that the system could be made more robust on the users side. And so in terms of the question of leverage -- so I guess I will just throw out a question because we have heard that through the process that the OPTNs, etcetera, and their Conditions of Participation with CMS that have to be met. And a question is so could the tracking, the record keeping, if you will, be improved if that became a Condition of Participation. So I will just throw that out to see what the thoughts are from the Committee members.

Dr. Ison?

DR. ISON: I mean, it definitely seems as though it would be away of requiring the hospitals which we currently have no regulatory oversight over to do some degree of tracking and then would have infrastructure from CMS for monitoring and ensuring that that tracing was being done appropriately.

CHAIR BRACEY: Dr. Kuehnert.

DR. KUEHNERT: So we have seen a review of Conditions of Participation for organ transplant centers but what Conditions of Participation are there for tissues?

CHAIR BRACEY: That is the question and I would think that perhaps the same --

DR. KUEHNERT: So you are saying to develop?

CHAIR BRACEY: To develop, yes.

DR. KUEHNERT: Okay.

CHAIR BRACEY: Something, again, recognizing that currently that should be happening but from the stories that we hear it is not.

And so the question specifically directed to us is there something that the government can do to leverage its resources.

DR. KUEHNERT: The question I would have is what do we do in the meantime because it takes so long to create regulations, you know, as we heard from FDA.

CHAIR BRACEY: Right. Dr. Triulzi.

DR. TRIULZI: Yes, just to address Matt's point. In the blood product field, you know, AABB remains a voluntary accreditation but when it is linked to CLIA, the teeth in meeting AABB come with reimbursement. If the same teeth were applied to tissue, in other words, if you want to be reimbursed for tissue you have to be accredited and it might by AATB or AABB, I don't know at this point now which one would be fastest to do it but that might be a strategy that would get the hospital to a point that well we have to do this if we want to get paid for these tissues.

Right now for voluntary accreditation, what drives a lot of the AABB participation in addition to just it is good medicine and is good practices.

CHAIR BRACEY: There is one question that I have got in that regard and that would be the degree of specificity that we could have. Because in the general

accreditation view, and Mr. Nether can you comment, the TJC accreditation could be used to say that, and I don't know that we would be able to specifically say, well, you know, you need to go get accredited by AABB or AATP, someone that has a focus on this.

MR. NETHER: Yes, I mean, the requirements are already in place. One caution I have for the Committee is we heard today that we couldn't trace, in terms of tissues, where did that exactly drop. What was the root cause? You know, we are hearing right now the recommendation for CoP to be addressed all the way through but if it is getting dropped by the distributor, there is already a CoP in place for the distributors, isn't there? Or I mean, there is already requirements in place for tracking.

DR. AXELROD: But we heard that the disconnect is at the hospital. It sounds like the oversight actually up to the distributor seems to be covered.

CHAIR BRACEY: Yes, that is a point that was made by Mr. Brubaker, I believe because the tissue banks have oversight over the distributors. Dr. Sarode.

DR. SARODE: Yes, I think if The Joint Commission thinks that they already have in place a process for tracking each and every tissue, I think that needs to be emphasized. Because the whenever we have our joint commission inspection, no one even cared about they were worried about tracking tissues. They were worried about tracing the specimens from the patient to the lab and back to the patient. They were worried about blood. So they would come and make sure that the sample was drawn properly on the patient, it went to the blood bank, we did the work properly, and the unit was dispensed properly, and there was a trackability. But that is not happening with the tissues.

And I think that can be emphasized by JC. And it needs a lot of education on the

end-users. And I think that can be improved by including an informed consent for the patient. Because if you are going to use any tissue on a patient, I think physicians should be able to explain to them if there are any side effects or any infectious risks with that.

CHAIR BRACEY: Yes, I forgot that detail.

So does the AATB in its standards require informed consent when tissue is implanted? No. Okay, the answer is no. You are saying that is a big -- Dr. Holmberg.

DR. HOLMBERG: I think that that is a real big problem. And I think that one of our speakers tomorrow, if he can fly in, if not maybe we can have him by phone -- but at any rate, I think that one of the articles that was reported in New England Journal really highlights a lot of the issues with informed consent. And I really I think that maybe we need to listen to him and maybe

tonight read that article over.

But I want to address another issue. I guess what I was thinking about when Dr. Lazarus and Scott Brubaker were talking earlier and it almost got me to the feeling that well, this is covered but it is part of our standards they are part of the GTP. And I guess the question I have is, is there a problem. Is there a problem with the distributors? Is there a problem with the standard process?

I will go back to what a former Assistant Secretary said to me. Do they ever fail anybody on their accreditation? And so I ask that question. Do we have a problem? How effective are The Joint Commission audits? How effective are the AATB audits? How effective are the AABB audits? How effective are the standard process that we have in place, let alone the regulations?

Because what we have clearly heard from the regulatory side is that the FDA is

limited to Section 361 and that is infectious disease. Okay? So they are limited there. I hear from the discussion came out this morning that the policies and the parts of the contract that are given to the OPTN, that safety is not even addressed there.

So you know, I am concerned that on the regulatory and on the oversight that as the federal government, do we have the full capability and the other part of that is, if we don't have the full capability, is the private sector doing its job?

CHAIR BRACEY: Comments? Questions? Dr. Lopez-Plaza.

DR. LOPEZ-PLAZA: I tell you, you know, the consent issue is a very important one. Because again, regarding tissues, I think that if any consent is obtained, it is just like oh by the way we are going to be doing this kind of surgery and we might have to put a graft. I don't think that, you know, that is part of the consent for the entire

procedure, not that you might get something that might be X, Y, and Z. But to be able to consent we need to be able to understand what can be the consequences of getting any kind of tissue, organ, blood, whatever. And for some things we know more than for others.

So again I think that, especially for tissues and for solid organs, we need to know a lot more about what really are the adverse events that we can find before we can really mandate something that we are not sure what we are talking about.

CHAIR BRACEY: Right. I mean, it gets back to that point is if you are going to consent it should be based upon having good information. The information at this time is not all there.

Dr. Kuehnert?

DR. KUEHNERT: On the other hand, it becomes a chicken or egg sort of situation because you can't implement a system until you know what the need is but you don't know the

need until you implement the system.

So I agree with the comments about a pilot. I think that is always a good place to start. The question I think goes to really focusing on the biologics that are of greatest risk and finding a way to start that doesn't make it so overly complex that a pilot isn't feasible. I think that is some of the key points and the other is tying into informed consent and patient and clinician awareness is that you are not going to be able to drive something like this until you convince clinicians and patients why this is needed.

CHAIR BRACEY: And then the other thing that struck me is clearly with solid organ transplants versus tissue, there is a whole range of -- it is not all the same. You have a multiplier effect with certain tissues, wherein a tissue from one cadaver can go into scores of individuals. And scores of individuals that may have a very short survival versus the walking wounded who are

going to get these various procedures and you add these tissues.

And so it just seems to me that the risk-benefit assessment of certain tissue interventions as contrasted to solid organ interventions is tremendously different. And in that regard, I guess the thing that concerned me as I was listening to much of what I heard today is that the regulations were sort of generated to make them all one in the same, in a sense. I don't know to me that seemed problematic because the effort that I think once you put into trying to absolutely, well I won't say absolutely, but you know, really really eliminate as much risk as possible on the tissue side, would just seem to be something that makes sense, whereas the benefit risk as pointed in the papers that have been distributed for the solid organ side, that is a different consideration.

Dr. Ison?

DR. ISON: Well I think in some

areas I think you have to realize that the rules and regulations are different. So and there is huge differences in tissues from organs. And so high-risk donors are not eligible to be tissue donors, whereas they can be used for organs. The timeline for evaluation. So you have to collect a bunch of information, do a bunch of testing. And the time frame between procurement and actual utilization is very long for tissues as compared to organs.

And then the level of processing is also, for most of the tissues, substantial. And there is degrees of inactivation that do modulate the risk.

I think the way that I would look at it is that the policies do need to be different for blood, organ and tissue. But there is a certain degree of intersection where there is clearly common themes. I think that the way that it is implemented for example with biovigilance is going to be

slightly be different for organs, blood and tissue.

There are some common themes. We need to know who is getting the product, what happens to them and how to trace that. So that is common irrespective of what is being transplanted or transfused. But the one thing that I have learned from this committee is that there is actually a lot more in common than difference with these different tissues and I think trying to focus on that.

And then going back to what Matt, and I think several others have commented about, a pilot project or a study to look at this, this is definitely something I have thought a lot about. And I think we can look to the Spanish for a model on something along these lines. They sponsored what was called the Residra Project which for a year every transplant organization within Spain had very detailed information and samples collected on all donors and recipients where they very

detailed took a look at what infections happened, what infections were present in the donor, did expanded testing of the donors, expanded testing of the recipients. We couldn't do that in the United States. It is too large but I think you can easily cobble together a project or maybe a couple of projects; one looking at blood, one looking at organs, and one looking at tissue. And really the goal of that was to look at what is the incidence of disease. What is the incidence of bacterial contamination? What is the incidence of all these markers? And I think this is important as we will talk a little bit tomorrow, thinking about what new tests to add.

So what is the prevalence of Chagas? What is the prevalence of West Nile virus? What is the prevalence of dengue fever in the donor pool? And what is the utility of all of these different assays that we could apply? It is going to be expensive but again

I think it would be a robust way to get a confined sample of patients and really start answering what is the risk. And in my opinion, that is really the only way to do this. There is no mechanism to fund that at this point.

CHAIR BRACEY: Dr. Williams.

DR. WILLIAMS: One sort of disconnect that I noticed through the discussions are references to infectious diseases in recipients and it was a little hard to figure out where this is coming from.

One of the things that helps keep blood safe is computerized management of the blood center on demand labeling so that a unit of blood never gets labeled for distribution, if it hasn't passed all of the qualifications, including all of the tests.

There are automated systems that have modules to control tissue. I don't know, maybe it is known but how many of these establishments use good inventory management

practices, computerized or not, so that if a problem is found with a donor, that you can assure that these many samples of the donation from the donor are in fact taken out and destroyed and don't get put into use.

So I think that is another area that could be investigated.

CHAIR BRACEY: Let me ask one of our Committee members, Dr. Arnold, who have probably put in some of these tissues, what we are talking about in terms of developing these more rigid systems for recording, how much of an impairment do you think that would be in clinical practice?

DR. ARNOLD: In clinical practice, some of the things that we are talking about are quite onerous. The informed consent, ideally people would come to understand and have a Ph.D. in molecular genetics and everything else that some of us kind of throw around. But trying to get a kidney in somebody or get a heart in somebody over the

course of the next few hours and having them, no matter what you have in terms of a relationship over time, two weeks, three weeks, and think that you are going to have informed consent. You know it is a compromise at some point. I mean, they have to accept that there is a level of trust from a committee standpoint, from a government standpoint, from an inflict standards standpoint.

Perhaps there could be a Wikipedia-type arrangement where the concept of what is ethical informed consent can appear in one place, one document, where people would work on and a common document would exist across a system, just one idea.

Dr. Ison, I think, summarized things nicely in that the intersection is where, as I sit here, the committee should be working on. And many of the things that we are working on at this point would be the communication of, at least today's theme seems

to be the communication of possible problems in materials that are available to put in another human being.

I haven't heard at any point the incidence of the problem. You know, what we are trying to sort out. We are talking big money. If we are going to throw another level of regulation in here, or another level of forms, or another level of vigilance, or surveillance, or recording at the hospital, it is extremely expensive. And I haven't heard one number. I know we can all think about USA Today and understand that sometimes tissue gets through and it has got stuff on it and it hurts people and nobody wants that. But we may be talking about saving seven people and those resources probably would be spent better elsewhere.

And when it comes to finding these pieces of tissue that got off into other people, at least my understanding of the more colorful examples in the lay press would be

that when the resources were turned in that direction, they figured out where that stuff was. You know, infectious knee ligaments, or whatever, and it infected this guy. And they figured out that this tissue came from this person and it went into X number of people.

It's like Tim McVeigh made a phone call from a cell phone X number of hours away from the bombing with a card and they figured out it was him. I mean when the resources are directed at an acute event, they exist and they can solve the problem. We are talking about a constant maintenance at a certain level of expense and resources and trying to incorporate the needs of the patients and utilizing the vigilance that already exists in several levels in several agencies.

And back to the one tiny point that I made is I don't know the incidence of the particular problem that we are trying to deal with in tissue today.

CHAIR BRACEY: Dr. Triulzi then Dr.

Axelrod.

DR. TRIULZI: Between the gap analysis report and the statements we heard today, I think we have a much better idea of where the gaps are, where the problems are. And I think it is also pretty clear that it is somewhat different for tissue than it is for organ, based on the risks of inherent difference in risks between the procedures.

And I also am sensitive to the statement that I think we need to give some recommendations to the Assistant Secretary that are feasible in the near term and then maybe some that would be longer term goals. And so I am making a suggestion that we might have one subgroup of people develop a list of what would be some practical things that would be most important for tissue and then another group do what might be most important as a practical group of recommendations for the Assistant Secretary for organs because they may not be the same.

In fact, traceability is the big issue right now, we seem to be talking about with tissue. That is not the big issue with organ. That might be donor test prevalence of infectious disease test results and lets see what comes out of those groups and then we could discuss making recommendations about the prioritization that comes out of that suggestion.

CHAIR BRACEY: Are you volunteering for one of those subgroups?

DR. LOPEZ-PLAZA: I want to add something to that, Darrell. And that is I have seen this reporting of the adverse events. Again, I want to emphasize that I don't think we really -- I have seen some tissues that has to be someone that the joint is real infected and they have to take out the joint. If not, that is not going to be reported. From a solid organ, how many times do we take for granted that the patient already has all other complications?

DR. TRIULZI: That's fine. That could be one of the --

DR. LOPEZ-PLAZA: So I think we need to add that one, too.

CHAIR BRACEY: Actually I agree with your concept. And that is something that I feel comfortable with, as long as the rest of the committee feels comfortable with having subgroups, two small groups work on the two respective areas, if that is okay with the rest of the committee.

DR. LOPEZ-PLAZA: I have another --

CHAIR BRACEY: Obviously, we would discuss this. You know, it is just a draft form and then we would come back and work it.

DR. LOPEZ-PLAZA: I have another comment for Darrell. If you are going to divide it into subgroups, should we first try to identify maybe, you know, five or six items that are really, really the hot topic and then from there, then assign to each of the groups

to categorize that; what is needed, what is not needed.

Because I think if you really split them, we might lose some of that commonality they have. So maybe we should have six items that then each group will discuss it.

CHAIR BRACEY: Right, that is what I am thinking. That is the purpose of this discussion is we want to get those ideas out so that we can get the hot -- oh. I didn't look to my left. See if you have on your screen what I have on mine.

The idea is to get some ideas about what we think the hot buttons are that should be included in consideration of the subgroups. Dr. Axelrod.

DR. AXELROD: I think actually Dr. Triulzi summarized it well. Because for me, out of everything we heard, one of the, I guess, processes that makes me most uncomfortable -- I mean there is a process now of testing and we are talking about is there a

way to improve it and do something better, but this issue of what appears to be a deficit or non-requirement for an actual tracking or traceability of the tissue products going to the donors and actually being able to say if it has gone to seven places, that we can at least know who they went to, that inherently makes me feel uncomfortable and appears to be sort of a low-hanging fruit that we should really be addressing.

You know, it is surprising to me and I wasn't aware that that type of documentation was not available. We document so many things in the hospital and every blood product is tracked. It would seem to me that this could easily be implemented and aligned as a requirement.

DR. TRIULZI: The other thing I wanted to emphasize was I think we could cobble together in an optimal situation that there could traceability throughout. If you really tried hard and got a little lucky to

some of the times from donor recovery all the way to the recipient.

Unfortunately, the optimal is not often reality. And some of the things that we have seen in CDC have involved situations where the organ community and the tissue community need to be in communication, not only within the organ community or within the tissue community. So the data on adverse events that occur in organ transplant recipients are vital to know as far as the clinical care of tissue recipients and vice-versa. So there have been situations where a donor is both an organ and tissue donor. The organ testing is completed and then tissue screening is done, which includes more tests and there is a positive. It may be a false positive but sometimes it is not. It is a true positive. And that actually gives important information for organ recipient care. And you could imagine a situation going the opposite direction from organ to tissue.

So I think, you know, if you split into these two groups, I think that is fine, as long as you also have for both of them, a category for communication between the communities.

CHAIR BRACEY: Right. And one thing that really struck me in looking at the White Paper was the input, the model -- the input models. You know there were those models where you have got the silos and then there is that model where everything goes into a central database and then it is distributed intelligently to where it needs to go to and it may be several places.

But that brings me back to another important thing that we need to discuss and comment on. And that is the work that was done by the working group in the White Paper and the summary is on pages 10 and 11. But I think that as a committee, there are two things I want to accomplish today. And one is to hit the common things in terms of what we

think is important for a recommendation might come up and then have the subgroups discuss that but then also to be able to comment back to the assistant secretary on the work that has been done thus far by the working group.

So you want to continue with the specifics or does anyone want to talk about the White Paper right now, what we reviewed in that document?

Dr. Corash.

DR. CORASH: Well just I think again, a high-level comment. But in terms of outcomes for patients, we are not entirely dependent upon a passive reporting system.

CHAIR BRACEY: Right.

DR. CORASH: And I don't think that there is any way with that type of reporting system that we will ever know the true incidence of these outcomes. And if we want to rationally stratify the intensity of what you might do for different types of tissues and different procedures, I think you need a

database from which to operate because I don't think we can make good decisions until we know that. And I think the presumption on which the two different types of regulatory pathways were stratified were based upon assumptions years ago that no longer hold.

And so I think if we are going to undertake this activity, we have to recognize that as a fundamental problem that has to get resolved.

CHAIR BRACEY: Okay, Dr. Ison.

DR. ISON: I agree with that, incredibly. The one thing that concerns me though is that both of the pilot systems that have been developed so far, the TTSN and the hemovigilance systems still are very passive. You know, they require active input by groups that don't have any requirement to do that.

So I agree, until you have, I think it is probably a combination of things where there is requirements to actually input and some degree of passive auto-surveillance of

existing databases that you are not going to really get the most robust system that you can possibly have. But I am not sure, at least as the way that they have been designed, that they will overcome the passive nature of reporting.

DR. CORASH: Yes, I don't think they are getting at the problem. And you know, I am struck if you turn to page 17 and you look at this table.

CHAIR BRACEY: Oh, yes.

DR. CORASH: There are only a few countries in Europe that have mandatory, and for the most part they are very small countries, there is only one large country that really has a mandatory system.

CHAIR BRACEY: Dr. Triulzi and then Dr. Williams.

DR. TRIULZI: Larry, I hear what you are saying. And the thoughts that come to mind are I think fact accreditation is a good example where outcomes and the clinical of

fact accreditation requires reporting of outcomes of transplantation of stem cells. So time doing graft, and then survival, graft versus host. That is a little different than adverse events.

And required reporting from adverse events gets into the willingness of hospitals to share adverse event reports that have become mandatory, as opposed to the voluntary. And so I think we even heard earlier today from The Joint Commission that the culture of safety was predicated on volunteer reporting.

And so that is different. When you say outcomes, then maybe you need to define what you mean by outcomes. If it is clinical outcomes absent adverse events, I think that is fine. I think that makes sense. I think adverse events is a little bit different issue.

CHAIR BRACEY: Dr. Williams.

DR. WILLIAMS: You know one other way to approach the data collection is the way

the Transfusion Committee collected adverse event data for many years and that is by investigator-initiated and targeted funded studies. And those data could be collected that way in a much more controlled fashion.

DR. ISON: I think that in my opinion you have to do that up front for organ and tissue because you have to prioritize where you are going to direct your efforts. And at this point, even as someone who does work on disease transmission in organs, if you ask me what is the number one transmitted disease, I would actually have a hard time giving you that answer, until we actually did a robust, you know, how much hep C is transmitted by doing significant research in the donors and the recipients and how much is transmitted. How much bacteria?

My suspicion is there is probably a lot of bacterial transmission that is under-recognized. And until we really understand that and the only way to do that is a very

focused research project. Once you have that, then you can intervene and come up with proposed interventions to hopefully mitigate that and then do them serially from time to time to see if those mitigating features have had the intended effect.

CHAIR BRACEY: Dr. Lopez-Plaza.

DR. LOPEZ-PLAZA: I agree 100 percent with that. And again, I think that there is something common in the three different human-derived products are the tissues, the organs, and the blood that -- I mean with blood how many people have tracked to see what happened with that recipient in 24, 48 or 72 hours afterwards? So I think that would be very surprising to find what kind of outcomes are there that we have completely missed because of just passive reporting.

CHAIR BRACEY: I am struck also by Dr. Corash's observation of the voluntary nature of all that exists. And I think to

really be able to bite it, you need to do some studies.

So, if the interest is to public safety, then why would voluntary be the preferred option to mandatory? Dr. Kuehnert.

DR. KUEHNERT: Well, we have a little bit of experience with this at CDC with hospital infections and found that if you mandate something, in some ways you get less reporting because people are afraid of retribution. If you are a regulator, that is the way you have to do it. But in Public Health, the way that we found most effect is to develop a system that is a benefit to the individual facility. So it allows them to look at their own data, learn from that, but then also to compare it to other facilities and say how are we doing compared with other facilities. And that can be done at a transplant center level. It can be done at an organ procurement organization level, recovery organization level, but the trick is to

develop a system that is actually useful to them, so that the data is actually fed back to them and it is useful to them. Otherwise, you have to have a hammer. That is really the only way to get the data. Because if it is not of use to them, you have to have some incentive.

So, it sounds like the discussions here have sort of revolved around a sort of idea of there needing to be a study. You know, sort of a Holy Grail study, which takes time to fund but would be very detailed and could provide very useful answers. I mean, something like that is already being done in the blood field with REDS for many years. It has been very successful.

So something that is dedicated to organ and tissue, in addition to blood, would be helpful. That probably is going to take some time.

So the next question would be, what is the low-hanging fruit. And it is

interesting in listening to the Committee discussions come to the same conclusions that we did when we started to develop the Transplantation Transmission Sentinel Network like a pyramid and said the first thing you need is a common donor identifier across organs and tissues. Because if you do not have that, when it comes to rapid communication, you don't have immediate linkage and therefore you can't get from provider to provider, which of course goes through that recovered donor.

So I guess I just urge the Committee to think on two levels. Think on the level of what do we really need if we had all the resources in the world and what would answer all the questions. And then the other level is what do we need right now. What is the glaring gap that we could fill with the resources that we have right now?

Then the third thing I wanted to just briefly mention is this whole thing about

active versus passive surveillance. And it is a hard thing to grasp.

What I think of when I think about active surveillance is a situation where you have data on each and every procedure that happened and whether something happened specifically. Your data elements list. What happened and what didn't? Vital signs, laboratory tests, clinical exam. All that is entered into the database and all fields are filled yes or no. And that is extremely labor-intensive and I think there you are talking more on the Holy Grail level of the study, rather than on something that we could implement immediately.

CHAIR BRACEY: One thing that does come to mind and perhaps it is the Holy Grail, there is a focus on the electronic medical record these days. And the capture of, you know, whoever is designing this thing probably has no idea about this kind of stuff but trying to figure out a way to tag those people

to let them know the problem that we have.

Dr. Corash.

DR. CORASH: But you have to know what you are looking for. And that is the thing. When we heard Walter Graham's presentation on well all the data is readily accessible but it is not the right data. And so maybe what the Committee can help do is delineate is what are the right data that would need to be collected.

CHAIR BRACEY: Okay. Dr. Corash.

DR. CORASH: So I think you made an important point about active birth versus passive and the first-hand experience that I have had is in the French National Transfusion System which has an active system in that every transfusion has a one-page sheet that has to be filled out to cover the 24-hour period after the transfusion. That has some limitations because it only covers 24 hours.

But interestingly enough, you have a hemovigilance officer in the blood center

and you have a check and balance to that. You have a hemovigilance officer in the hospital, in the clinical transfusion service and they have different interests, if you will. But one of the outcomes from that system was that it led to a national policy decision, based on adverse reactions to shift away from driving to 100 percent single donor platelet concentrates back to the use of whole blood with savings in dollars because they had better outcomes with pooled whole blood products as opposed to single donor.

So you can get some payback from these types of systems.

CHAIR BRACEY: Okay, so other comments or discussion from the Committee?

Let's go -- one of the things that the Executive Secretary points out and again we do need to address the recommendations and they are on page 12, four bullets, or four recommendations.

The first addresses a critical

issue and that is an issue that we heard loud and clear from the AABB because there is a nice program that is getting started up and it is not rich in resources.

DR. ISON: And there is the TTSN, which is for organs and tissues as well. So it is not just that.

CHAIR BRACEY: So perhaps is the consensus of the Committee that this is the appropriate thing to do?

DR. ISON: Well, didn't we pass last time?

CHAIR BRACEY: Well, we did. We did mention that.

DR. ISON: Basically do the same thing.

CHAIR BRACEY: Yes, but they are wanting feedback on this, parsing it for tissues and organs now.

DR. TRIULZI: I think we concur.

CHAIR BRACEY: We concur.

DR. TRIULZI: Yes.

CHAIR BRACEY: Okay. And so the next piece is to recommend the integration of the systems with the private sector, which I mean in essence, that has evolved for the blood world. And it seems to be working well. And so would that be another point of concurrence?

DR. ISON: And so one thing along those lines that I sent an e-mail earlier is I almost wonder if there is a need for a dashboard that is reported at the Executive Committee level on their regular meetings. And then at every single one of the Advisory Committee meetings here, where we get just kind of a feed out of what are the current adverse events that are being seen in blood, organ, and tissue since our last meeting.

Because I think if our job is to comment on safety and yet we don't know what is going on from a safety standpoint, I think it is hard to actually make a comment.

CHAIR BRACEY: Dr. Kuehnert.

DR. KUEHNERT: I think this is a really -- I mean I like the analogy and I guess I will extend it.

The Advisory Committee hears topics for discussion but as far as I know, hasn't really evolved to make decisions based on data that is primarily coming in to it. You know, sort of like a data summit, which is something we have talked about a lot for hemovigilance and for which there are models in other countries.

But again to extend the analogy, if it is a dashboard, who is the pilot? And who is flying when we are not meeting? And that is an important issue that I know the Department is very much concerned about in trying to work out solutions to. But perhaps the Committee could help with that. But it is just something to keep in mind that we always think about at our agency, which is okay, you can collect the data but who is looking at it. And what do if we something of -- how do you

decide when there is something of concern and then what do you do about it when it reaches that threshold?

But I think it is a great idea it is just we have to realize what are taking on by doing it.

CHAIR BRACEY: I was thinking, I was just talking to Dr. Holmberg about your internal group that meetings frequently. It would seem to me that that would be the ongoing monitor, the pilot, if you will, while we are away at the beach or somewhere.

Dr. Pomper.

DR. POMPER: One thought to consider, for me at least, is I want to applaud the FDA for defining what a 361 is. And then I know what blood is. But in many ways, I'm not sure what all the rest is. So there are certain things that are clearly defined and I think there is a need to tier what tissues means. So the recommendation summarizes blood, organs, and HCT/Ps. And so

I am thinking okay and tissues is probably included in that.

And what I am asking is, it might worthwhile to come up with some categories that have an urgency to procurement, which basically gets down to clinical need and a feasibility of the process on one side. And I guess I think of -- so there is the very urgent tissues and then there is the not so urgent tissues. Do they all need to be harvested at the same time? If they do then how do we have recommendations that just cover tissue?

So what I am trying to say is I think there is a need to, frankly, define in a little more detail what is relevant for each group of tissues. Because solid organs should not be lumped into the same group as a patella tendon, probably, or a chip of bone. And so to me right now, I mean I can understand an organ but the tissues seem, there is cornea, there is patella, there is whatever. So I

think that is one thing. There needs to be some sort of tier-based concepts that I think there are organizations that understand what their particular interests are. But we are not all speaking the same language. So that might be helpful. That is number one.

The second comment is about data collection. I agree we haven't heard any numbers. It seems that the numbers are acquired based on events already. So I think that 60,000 foot view is the goal is patient safety. And availability gets down to patient safety as well.

The 60,000 foot view I am trying to get to is how can we collect data that is going to avoid an event, rather than tracking the data after the event occurs. So it would be nice to gather information and the purpose of gathering that information is not just to make a regulation but to somehow help the system to avoid those problems in the future. I think we are all trying to do that.

I think there is many people over the years that have brought the system to where it is, so I guess that is why we are a looking of the gaps in the process. But just to assign a need to do this or that, one of the purposes needs to be that we will identify spots in the process that can avoid this from happening.

So if we do a test and we find out a donor has HIV but the process has already gone on, then we are really not having a lot of impact on safety.

Conversely, I just wanted to, we have been asked twice about cost-effectiveness analysis. I was thinking about that and I don't know much about the process. Is there a way to say that the cost of something may not be monetary but the cost would be say lack of availability or the impact -- the cost would be lack of availability and, therefore, patient harm.

On the other side, improvements in

patient safety minimize patient harm. And yet if they affect availability, then the next cost is that how many patients will suffer if we add a test and then therefore organs get kicked out.

Is there a way to apply this cost-benefit analysis or cost-effectiveness analysis without actually using dollars?

CHAIR BRACEY: Dr. Ison.

DR. ISON: And I think that is important to point out because we have heard a lot of comment about actual dollars costs but you can, using qualities and things like that, I think adjust for that.

And then the other question that I would raise along those lines is how are we going to do that cost-effectiveness analysis? Because I think most blood screening would not be cost-effective by traditional standards. And so are we going to apply the blood cost effectiveness to the screening? I think it is a real challenge in some regards.

You know, one infection say for a million or a couple million dollars isn't anywhere near the $50,000 that is traditionally felt to be the cost-effective margin.

CHAIR BRACEY: Dr. Corash?

DR. CORASH: You know, the one thing that I think is pretty high priority and we heard a little bit about it this afternoon, I guess the gentleman from that organization is gone for the day, but getting an ISBT coding system for any tissue that is put into a human, that seems to be a critical point to me. And we have moved from the paper system to electronic data capture. We ought to be able to manage this.

That seems like a very high priority issue.

DR. ISON: And I think it would keep us in line because the Europeans are moving towards that as their goal. And at least since tissues in particular are shared globally, I think it would make it a lot

easier to incorporate non-U.S. systems as well.

CHAIR BRACEY: Actually that is a very good point because this is really an international exchange of these, even some of the hematopoietic progenitors, etcetera.

One of the things that I thought may have hit a little bit on what Dr. -- I'm not necessarily pointing you out -- but the third recommendation here and I guess you know, this is not really specific but I think we have been saying as much that yes, we agree. We recommend steps to enhance mechanisms for surveillance and we are just not talking about surveillance for the purpose or surveillance but surveillance for the purpose of improving outcomes is what we are saying. So shorten the time as close to real time as possible.

And so I think to me, now the one question that is an interesting concept is the notion of benchmarking. It is the notion that

as you perform your surveillance, you will pick out the good performers, the best practices versus those that aren't out there. So what are your thoughts about that? Dr. Ison.

DR. ISON: Well I was actually going to question can we at this point have a benchmark. You know, we don't actually know what the incidence of disease transmission is, malignancy transmission and it is clearly something that is going to change.

And I think what we have heard, for blood at least, the goal is zero. For organs, that is definitely not the case so we can't set an arbitrary benchmark for organs. Tissue I think you could again shoot for zero or pretty darn close to it as well.

CHAIR BRACEY: Okay. And then so the other thing, getting back to the recommendation, so really a lot of this, we in our last meeting said, recommended that a plan be developed. We were looking for action in

blood. And so I mean in parallel, I mean I think the discussion, we would love to see an action plan for tissue. I mean, I think that is a pretty easy consensus point. Dr. Corash.

DR. CORASH: And I just want to throw out a benchmark. If you had, in electronic data capture form that was linked to each piece of tissue through an ISBT code and you could then measure how frequently that one page capture form was filled out in terms of where did that piece of tissue go and what happened in some period of time, depending upon the procedure, after it was put into the recipient, you would then have at least a benchmark of how much data you captured back. That is a simple benchmark about your intervention, at least.

CHAIR BRACEY: One of the things I was thinking about is you know, what sounds like is not currently happening in a large degree is people go out. For example, in my

hospital, there is always these doctor pyros. You know, they are practicing these drills. And it sounds as though there is not a lot of practice in terms of find the tissue drill. You know, that sort of thing.

So something to that effect where you could actually go out and see here is the performance of X number of labs or facilities. We asked them to find these points of tissue and 25 percent of them couldn't find it.

Dr. Holmberg or Dr. Arnold? Dr. Arnold.

DR. ARNOLD: Well, I'm sorry but I haven't heard any objective evidence or report today of the magnitude of the problem with the tissues. I mean, there is zero number associated with this. It sounds like a terrible problem but we won't even know if we enact a lot of great ideas, we don't know if we have changed anything if we don't --

I mean, maybe we can agree where to look even in the literature and establish that

there is number X that we want to effect an improvement upon.

CHAIR BRACEY: No, I think that the statement that I opened up is the need for more knowledge. And I think what we are going toward is a recommendation that we set up a robust clinical trial just like we had with transfusions so we know what the risks are.

Dr. Holmberg?

DR. HOLMBERG: Well, my comment is really one of the same of what you are saying. And that is that I think we have two aspects. If we sort this out, we have risk assessment and then how do we manage that risk? So risk management of that.

I think that one of the things that I heard loud and clear and you are exactly right, we haven't heard any hard numbers today as far as the depth of the problem and that is why I asked the question, you know, are we really that bad off, earlier.

Well first of all let me go back

and say I think what I need to do is make copies of the presentations that were made a few years ago by Dr. Ruth Solomon and also Dr. Ortiz that actually gave numbers of the different types of infections. And also I think what was very revealing about Dr. Ortiz-Rios' comments at that presentation was actually the number of follow-ups and how the patients were lost over a period of time and not necessarily deceased but lost. That they were lost to follow-up.

So I think what I will do is I will try to get those copies made tonight and bring those in because I think that that is something that we are missing this morning. this whole day is really some of the hard numbers.

But there is also something that I heard earlier and Mike you are really hitting on this and that is I think that we have identified that there is really no place within the federal government and we always

turn to NIH when we think of research on really is there research for organs and tissues. You know, and I think that that is something that is a real void. We have the National Heart, Lung, and Blood Institute but their mission really doesn't get into some of the things that we are talking about.

DR. ISON: Yes. So there is actually a lot of NIH-supported transplant research that is actually part of NIAID. They have a whole group that sponsors large transplant studies. The one challenge is, there is no one even looking at transplant safety. There is not a single RFA related to transplant safety and it is important because it goes beyond defining what the risk is, if we have been working on with the loss of HTLV-I and II assays there is not small grants available to develop new assays for new test platforms. There aren't funds to support studies to look at novel testing in the donor population. How to optimize NAT testing, for

example, for organ transplantation. How to collect data on a number of different transplant safety issues. And really, that is kind of an unmet within the government.

So there is a group that is focused on transplantation. And I think the number two in command a NIAID is actually a former transplant surgeon. But it is just that this issue hasn't been raised as a fundable topic by NIH or CDC or other groups to specifically look at this issue. And again, there is issues related to consenting.

I mean, how effective is the consenting? Is it actually, there is a requirement for high-risk donors to be consented. Was that impacting utilization? Do people, to the clinicians understand the data to give appropriate informed consent? Do the patients understand the information that they are given. So there are a lot of issues that I think are important that affect organ availability, patient safety, and utilization

of organs that really just isn't being met from funding from a research perspective from any of the U.S. government agencies.

CHAIR BRACEY: And this is probably just a detail but well, maybe it is an important detail. But in the assessment of risk that we not focus solely on the testing but that we also incorporate the screening methodology or process to validate, to make sure that we know we are not losing people or we are not missing people.

DR. ISON: And even the unified organ donor questionnaire, I mean, there are no funds to move that forward, to look at validation and whatnot.

Every phase of the evaluation process for organs and tissues really has not been looked at critically and I think it is time to really think about it.

CHAIR BRACEY: Additional comments? Yes, Dr. Bowman.

DR. BOWMAN: Yes, along those

lines. I believe that AHRQ or AHQR, Agency for Healthcare Research and Quality has some funding this year on patient safety initiatives. I am not 100 percent sure on that. I can check on that this evening but I believe they do.

CHAIR BRACEY: I think one of the things then that we can discuss -- well we have already discussed the notion of having a subgroup work on a draft statement.

So Dr. Triulzi, would you be interested in heading up one of those institutes?

DR. TRIULZI: Okay. I think I need to do it. I will just tell you that I don't run a tissue bank.

CHAIR BRACEY: No. Well, I am just trying to capture here.

DR. LOPEZ-PLAZA: Dr. Sarode is in charge of tissues.

CHAIR BRACEY: He's out of the room. That is a perfect time.

DR. LOPEZ-PLAZA: When he gets back -- I think he has a lot of things he would like to fix so maybe his opportunity to try to get some input from him.

CHAIR BRACEY: And perhaps Dr. Ison, would you be interested?

DR. ISON: Definitely.

CHAIR BRACEY: All right. So, I will volunteer to work with, Mike, I can volunteer. I will work with you. Any other volunteers interested in participating in these small groups?

Okay, which group? Let me just write these down.

DR. LOPEZ-PLAZA: Whoever needs me in one of these groups, I would be delighted to work with them.

CHAIR BRACEY: Mr. Nether, which group?

MR. NETHER: Tissues.

CHAIR BRACEY: Tissues. Hold on one second. All right. So

what I have got thus far is Dr. Nether on tissues. Dr. Haley on tissues. Dr. Lopez-Plaza on tissues and we will have to wait for Dr. Sarode to come in.

DR. LOPEZ-PLAZA: He has already volunteered.

CHAIR BRACEY: And then as far a the organs, Dr. Triulzi, myself and Dr. Ison. Anyone else interested in the organs? Okay, Ms. Benzinger.

All right. So, what we talked about, we are making sure that we had some commonalities here.

Oh, Dr. Sarode.

DR. SARODE: Yes, I am back.

CHAIR BRACEY: So when you left the room, you were volunteered to head up the subgroup to develop some recommendations on tissue. Are you comfortable with that?

DR. SARODE: I don't think I can head it but I can be part of the subgroup.

CHAIR BRACEY: You can be part of

the subgroup. So here is what we have is we have a subgroup of Dr. Sarode, Mr. Nether, Dr. Haley, and Dr. Lopez-Plaza. What's that? So we will work out who takes the lead later on.

So one of the things that we talked about is making sure that we have all the highlights in terms of the commonalities here. We have got the piece on ISBT and labeling. Where is the piece on design of a study that would assess the real risk? Is that incorporated?

So perhaps you would change that from a pilot study, we were talking about something more than a pilot study. Is that right? We are talking about a targeted research study to assess in the broad sense of risk, not infectious -- well, are we speaking of the broad sense of risk or are we speaking of infectious disease risk?

DR. POMPER: The broad sense.

CHAIR BRACEY: Okay, to assess the risk of, you know, solid organ and tissue

transplantation. And included in that, this is just detail, something like a sero survey as in REDS or other.

DR. POMPER: I just think that would be two different studies. I mean, solid organ, at least what I am starting to glean is that solid organ and tissue transplantation really have --

CHAIR BRACEY: Oh, no.

DR. POMPER: -- entirely different things. So targeted research studies, I mean, two --

CHAIR BRACEY: Yes.

DR. POMPER: Again, I think there needs to be some nomenclature to define what are in these groups. I think we can maybe handle solid organ but tissue is a broad group.

CHAIR BRACEY: Right. No, I think that it would be two different studies. Yes, we are just trying to get something that both groups can take home or to their rooms and

mull over.

Dr. Kouides.

DR. KOUIDES: You mentioned a study but could you clarify, is there any published literature of other experiences worldwide of the risk prevalence?

CHAIR BRACEY: Dr. Ison?

DR. ISON: Having looked at this, the Spanish group, as far as I am aware of, is the only one that is a prospective study, that I am aware of.

I mean, there are other countries that have done retrospective reviews. The British has done this, looking at their transmit. I am not aware of tissue but definitely from an organ standpoint, I know that the British have done this. There have been publications that have been small case series and whatnot. But really from a comprehensive standpoint, the Spanish are really the only ones that have done anything prospective.

CHAIR BRACEY: The other sort of low-lying fruit in a sense relates to what we have in two bullets here which are the computer system and tracking and ISBT-128. I think the notion is to have a standardized system for tagging these units and then linking that to tracking, computer systems. You know, making sure that we can track these things.

We talked about informed consent but I am not sure where we ended up on that one because the problem is that we don't -- we will have more discussion on that tomorrow.

Dr. Sarode.

DR. SARODE: I think we talk about informed consent once we know what the risk is.

CHAIR BRACEY: Yes, right. Exactly. And we are going to have someone discuss that tomorrow. So maybe that is not a big ticket item for consideration right now.

The communication piece. So we

want to make sure that when we find these things that we can communicate across the system. I think that is one that we want to put up at the top of the screen.

I think we were sufficiently impressed by Dr. Keuhnert's comments on mandatory reporting or were we. You know, we are talking voluntary versus mandatory reporting. Is that something that we want to -- a unified data base? Yes, we are talking about a unified database but the question is whether we would have -- well, we talked about the database first because we are using the ISBT. We are tracking. We have got the database. But for AEs, whether or not we would have a voluntary versus a mandatory reporting system. I thought we got soft on that.

DR. WILLIAMS: It is not only voluntary versus mandatory but also linked versus unlinked. You know it could have a lot of cases to be made for both linked systems

and mandatory systems. It gives you the ability to look into a situation and pull a bad product off the market, if you need to.

CHAIR BRACEY: Dr. Triulzi.

DR. TRIULZI: In hemovigilance, in general we already discussed this and said we support the voluntary reporting.

CHAIR BRACEY: Yes, okay. So, you know, we will leave the voluntary piece there. And I think the issue is making the data useful to improve outcomes. And therefore, you build it and they will come.

More active engagement of this body and PHS and periodic review and comment on data gathered.

Ensuring that we think about a tiered system. It is not all the same.

What is missing? Actually I don't think there is much missing. What should be clearer from what you see up here?

Risk assessment versus risk management. I mean, that kind of gets back to

the dearth of information. I don't think we are ready to risk assess. I don't know. What do you think?

Dr. Lopez-Plaza.

DR. LOPEZ-PLAZA: To be able to manage you need to assess them. To be able to assess, we need to get data that is actually going to be interpreted. And while these things if we are going to do something like that, do we have already some kind of system that we can design? The key words that we are going to use to start reporting these and that will go to a place that will study and analyze it. It is received. So you have that in place.

If we would decide to do that, can the CDC be the one receiving all that data and start analyzing it as it goes along, like a biovigilance type of system?

CHAIR BRACEY: Well actually as the monitoring group sees information come in, then they could participate in at least some

form of risk assessment and risk management.

So if there is a working group that is looking at this on a periodic basis. I don't know.

Dr. Pomper?

DR. POMPER: There might be a convergence of technology occurring. There are organizations already that are, and by that I mean hospitals or hospital groups that have in place, or close to putting in place public health records, access, patient healthcare records. So patients can log online and look up information on themselves. As those processes evolve just between an organization and the patient, the next steps are already being thought out and are already starting to be laid down, are how to coordinate within a region and then how to coordinate within a state.

And I am assuming then that the next step is going to be how to coordinate within a nation. So there are, it might be

worthwhile to consider how could say information such as this be incorporated into the patient's record that anybody can look up, is what I am trying to say. If you get a chest x-ray done here that the doctor down in North Carolina can take a look at it and see what is going on without a HIPAA rule, if it is their patient. And then at the same time, that same information might be available for quality assessment as well, at some level.

So I am just putting that out there because there are people thinking about this, not just for tracking adverse events but for tracking a lot of things and actually just for patient care. So it somehow might be able to be dovetailed into that.

DR. KUEHNERT: I just wanted to just lay out general things without giving an answer to who can do this without knowing where the resources are coming from.

One is that there needs to be a day-to-day location for the infrastructure,

for any surveillance system. There also needs to be a day-to-day place for monitoring of the system. Usually that is in the same place where the infrastructure is but it doesn't necessarily need to be that way.

And then there needs to be periodic analysis done, which again can be in the same place but can be in a different place. And I think you are talking about the latter or a third issue there. And if that can be periodic in terms of a larger group and then more often in a smaller group. So it is just some things to think about in terms of governance. So I mean, I think these are all governance issues, which I know that HHS is looking at in terms of biovigilance system.

So, the point when we talk about where we discuss the monitoring, the issue of having the infrastructure for frequent assessment versus more periodic assessment, and what is the infrastructure, what is the resource commitment.

So that would probably go up there with the monitoring piece. Somewhere up there where we talked about -- where is it? Oh, right here. Was that, do you think an appropriate place just to lump, just a thought now, the dashboard piece?

And then consider development of infrastructure with need for really frequent monitoring (daily).

DR. LOPEZ-PLAZA: One of the things I think is going to happen right now is going to be like later but once we have the information, like we have accrued some information that we know some of the features that are very valuable tracking, would be that there would be one place where you could actually enter the number of that tissue, or again, human tissue or whatever you want to call it, and that immediately that would be able to track anything that has been used from that particular source.

CHAIR BRACEY: Right.

DR. LOPEZ-PLAZA: It would come immediately so everyone would know at the moment that anyone else that could be involved with that adverse event.

CHAIR BRACEY: Right. So up under the ISBT-128 piece, there would be real time tracking.

Well we are getting close to the bewitching hour or the transplant hour. The golden hour. Dr. Holmberg?

DR. HOLMBERG: Yes, I just, we have been capturing this information. What is the best way to get it to the groups? We have access here. If you give us one or two people, we can e-mail it to you tonight and you could download it at the hotel. Is that an option?

CHAIR BRACEY: Yes, e-mail, I think would be good.

DR. HOLMBERG: E-mail it to the group? Okay. We will do that.

The other thing I just want to

remind everyone is that when you work in subgroups, this is a subgroup of the Advisory Committee and so, any decisions that are made, your comments have to come back to the whole group in a public forum. Okay? So that there is no perception of a backroom agreement. Okay?

DR. KUEHNERT: One other thing. I hate to do this but has the report actually been approved by the Committee?

CHAIR BRACEY: Oh. Well, yes. As we number one, we went over the recommendations on page 12 and the executive summary and there was consensus. But let's go beyond consensus.

Is there a motion on the floor for approval of the recommendations as submitted by the Committee?

DR. ISON: So moved.

CHAIR BRACEY: We have a motion. Second?

DR. KOUIDES: Second.

CHAIR BRACEY: There is a second. Discussion?

(No response.)

CHAIR BRACEY: Discussion? We have had lots. Okay, then all in favor of approval of the report as submitted?

(Chorus of ayes.)

CHAIR BRACEY: Okay. Any opposed?

All right, then it is unanimously approved. Good work.

I guess we are at the end of our break now. Maybe the subgroups can strategize on how we will approach the evening.

DR. ISON: And we have time tomorrow as well. Correct?

CHAIR BRACEY: Oh, we have time tomorrow.

So, motion for adjournment?

DR. AXELROD: So moved.

CHAIR BRACEY: All right. We stand adjourned.

(Whereupon, at 4:58 p.m., the foregoing

meeting was adjourned to reconvene at 8:30 a.m. on Friday, November 20, 2009.)