UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

Friday,
April 6, 2001

The Committee met in the Second Floor Ballroom at 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:30 a.m., Daniel R. Salomon, M.D. Chairman, presiding.

PRESENT:

DANIEL R. SALOMON	Chairman
RICHARD E. CHAMPLIN	Member
RICHARD C. MULLIGAN	Member
EDWARD A. SAUSVILLE	Member
ALISON F. LAWTON	Guest Industry Representative
GAIL DAPOLITO	Executive Secretary
ROSANNA L. HARVEY	Committee Management Specialist

OPEN

ALSO PRESENT:

ABBEY MEYERS
W. MICHAEL O'FALLON
MARY D. ELLISON
BERKELEY M. KECK
AMY PATTERSON
PHILIPPE BISHOP
SUZANNE EPSTEIN
PATRICIA KEEGAN
PHILIP D. NOGUCHI
JAY P. SIEGEL
KAREN D. WEISS
CAROLYN A. WILSON
KATHRYN C. ZOON
SALLY SEAVER
MICHAEL WERNER
MALCOM McKAY
ELLIOTT GROSSBARD
JANET CHRISTENSEN

AGENDA

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

8:30 a.m.

CHAIRMAN SALOMON: Welcome, everyone, to the second day of the BRMAC meeting. And what we'd like to do to start off with is introduce Kathy Zoon, the Director of CBER and Jay Siegel, the Director of OTRR in CBER to present a certificate of appreciation for Committee service.

MS. ZOON: Good morning. And it's a great pleasure always to attend our advisory committee meetings and take the time to recognize the service that our advisory members give us, and to recognize how important the advice that these members provide to the Agency on many difficult and important issues. And today I have the pleasure of giving Dr. O'Fallon official recognition for his service on the BRMAC. He has been one of our outstanding members, and I want to thank you from the Center's perspective, not only for your contributions on the BRMAC, but your participation as a consultant on some of our other advisory committees. And we look forward to working with you in the future.

I always say this in gist, because it seems once you're on an FDA advisory committee you're asked to call back to service for important issues

that the Agency faces. And I'm sure, Dr. O'Fallon, we will be asking for your help along the way.

But as a special recognition, we have a plague and a certificate we would like to give you and to then say thank you very, very much.

DR. O'FALLON: Thank you very much.

DR. SIEGEL: You know, we never rehearse this and it always seems awkward. And I think the reason is because it really only takes one person to do an introduction, but I always feel like, you know, after years of working together and receiving the donations of time -- well, they're not donations. I guess we pay you well with the Government per diem

DR. O'FALLON: That's called a donation.

DR. SIEGEL: But I do feel like I have to express my gratitude. Dr. O'Fallon, your contributions I guess in the first two or three years you were on our committee as we dealt with many clinical trials and drug approvals were extraordinarily insightful and valuable. And we had a talk, you know, a couple of talks over the last couple of years as we moved to other equally critical but very different sorts of issues in product development for cell and gene therapies as to just viewing together and assessing what your role would

be. And I have been endlessly impressed with the value of your approach to data in general and insightful comments about how to look at data and how to assess what we're looking at, and how to collect data and how to evaluate the data that we've collected. They've been extremely helpful and we're most appreciative and I think most fortunate to have such a distinguished scholar, scientist and statistician in our group. And so thank you very much.

DR. O'FALLON: Thank you.

CHAIRMAN SALOMON: Well, given the 45 second rule that we had, Kathy gets the television. My wife made we watch that.

I also just would like to say that transplanters like myself are a dime a dozen, and aren't missed when we roll of the committees. But Michael really represents and has continued to represent for me a really unique perspective. And I'm always looking forward to his contributions. There's no way we're going to replace you, Michael.

So in the beginning of this Session III of this meeting we're going to pick up the theme of long-term follow-up in gene therapy. And this is an issue that came up in the last meeting in November and

generated quite a lot of concern by many of us that transcended issues regarding sponsors and their responsibilities and issues regarding investigators and their responsibilities. Because the issues here, in my opinion, are extremely high.

On one hand these therapies, and hand-in-hand the other area that I'm interested in xenotransplantation, I mean in both these areas the public is appropriately aware of issues that we're manipulating genes and other tissues in such a way that you can't look at two and three year follow-ups with any sort of surety that you're covering all that might happen later. And everyone in the room here is well aware of that.

However, we're also well aware of the fact that this transition in our thinking is easy to talk about, but when one deals with the practical reality of taking four or five year grants, for example, and talking about 20 year follow-up, that these have just profound implications on institutions, responsibilities of individual investigators as well as small biotech companies and large PHrMA. So this is really a really serious set of discussions.

It's easy to talk, but we really need to make sure that whatever decisions we make, make sense,

can be pragmatically administered in all these different institutions and not cause such a situation that it would be a damper on investigation, particularly in academic institutions.

So, with that background, these were issues that we grappled with already and certainly have much more to talk about. And so I'd like to introduce Philippe Bishop. Dr. Bishop's in the Division of Clinical Trial Design and Analysis at CBER. And he's going to introduce the whole issue. Then we're going to have a presentation from UNOS, which Philippe will introduce. And then we'll go on to an FDA presentation. And then at that point we'll end our discussion.

DR. BISHOP: Well, thank you very much, Dr. Salomon. Good morning, members of the Committee.

Last November Carolyn Wilson and I presented issues pertaining to the long-term follow-up of subjects involved in gene transfer studies. And what I would like to do today is to resume this discussion.

Dr. Wilson presented issues pertaining to vector classes with potentials for long-term risks. And in our discussion last November she outlined a number of factors that can influence long-term risk,

including two vector characteristics; namely integration and replication, but as well as other factors such as the route of administration for these vectors. And then yesterday in addition to Carolyn's talk, we heard from Dr. Chanock that the immune status of recipients is also very important in considering potential risk.

My discussion last November focused on barriers to long-term follow-up as expressed by some of the current sponsors of gene therapy trials. And what we heard from our sponsors is that essentially long-term or life long monitoring is very burdensome. It requires an awful lot of resources to implement. The clinical follow-up is not always practical, especially for participants in these trials whose life expectancy is measures in decades rather than months.

In addition, we heard that it is very difficult to obtain autopsies for a number of reasons. Something else that we heard is that unless there is a clear reason that is obvious to all of the investigators and the individuals who are collecting these data, that it is very difficult to collect complete data sets or to get people motivated to collect these complete data sets. And, therefore, the clinical relevance currently is not always obvious to

those individuals who are charged with collecting this data.

And then we heard from our sponsors that it is also an unusual commitment.

Your Committee, Dr. Salomon, considered all of these points and made some recommendations to CBER to consider in formulating new policies and maybe new guidance with long-term monitoring of individuals in gene therapy trials. And let me try to summarize in just one slide. Certainly there was a lot more discussion that ensued around each one of these points.

But I think there was overwhelming consensus from your Committee that long-term clinical follow-up is indeed needed in order to determine the true risk to participants. There is public concern in addition to scientific need to really document what those risks might be.

In addition, your Committee pointed out to us that rather than focusing on vector classes, we should really consider principles that would be governed by the biological properties of gene transfer vectors when considering changes in long-term follow-up.

In addition, the practical barriers that

we had enumerated were very important consideration for future guidance.

Your Committee pointed out to us that there are existing models and successful organizations that have been able to collect valuable information. And you pointed out to us that the United Network Organ Sharing organization, as well as the International Bone Marrow Transplant Registries would be examples that maybe we could learn from them when formulating new guidance.

What I would like to do today is to turn over the podium to two distinguished representatives from UNOS, Dr. Mary Ellison, who is Director of Research and Mr. Berkeley Keck, who is Director of Information Technology to actually come up and share with us some of their experience at UNOS.

After their presentation, I will come back and resume my discussion about long-term monitoring.

Dr. Ellison, Mr. Keck.

DR. ELLISON: Thank you very much.

Berkeley and I were asked to come today to share with the Committee how it is that UNOS came to collect follow-up data on transplant recipients and what our experience has been with the collection of these data.

The story of transplant follow-up data collection began with the National Organ Transplant Act in 1984 which provided for the Secretary of Health and Human Services to establish and maintain a scientific registry by grant or contract. The registry would include such information regarding patients and procedures as the Secretary deemed necessary in order to evaluate the ongoing success of organ transplantation.

Further, the Act provided for the Secretary by contract to establish an organ procedure and transplantation network, which a lot of people know as the OPTN. And in 1986 the first OPTN contract was awarded to UNOS. And in '87 that was followed up by a contract to establish the scientific registry through which data, the follow-up -- more than follow-up data were to be collected. We collect data not only on recipients after transplant, but also on donors, demographic and clinical characteristics, candidates on the waiting list, information about the transplant procedure itself, and then follow-up data thereafter.

In 1986 Section 1138 of the Social Security Act stated that in order to be a Medicare or Medicaid provider transplant hospitals and organ

procurement organizations must be members of and abide by the rules and requirements of the OPTN. However, the authority for establishing conditions of participation in Medicare and Medicaid reside only with the Secretary and cannot be exercised by another party, including UNOS, without Secretarial oversight.

Therefore, in 1989 a Notice of Proposed Rulemaking was published stating that No OPTN policies could be legally binding without a mechanism for Secretarial oversight. And subsequentially the UNOS contract with HRSA was amended to indicate that OPTN policies, including those governing data submission, were voluntary. And UNOS adopted its own private corporate policies requiring data submission, policy compliance as a condition of UNOS the company membership, but no strings could be attached to OPTN membership if hospitals did not submit data according to UNOS policy.

The OPTN final rule was finally implemented in March of 2000, having been originally published in '98 and subsequently amended. And this rule does lay out the structure for Secretarial oversight mentioned in the NPRM of '89. And it stipulates that the OPTN Board of Directors with at least 60 days notice shall provide proposed policies

that it recommends become enforceable, and that the policies will not be enforceable until approved by the Secretary.

Therefore, until and unless data submission policies become enforceable, as approved by the Secretary, UNOS can only do what it has always done in order to get follow-up, which is to hound, cajole, threaten, entice and use peer pressure and a corporate "member not in good standing" status as determined by the UNOS Membership and Policy Committee.

To date, as a peer, consensus-based organization, we think that UNOS has been relatively effective in achieving data submission compliance through its voluntary system. And to give you more information about the factors related to compliance and about the success that we have had in this, I'm going to turn this over to Berkeley Keck, our Director of Information Technology.

MR. KECK: The current iteration of the UNOS data collection system was implemented in October of 1999. It is completely Internet based through a secure private site that we administer in Richmond at UNOS. We currently have over 6,000 users for that system that are imputing data into a rather large

database of 16,000 data elements.

We collect information from the time of wait listing throughout the listing period, the transplant event and then follow-up for the lifetime of the transplant patients.

For the follow-up system, it is basically event driven in that the event being organs have been procured from a cadaveric or living donor, and the OPO or transplant center comes into our system and lets us know that those organs have been procured.

We collect data about those organs which then triggers us to get transplant centers to remove patients from the list. And we collect standardized data on all of those. That allows us to classify the event being, more or less, the organ type. We follow the organs from that point on, which determines our future data needs. And the computer automatically will generate records based on those needs that we determine.

We are currently generating between 500 and 600,000 records a year of various types. We have -- I lose count sometimes, but I think right now somewhere between 25 and 30 different data collection systems or form types.

We collect data specific to the event at

the time of the event; clinical information, demographic information and use that to kickoff our follow-up for the rest of the lifetime of the patient. The computer will automatically generate those records on the transplant anniversary date. They are inserted into the database and those centers that are responsible for the follow-up are notified of the fact that those records have been generated and to come in and please fill them out.

Achieving compliances, Dr. Ellison mentioned that is a challenge and there have been several barriers to compliance and some solutions that we've implemented that I think have been fairly successful over the years to help us achieve compliance rates that we do have.

Obviously, barriers are a burden of reporting and, you know, there are human resource factors time and financial implementations to supplying the level of data that we require. The centers are not paid to provide this data to us. It is voluntary, as Dr. Ellison said. And as health care has changed and there has been less and less money for this kind of thing in the transplant centers, the people that have been available to provide and fill out the forms have decreased. And so that creates

time constraints on the people that are there, as well as cost factors for the transplant centers.

The volume of data that we collect has grown tremendously over the years. I first became involved with the UNOS database nearly 10 years ago. At that time there were 3,000 data elements total that we collected. Now there are over 16,000 and it grows every time we have a Board meeting. So, it's constantly changing.

And that, I think, is one of the barriers that committees need to look at and begin to control. As technology advances there is a push to collect more and more, and more data. But as more data needs to be collected, compliance tends to drop because of the burden of reporting factors that we've already discussed.

One of the issues that we've seen is mobility of the patients. We are a much more mobile society than we've ever been and loss to follow-up does become a problem over time.

Along with that is managed care, and that has become an increasingly big issue with follow-up of patients in that managed care corporations, insurance corporations are not allowing patients to be followed at the transplant centers following the initial

transplant surgery. They will go back to their nephrologist or their cardiologist who, you know, can be anywhere and centers tend to lose track of them because of that. And I think that is probably the most significant issue that we face today.

Some solutions that we have implemented are allowing -- we have developed import schemes for people that have large databases in their own centers to create files and import them directly over the Internet into our system as long as they meet the standards that we have developed for all of the data that enter.

We do have computer generated reminders that we email out to those people responsible for providing the information. And that has helped. We send compliance reports to program directors, to the transplant administrators and that provides them with a method of evaluating those people that are responsible for imputing the data.

And electronic submission, we now are getting 98 to 99 percent of all of our data through the Internet system. Very, very, very few paper forms are coming in at this point in time. And we've had the system up, you know, for about a year and a half now.

While electronic submission may seem to help compliance, I will say that that alone does not. What it does help is improvement in the quality and completeness of information that you get in terms of online editing, rejection of information that does meet the standards at the time of entry. You know, those people entering the data know it doesn't meet the standard and need to, you know, provide complete, concise information based on the standards and edits you've built into your system.

The other thing it does is increase the timeliness a little bit because you are not getting pieces of paper that get shuffled around your organization, potentially get lost and then have to be hand entered. Once it's in, it's in and it's there available for research immediately. So the timeliness factor, I think, is helpful. But, we have found that centers that were noncompliant on paper or slow to comply on paper are still slow on comply on electronic submission.

I thought you might be interested in some of our experience with achieving compliance over the years. For follow-ups that we have generated in 1998 and 1999 these indicate percentages of that data that were received within 3 months all the way through 12

months. And to date, for both of those, we have received 96 and 91 percent.

Loss to follow-up, also as I indicated, is a problem for many patients and many centers. And to give you an idea of the longer term, I have '90 and '91 follow-ups that were generated. Of those transplants that occurred in '90 and '91, these are the percent that are lost in our system.

As you can see, the largest area is kidney, and that is because those patients tend to go out and be followed locally as time goes by.

And then for short term loss to follow-up, I think from '98 and '99 transplants those figures are fairly low.

So that gives you an idea of the effectiveness of what we're doing.

And that's all I have. Thank you.

MS. MEYERS: Before you go, could you just say what do you do with the data? Who studies it? What kind of reports do you get?

MR. KECK: What do we do with the data, how do we use it, what research is done?

DR. ELLISON: The data are used in a variety of ways. One of the primary uses is for transplant policy development,the OPTN committee and

Board use the data in their deliberations over how to rank patients on the waiting list, and various other policies.

We have a public data request system. Anyone; transplant, profession, scientist, patients, Boy Scouts, anybody can call a request data and analysis. We provide data sets for researchers.

A primary use are deliverable reports required under contract, our HRSA contract: hospital specific outcomes reporting; the annual data reports that UNOS publishes; specific studies that the government is interested in having done or that the transplant community is interested in having done or specific individuals doing research.

CHAIRMAN SALOMON: I would give you an example. Actually, let me do one thing.

Dr. Ellison, if you could join us here, I'd like you to join us at the table for the discussion that follows, just because we really value the kind of input. And I think that some of the members have some more questions for you.

DR. CHAMPLIN: Yes. Can you continue to get organs through the network if you don't report?

MR. KECK: Yes.

DR. CHAMPLIN: The National Marrow Donor

Program for bone marrow transplants has a policy where you need to submit data, and if you're delinquent or deficient in your data submission, both in quality as well as timeliness, they will stop you from receiving further bone marrow transplants through the system, which is a powerful incentive.

DR. ELLISON: Well, the OPTN does not operate that way, because the data submission policies are voluntary. And if you don't submit your data, you can't be excluded from participation in the OPTN.

CHAIRMAN SALOMON: I mean, just to show you kind of how it works, I was writing a review for the FASEB Federation, Federation of American Society for Experimental Biology, and I had a question about needy and waiting times because I was trying to make a dramatic point about the waiting list. And I went to the UNOS website and there was able to review a number of different online reports, but I still had a question. And given the quality of what I was trying to write, I wanted the perfect data. And I actually emailed them, within 3 days had gotten a spreadsheet with the specific answers to my question. And I thought that was really a remarkable testimony to the quality of the way that the system works.

DR. SAUSVILLE: Could you give some

general rough idea of the magnitude of the cost associated with running the contract and how many sort of dollars per deliverables from your point of view?

MR. KECK: I can tell you what my budget is from an IT perspective in terms of collection and implementation of the data system. And it's I would say around $6 million a year for the personnel, the equipment, the maintenance of the databases. But it is a very large database and it is dynamic.

CHAIRMAN SALOMON: So I should add just so that everybody has an idea of what the size here. We're talking about there are 75,000, and that'll change, patients on the waiting list right now. There are about 20,000 transplants of 13,000 kidneys, about 5,000 hearts and a distribution of the rest of lung and pancreas.

MR. KECK: Right now we're following around a quarter of a million patients that are alive at their last follow-up.

DR. CHAMPLIN: Now, this is going to -- the National Marrow Donor Program probably is analogous organization for bone marrow transplantation and they have a system for reimbursement, which is important. And that there is a fee that they will pay per form that is submitted. And this is one of the

big issues in follow-up, of course, if you're going to have people dedicated to doing this work, they have to be paid somehow and that reimbursement from the organization is a logical process.

In gene therapy it's going to be more complex, because you don't have the opportunity, at least, to simply limit their access to genes or DNA because that can be obtained through a number of ways. But I would think that you really need to deal with the center of the academic center in some fashion and require assurance from them that they would be reporting over some length of time, because they're probably going to be the only stable player in this whole ball game.

And the investigators and the junior faculty move frequently. Their half life in any one institution is often short. Companies come and go. But the academic centers, by in large, are more stable than any of the other components of the system, and they're the ones that you can probably count on for some long term follow-up. But they need to have some budget for this, and so somehow that has to be built into what ultimate system is provided.

CHAIRMAN SALOMON: If we're going to continue discussion, at this point it should only be

just some questions toward UNOS in terms of their practical stuff. Then what I'd like is Philippe to complete the process by kind of focusing on what he wants to, and then pick up these sort of discussion points again.

Yes?

DR. SIEGEL: So you showed data on lost to follow-up from 10 or 12 years ago -- from patients over a 10 or 12 period that was in the neighborhood of 80 percent, I guess, in pancreas and maybe 90 percent or better for other organs. My question is could you summarize what is the extent of follow-up information that you attempt to get on those patients and how often? How much data are you collecting on patients that were transplanted 10 years ago?

MR. KECK: We collect, I would say, the follow-up forms in general on each organ is around 35 data elements. And they are collected annual at the time of the transplant anniversary. And we have follow-ups. We're now generating our 13th year of follow-ups. The UNOS follow-up system originally began in 1988. But we inherited around 20,000 kidney transplant patients in 1994 from the ESRD Networks, and they have follow-ups that are over 20 years now.

DR. SIEGEL: That's the same elements then

annually for the remainder of the life of the patient?

MR. KECK: Yes.

DR. CHAMPLIN: I think one of the other points you illustrated that's going to apply here as well is that the patients come back if they feel they need to come back. Now, if the center has some special expertise that they really require, and then over time there's more and more fall off as people go elsewhere for their care, they move around the country and they feel no obligation to stay in touch with you. And if one is particularly treating diseases where perhaps the gene therapy didn't do anything or that no ongoing care is necessary, it's going to be very difficult to keep tabs on those people beyond the first several years. And when you talk about 20 years, I would suspect it's going to be very difficult to keep track of those individuals.

CHAIRMAN SALOMON: Michael, Karen and then Amy.

DR. O'FALLON: 16,000 was the number that I heard up there, 16,000 data elements per patient -- per organ, I mean.

MR. KECK: That's in the entire database there's 16,000 different data elements. And we have 6 organ types that we follow. Some of the data are

common amongst them, but on any given patient I would say that we collect 500 or 600 different data elements throughout their span of collection. And that changes because the information we collect at the time of listing through the time of transplant changes frequently.

DR. O'FALLON: So how do you define compliance? You had 90 plus percent compliance in one year. It's certainly not with respect to everyone of those data elements?

MR. KECK: It is compliance with the follow-up forms only, those 35 that we collect on an ongoing basis.

DR. WEISS: Are there any procedures that you put in place additionally when you get a report back of lost follow-up? And much sort of control and ability do you have to dig deeper to try to really retrieve information when you get a lost to follow-up type of report?

MR. KECK: Not a lot. You know, that would require a fair amount of staff to do that, and traditionally we have not done much of that. However, I will say that that is one thing that the electronic system has changed, because for the first time centers were able to see, view, manipulate and modify all the

information they have ever sent to UNOS. So every patient they ever had, they could then all of a sudden follow-up, you know pull up on the screen and see what we had in our database about that patient.

And some of those patients that we had lost have now been resurrected, so to speak. And that's actually an issue that we have on our plate to discuss back home next week is how are we going to handle those situations.

DR. PATTERSON: I was wondering if you could address three issues? One is access to the data in the registry both to the public in general and the scientific community.

Secondly, if you could discuss the type of clinical outcome information that you collect on patients.

And thirdly, and this reflects on the second point, outcomes. How do you handle information from transplant studies that are conducted when there's an investigation on new drug application underway and an investigational agent that's being studied, and therefore there may be commercial interests involved and some of the outcome data may be viewed as commercial confidential information? And answer that question with a mind to who has access to

the data and what type of outcome data you collect.

So, three points: access, outcome and when you have a commercial sponsor or an investigational study underway.

DR. ELLISON: Virtually no one has access to patient identified information.

DR. PATTERSON: I should just interject, I don't even want to go down patients' identifiable information. I just want to talk about clinical outcomes of the transplant work, what were the adverse events or complications not traceable to an individual patient.

DR. ELLISON: We produce data sets upon request by anyone wishing to look at data. Hospitals, of course, have access to everything that they have provided. But researchers wanting more detailed information can get data sets that have identifiers encrypted. And they can see the specific data elements so that they can associate any of the variables that we collect with regional characteristics, status, organ type, procedure type, that kind of thing.

CHAIRMAN SALOMON: Mary, I think that is not clear to Amy is if I'm at a center, like University of X, and I'm doing a study, there's no way

to get that kind of data -- I'm not talking about patient identifiers -- out of that system. You can find out like how many kidney transplants and what their survival was in region 5, which is the region we're in. But not a subset of patients within University X.

DR. PATTERSON: If I may just try to clarify. What I'm trying to get at because this whole discussion is aimed at shedding light on how this system is applicable and may provide insights into data collection for gene transfer research and clinical trials. And one of the concerns and questions among investigators and commercial sponsors in gene transfer for the types of data that both FDA and NIH are proposing to collect, is who has access to this information. And is information about outcomes, adverse events, things working, things not working; similar to the types of data you collected. How long were survivals? Did the organ function properly? What rates of rejection did you have?

Are those types of information that in the transplant community, and especially when a commercial sponsor is involved, are viewed as commercial confidential information? And I'm not talking about things that are traceable to an individual patient,

per se, but I'm talking about data that may be traceable to a particular drug regiment, a particular investigational agent, a particular organ that drugs are administered through a particular route. Because I think this is a very critical question for the development of the database in gene transfer and what types of data are collected long-term and certainly types of data that are shared with the scientific community in gene transfer.

DR. ELLISON: I don't think that historically we've been involved in much of that. The hospital specific data have been considered confidential commercial information, and there is on the horizon a discussion of broadening the data release policy such that hospital identifiers are available.

We don't do much analysis for pharmaceutical companies for FDA approval. We have done some of it for them. We provide them the analysis and the data sets.

CHAIRMAN SALOMON: So the first question is you can't even now breakout hospital specific data. So if you know that at this hospital we're doing a trial with such-and-such a drug, you can't get that data. The hospital can, but then that's the

investigator.

But the question, Mary, if we do a kidney transplant and we use an investigational drug; it's listed on the data entry form for that kidney transplant patient or that heart transplant patient that they got cyclosporin, prednisone, celsept investigational drug, right?

DR. ELLISON: Right.

CHAIRMAN SALOMON: Okay. So that's what Amy's concerned about. Can anybody get at --

DR. ELLISON: The participants in the study --

CHAIRMAN SALOMON: Can anybody get to your system and say the 10 kidney transplantations done with investigational X, what was their one year outcome, instance of rehopsitalization and rejection rate?

DR. ELLISON: Not now, and the new regulations stipulate that such data be made available to bona fide researchers. And the next step is for the data release policies to be reviewed in light of that.

MS. LAWTON: So currently as a member of the public if I came to you and said "I want to know that data," you couldn't give me that information, is

that correct?

DR. ELLISON: Not with hospital identifiers.

MS. LAWTON: No, I'm not interested in hospital identifiers. I'm interested in generally if I come to you and say "I would like to see for all kidney transplant patients that were given cyclosporin, what was the outcome in those patients.

DR. ELLISON: Yes. Yes.

MS. LAWTON: You can give me that information?

DR. ELLISON: Yes, we can do the analysis an we can provide the data.

CHAIRMAN SALOMON: But she's asking not for cyclosporin, which is an FDA approved drug. She's talking about for let's say rapamyacin when it was being studied. Could you have gone in during the rapa studies before it was FDA approved and track all the kidney transplantations on rapa?

DR. ELLISON: No.

CHAIRMAN SALOMON: And the answer is no, I don't believe so.

MR. KECK: Well, it's yes and no. We collect information on all of the FDA approved immunosuppressants. We start putting them on the form

when they're in phrase three trials or we start seeing a lot of centers wanting to write them in in a report that they're giving this drug.

We do not release to anyone other than the manufacturer of the phase three drug the data or information about that phase three drug.

Now, we do analysis on the FDA approved drugs, and that information is readily available to anyone that wants it. But other than that, we do not release it and I would think that the Committee would say that if it's not approved, we're not going to release that information. Although they may, I don't know.

MS. MEYERS: Can I just clarify? In other words, if I wanted to find out what the long term survival of somebody on cyclosporin is compared to SK506, you would be able to tell me?

MR. KECK: Yes.

DR. SAUSVILLE: Actually then I'm confused. I mean, SK506 when it was investigational, I mean, you could break that out at that point in time in comparison but you couldn't --

CHAIRMAN SALOMON: Only when it's FDA approved.

DR. CHAMPLIN: The data, presumably, is

there it's your policy presumably not to release data on investigational projects that are ongoing?

MR. KECK: Yes.

DR. O'FALLON: You've been saying you do the analysis and then send the reports. Is that what happens?

MR. KECK: Yes.

DR. O'FALLON: So you don't send the data if Abbey requested it, you'd send some sort of a summary. Is that a standardized -- do you have a standardized sort of way that you do that or does she get to tell you how she wants to receive this comparison?

DR. ELLISON: We do it both ways. I mean, we can do it either way.

DR. O'FALLON: I'm amazed your budget isn't higher than you said it was.

DR. ELLISON: Well, his budget is separate from my budget. I mean, I have the analytical staff, so the programmers and the statisticians.

DR. SAUSVILLE: So he said $6 million. What approximately is your budget?

DR. ELLISON: About 1.8.

DR. SAUSVILLE: That's pretty good.

DR. CHAMPLIN: The International Bone

Marrow Transplant Registry does a lot of the same things and depending on the nature of the request, if it's a simple thing, how many transplants have been done for this diagnoses and what's their crude survival; they can spit that out instantly. There are other questions, of course, that are a research project to try to ascertain is cyclosporin better than techrolimus. You know, that you need to do a risk adjusted analysis, which is complex, and there is a several month project. So, those kind of things have to be done accurately and scientifically and so depending on the nature of their request, you may or may not be able to get a straightforward answer.

DR. SAUSVILLE: So, Dr. Champlin, an organizational question. The Bone Marrow Transplant Registry is different than the organ transplant registry. Why isn't the bone marrow considered an organ?

DR. CHAMPLIN: It's a tissue. But it's fundamentally, you know, there's different problems involved with bone marrow transplants than with solid organ transplants, and the field just naturally evolved to have a sort of separate system for analysis of the data.

The IBMTR is a voluntary registry, about

half of the bone marrow transplants and blood stem cell transports are reported to that organization. And they do pay a reimbursement fee, which is sort of minimal for the data being collected. When they didn't pay the fee, there was a lot less data submitted. So that was actually an important component to actually getting participation.

And they serve much of the same role as has been described for UNOS in terms of providing information to the public regarding bone marrow transplants.

DR. SAUSVILLE: Presumably this contract has been running for about 12 years or so, is that the -- right.

CHAIRMAN SALOMON: Actually islet transplantation is also not at UNOS, unless it was transferred there recently, wasn't it? Yes. Okay. So for a long time, though, you know UNOS had took a position that it was organs which had a lot of historical reasons for it, not cell transplant.

DR. ELLISON: I felt we sort of got bogged done in the investigational studies question, and I didn't address Dr. Patterson's questions about what exactly we collect in the way of clinical information post transplant. It's basically graft survival,

patient survival, what immunosuppression they're taking, whether there have been any rejection episodes since the last follow-up, whether they've been hospitalized since the last follow-up, whether they're working. And we've recently added questions about development of cancer.

DR. PATTERSON: May I just ask one follow-up question? How do you handle the instance when someone is on a combination regiment. They may be on an investigational agent as well as an FDA approved drug and Abbey calls you and asks for the information of how many people with kidney transplants are in shape or form taking cyclosporin, what is the survival rate on them? How do you give that data, particularly since there's a significant subset of those patients may in fact be on investigational agents as well? How do you provide data that's comprehensible to those who ask for it?

DR. ELLISON: Well, we provide a checklist of immunosuppressant agents and they put cyclosporin, yes, steroids, yes. And it's a little tricky. There's not much of -- the granularity of the immunosuppression data is not -- we don't collect dosages, we don't collect information about regiments. We know what they've been taking since the last

follow-up, but we don't know exactly in what combination. The immunosuppression data have limitations.

DR. KEEGAN: Could you possibly expand on your cajoling process in terms of those people who are compliant; how many people comply on the first attempt, how many attempts will you make, is it only electronic at this point or do you send additional types of requests like letters and things like that?

MR. KECK: It's every month we send a paper report to the person at each program that we call the data coordinator, and sometimes data coordinators will service multiple programs, of all the forms that are what we call outstanding. And it's broken out by groups of days outstanding in H, analyzed, and that kind of thing.

Every other month we send that very same list to transplant administrators who are more or less like hospital administrators for the transplant programs. And often times they are tasked with ensuring that all the requirements for the transplant program were met, data being one of them.

And once a quarter we send this compliance report of percent compliant to their program director of the program to let them know what their compliance

is with submission of data to UNOS with the incentive being that most programs are going to want their information up to date because it is used for center specific survival rate reporting.

In the past we would send printouts and say "Here's all your data we're going to use for this report, please verify it." And that gave them a chance to sort of get things cleaned up. That did not prove cost or time effective in terms of getting the information out.

We don't do that anymore, so now we are beginning to see people keep up with their data a little better.

We do call centers that are extremely noncompliant and ask them is there a problem. What's going on? Is there something we can help you with? And often we find that the person that did the forms, you know, quit and they haven't replaced them or the person that does the forms is on maturity leave and she'll get them caught up when she comes back, and that kind of thing.

But people that don't meet the standard of what we consider 99 percent of your forms within 12 months of their due date, get referred to the Membership Committee and go through a deprocess there.

DR. CHAMPLIN: Yes, there's some parallel and nonparallel things, as I would see it, with gene therapy. Part of the compliance is related to the fact that they need to collect this same information for their own institution. Often they need to provide that for insurance contracts. And they also want to remain a good member in standing in the transplant community and the colleagues that they're working with.

It's not totally clear that this will apply to gene therapy where there could be a sort of startup group that succeeds or doesn't. And the big issue is going to be the ones that don't succeed. Now the ones that fail and breakup and go away, they have no incentive because they're not continuing to participate in any program to maintain their long-term follow-up. So the successful ones, of course, will be part of the team and the community and be leaders, even, but the failures are the ones that are going to be hard to keep track of.

CHAIRMAN SALOMON: I think that's an excellent segue into Philippe's presentation.

MS. ZOON: Just a brief question. Can you talk a little bit about the security of the data and do you have any problems with people inadvertently

getting into your database?

MR. KECK: No. Yes, it is an Internet based system, it is a private site. It's password and user name protected, behind firewall -- behind two firewalls, actually. All the sending through, back and forth on the Internet, it's 128 encrypted. And we have been certified by HIRSA to be safe.

CHAIRMAN SALOMON: Philippe?

DR. BISHOP: Thank you Dr. Ellison and Mr. Keck for your valuable input.

Now to resume the simple task ahead of us, which is the problem of long-term follow-up of subject and gene transfer protocols.

Before I go on to resuming the comments from the Committee back in November and then uplining a sketch of what may be a system for discussion for long-term follow-up, I would like to revisit the guidance for retroviral gene vector studies. And the purpose for doing this is twofold.

Number one is to refresh everybody's mind in terms of what it is that is currently recommended, but also to clarify one point. Since the last BRMAC meeting a number of our sponsors were under the impression that maybe they didn't need to meet and spirit the current recommendations. And I think it's

important to stress that reviewers at CBER are currently when they look at retroviral gene vector studies are applying the current guidance document. And it is the expectation of those reviewers that there is some attempt at meeting those recommendations.

So very quickly, the guidance document, the current guidance document was finalized on October 18, 2000. It is available on our website.

The document talks about methods for testing for RCR and also defines some time points that should be obtained for blood sampling of patients or individual participants in gene vector studies. And namely being at baseline are 3 months, 6 months, at one year. If followed those results are negative for RCR, then yearly thereafter archival of those specimens is sufficient.

In addition to the laboratory monitoring there is also provisions for clinical follow-up, and it recommended that an individual be seen at least on a yearly basis for clinical evaluation. And as part of this clinical evaluation there should be an attempt at least eliciting some clinical history pertaining to denovo cancers, to neurologic disorders, hematologic disorders. In addition, the document recommends that

autopsies be obtained on individuals who may have expired and that tissue sampling be performed and RCR testing done on those tissues.

Currently there are two mechanisms for reporting those results. The laboratory and clinical results that would be positive, either for RCR or there was a significant clinical finding, it is currently the expectation of CBER that these be reported as expedited reports. And then all of the data should be provided to us in an annual summary.

Now to go back to our discussion, last November the Committee felt that life long monitoring might be a pretty big task for sponsors of gene therapy trials and rather than life long monitoring, it was suggested that we consider long-term follow-up monitoring. So let me try to summarize what your recommendations were. And essentially when we talked about long-term monitoring we implied that this would be monitoring that would take place approximately a year following the registration of a participant recognizing that monitoring that takes place during that first year would be probably specific to protocols and well described in each individual protocol.

So, for the purpose of this discussion we

will try to focus on long-term monitoring from one year and beyond.

The Committee had envisioned in an attempt to alleviate some of the burdens of the sponsors of gene therapy a bi-phasic long-term monitoring plan, one that might be intensive for up to 5 years. This, by intensive, we mean both a laboratory component as well as a clinical component in terms of the information that would be derived. And then subsequent to this the recommendations that your Committee put forth would be that we would focus on clinical information looking for rare events above the general population. And in order to do this, that this information needed to be collected and somehow be put into a centralized place in order to be visited periodically and analyzed for trends.

Once again, your Committee outlined to us general principles that revolved around the properties of gene transfer vectors. It was your recommendation that these properties govern our future recommendations for long-term monitoring; these including replication or the potential to generate replicating virus, integration and then also with looking at vectors with altered tropisms or vectors with long latencies.

What we have done at CBER, we've taken the summary of your recommendation and try devise an outline, a sketch for discussion of a proposal that could maybe be the basis for formulating future guidance with long-term monitoring. And what we have done is envision a three tier system. And what I would like to do now is take you through each one of those tiers; tier 1 being the least demanding category and tier 3 being the most demanding category.

So let's consider tier 1. It was the recommendation of your Committee that we have some provisions for studies that would involve vectors or studies that would involve essentially ex vivo gene transfer in non-replicating vectors that was put into cells with limited survival, probably less than 2 weeks demonstrated in vivo. And that the recommendation was that these types of studies probably could be exempted from long-term follow-up as they did not represent a comparative significant risk compared to the other types of studies that may be going.

So tier 1 would essentially encompass the types of studies that could be exempted from long-term follow-up.

For the purpose of discussion let me take

you now to the other extreme, which is the most demanding tier, tier 3.

And essentially tier 3 would be all the types of studies that would employ the types of vectors that had the characteristics that we outlined: replication; potential to generate replicating virus; integration; altered tropism of factors with latencies. And you had envisioned that this is the type of studies that would fall into this bi-phasic long-term monitoring plan that would encompass both an intensive laboratory and clinical follow-up for up to 5 years and then move on to a focus that is primarily tried to derive meaningful clinical information maybe through a clinical questionnaire.

As part of this kind of program also it was recognized that an essential component should be patient education in order to ensure participation.

The intermediate tier, or tier 2, is essentially a category that would encompass all other gene transfer products that were not in tier 1 or tier 3. And essentially for this category the laboratory component, which can be very costly to obtain and also the archival can be quite costly to sponsors, would be essentially eliminated and the focus would be primarily on trying to derive clinical information for

up to 20 years via a clinical questionnaire.

Within CBER currently we have essentially six vector types or vector classes that are commonly used in INDs of gene transfer studies; retrovirual vectors, adenovirual vectors, plasmid, poxvirus, AAVs and the herpesvirus.

What I would like to do in the next series of slides is consider each one of these vector classes and see how they would be effected under the proposed system for discussion.

So retrovirual vectors have a high potential for integration. They also have a potential for latency. Currently it is required that lifeline monitoring be implemented for subjects involved in these trials. Under the proposed system under discussion they would fall under tier 3, the intensive bi-phasic monitoring plan.

Herpesvirus by virtue of their high latency and the clinical implication there, and then also because they have the potential to replicate would also fall under tier 3. Currently there are no recommendations for long-term follow-up.

I will refer everybody to the March 7th FDA/NIH Gene Transfer Safety Symposium for details on the AAVs. There was much discussion there in terms of

the potential risk of this vector class, but for the purpose of this discussion I will focus just on the principles that we were asked to consider in trying to group those studies under a long-term follow-up system.

AAVs has variable integration potential. It has also the potential for latency. Currently because of the safety concerns that were outlined at the March 7 Symposium there is long-term follow-up that is required of some of the studies that are currently under consideration at the FDA. Under the proposed system they would fall under tier 3.

Plasmid vectors have a low potential for integration. They do not replicate, they do not have latency. Currently there are no long-term follow-up requirements. Under the proposed system they would fall under tier 2 where clinical information would be obtained through a questionnaire.

Poxvirus is one of those vector classes that we are going to ask you to consider in a discussion that will ensure following my presentation, but poxvirus by virtue of being capable of replicating would fall under the second tier. Currently there are no recommendations for long-term follow-up.

Adenovirus have the potential for

integration. Also have the potential for replication and currently long-term follow-up is not required. Under the proposed system they would fall under the category 2 or where clinical information would be obtained.

I would like to point out, actually just in passing, some information that is thought provocative that just appeared in *Journal of Virology* where essentially the traditional concept where you need to have sustained oncoproteins expression for adenovirus in order to have transformation is being -- at least there is a system that is being reported where present expression with subsequent clearance of adenovirus vector was sufficient in order to eventually lead to oncogenesis. And the authors of that article proposed a "hit-and-run" mechanism leading one to believe that it might be theoretically possible to see malignancies appearing at a later date.

The proposal for discussion, we envision that data collection should be the responsibility of the sponsors. This was articulated at the last meeting and there are good reasons for thinking this.

Number one, it's consistent with current FDA regulations that the sponsor be responsible for

collecting this data, but also it provides an element of patient confidentiality.

And normally selected data would be submitted into a centralized database that could be queried periodically for trends.

The type of data that a sponsor might want to collect in order to allow an effective process would be, of course, keeping track of patient identifiers, addresses, demographics. Also keeping track to the study site so at least being able to link that patient to a study site. And then also trying to understand or having some concept of when was the last time that the patient was seen at the study site.

And because long-term follow-up would require clinical information that might not be necessarily derived from the study site, it might be in the interests of sponsors to consider maybe trying to keep track of who the current primary health care provider is in order to try to facilitate some of this information at a later date.

The type of data that we would envision or would at least might be useful in the database, as was suggested by your Committee last November, would be: Whether or not a participant is alive or dead, lost to follow-up; whether or not an autopsy had been

performed and if an autopsy was performed, maybe having the results of the report.

The type of clinical information that could be included in this clinical survey would be the appearance of denovo malignancies, hematologic disorders, neurologic disorders, autoimmune diseases and vector reactivation being important with those vectors with latency. And then, of course, for all vector classes the potential for chronic infection.

So, in summary I have revisited the current guidance that are specific for retroviral vectors. We did not address other vector types or potentially new vectors that may be developed by industry. The current guidance is for long-term monitoring for both laboratory and clinical information, and a component of this is a requirement for specimen archival.

The new proposal that is outlined for you for discussion is essentially a three tier system that is based on principles that were outlined last November, namely relying on vector characteristics rather than vector classes, and therefore would allow some flexibility to encompass maybe new vectors that may be introduced at a later date into clinical trials.

We have tried to limit the laboratory monitoring and archival to up to five years in an attempt to address the cost that may be related to lifelong archival specimens. And we recognize the need to have some clinical information over an extended period of time for up to 20 years in order to try to detect rare events over background for the population being studied. And we envision that this information could be sent to a central database for periodic analyses.

This is my last slide. I will be happy to entertain any questions.

CHAIRMAN SALOMON: Philippe, why don't you join us and we'll sort of address questions to you and start the discussion as well.

Michael, do you have a --

DR. O'FALLON: I think several times you used the term "study." Certainly if the FDA gives approval these drugs or these cells would be implanted, not on study but we would still want the follow-up, right?

DR. BISHOP: That is correct. There could be some post-marketing commitments in order to continue providing this long-term follow-up.

DR. SAUSVILLE: So, Philippe, could you

give your vision of how this would work logistically? I mean, in other words you mentioned at one point sponsors' responsibilities and then you talk about a centralized database. So what do you see as the interface there?

DR. BISHOP: Because these studies are done under INDs for the most part, and it is the sponsor's responsibility to collect the information that pertains to this IND, we would envision that the information very much like UNOS currently collects information from their transplant centers. This process equivalent here would be that the sponsors would be charged with collecting that information.

And then we would envision logistically that some of that information could be forwarded to the Agency for inclusion into a database that could be queried periodically for analysis.

DR. CHAMPLIN: But the precedent to this is just what we heard, you know, similar to the National Marrow Donor program where the government has enacted either legislation or the FDA, or NIH have had an RFP to develop a registry. And in this case the registry's goal is to collect toxicity data and adverse events information. And if you're looking to pick up increases in the rate of secondary

malignancies or autoimmune diseases, these are going to be rare events. So in one small study you're never going to be able to see these things; you need to be collecting all of the adenovirus trials and see among thousands of patients is there an increase among the expected rate of any of these major adverse complications, will that occur in that population.

And I would think that the logical thing is you would require that people who file an IND pledge to enter their data into that system and then require that the institutions that are supporting, not the pharmaceutical sponsor but the academic centers that are doing the clinical trial, commit to having providing long-term follow-up the clinical information for this registry as part of their agreement to participate in the IND.

DR. SIEGEL: Right. There are a lot of discussions. The Committee is aware that you've participated in some regarding the FDA -- with the FDA and the NIH and further database development. And I think that's exactly what we plan to do. Indeed, these data are currently databased, if you will, at the FDA. As safety data come in, long-term or short-term, on gene therapy it goes into our database. We're working in conjunction with the FDA to develop

a more targeted database with enhance functionality specifically focusing on gene therapy.

In terms of sponsor responsibility, we're really talking about two different responsibilities. One is the responsibility for collecting the data from the patient, something the FDA is not involved in in any areas that I'm aware of. And the other is maintaining, storing and analyzing those data cross studies. And that later responsibility definitely FDA and NIH will be very much involved in.

On the data collection we have been quite cognizant of the comment you made now and earlier, and probably at our past meeting as well. And as you'll recall from our last meeting, Philippe talked about a survey, an informal survey of sponsors which raised some of those issues, too, about the role of the sponsor, the institution and the investigator.

Our current thinking along those lines is that we would, I think, pretty much along the lines of what you're saying. We do not have a direct regulatory relationship with an institution where we can go to an institution and require a commitment for long-term follow-up. But we have a legal opinion that says that it's well within our authorities when a sponsor proposes an IND gene therapy study to us to

require that sponsor to have plans for long-term follow-up that might well include plans for how they will obtain long-term follow-up should the investigator leave or should the sponsor go out of business. And such plans we would envision would, in many cases, involve arrangements and commitments from the institution where the patients are being treated.

And, hopefully, as we can outline what the follow-up entails and put that in the protocol, then those things could be costed out in such a way that the sponsor proposing the study would be able to determine whether they can adequately fund the real cost of their study including follow-up.

CHAIRMAN SALOMON: Richard.

DR. MULLIGAN: You know, the premise of this is that it's definitely a safety concept. Is there any interest in collecting good news as opposed to bad news on these patients? Because if there is any interest in having success of a therapy or something, which there ought to be a mechanism for, then obviously the guidelines that we set up are not really appropriate because things that may be safe or less risky may be just as likely to be good things as bad things.

So, I'm just curious. I assume what we're

talking is strictly a safety monitoring, but will there be anything in the database of interest to people that has to do with efficacy, anything like that?

DR. SIEGEL: Well, FDA collects those data. We're not sure at this point the time in the field that -- of a role, if any, of collecting that sort of data integrated across many different investigations which have different dosing routes, vectors, entry criteria one can logically say that there are safety concerns. Does a particular vector class cause cancer or latent neurologic syndromes. But when you get to the question of treating particular diseases, it's often very difficult to try to pool data from studies. At least at the current point in time the design of studies of gene therapy at these early stages is so diverse that that's not a current focus.

DR. CHAMPLIN: I would agree that as much as UNOS and the IBMTR and the National Marrow Donor program are looking at adverse events, they're also trying to look at efficacy issues. And right now the field is in its infancy. It would be difficult to do that in a major way. But as things develop, hopefully in a positive direction, that would be a natural

evolution of the database as well. And so the logical process is to work with the Gene Therapy Society and community to put together the leaders to define the fields in the database that could be used ultimately for efficacy analyses as well as the public need for toxicity monitoring.

DR. SAUSVILLE: There isn't a live column that they have.

DR. SIEGEL: I guess what you're suggesting is it's just that at this point in time you could say, okay, for kidney transplants there's many different variable ways of doing it and you can, in a large database, study and look at those. If we had one particular disease, let's say cystic fibrosis and many different investigations looking at fine tuning how to treat it, then you might want to be collecting outcome data for multi-study analysis of outcomes.

But, yes, as I said, I think we're not there but I think as we envision our systems, and I know the NIH has expressed interest in this in terms of the nature of data collection systems, you want to build systems that will be able to address those sorts of questions as they arise.

CHAIRMAN SALOMON: Richard, and then Amy.

DR. MULLIGAN: The other premise of the

difference between the classifications for the vectors is that essentially persistence of the genetic material is guiding us in terms of the way we do the long-term follow-up. And I just wonder whether everyone's comfortable with that; that is a short term procedure can have a long-term sequel even though the genetic information isn't persistent. And so you'll miss the kinds of toxic events that has to do with a accumulative effect of the treatment that may have a longer term effect. So if you have a CNS gene transfer that's even short term, like for brain tumor or something, you may well do some damage that doesn't manifest itself for a very long time.

And it just seems like the total way we've looked at this is from the point of view of just what's the likelihood that the vector DNA persists?

DR. SIEGEL: You want to specify the type of damage in that case that you're speaking of?

DR. MULLIGAN: Well, there could be -- let's say there could be neurological damage due to an acute lytic infection that goes away. And, you know, I don't think that's particularly unlikely relative to other adverse events you might have. So it just makes the point that it's really the disease, first of all, and then the vector. But I'm not so sure that it's so

key to be fixated on how long the DNA persists. That line of reasoning is a very specific line of reasoning that pretty much, I think, has to do with integration causing cancer or something. And there's many other kinds of things that could happen.

DR. SIEGEL: Well, let me, and I'll cede to Philippe to address this further, but what we're talking about here are kind of generalized long-term safety data collection systems. For every protocol in gene therapy or elsewhere we look specifically every experimental protocol at the risks of that protocol and what the data collection based on what the disease and the intervention are, what the specific data collection needs of that protocol are to be.

So one should not take this system to mean, even if you took a vector that might be type 1 but you gave it in a way that raised or gave a treatment or a gene, or whatever, that raised a risk of a long-term outcome that you wouldn't have to study that long-term outcome.

Beyond that, it's my understanding of the system as discussed and based on earlier discussions with this Committee and others that it's not fully based on genetic, indeed on persistence of genetics and that there are other factors looked at.

DR. BISHOP: A couple of comments. Number one, immediate adverse events that would occur under a protocol would probably be covered under the specific requirements of the study. The purpose for long-term follow-up was to detect rare events in the total population and, hence, the need to have that data collected in a centralized fashion and analyzed periodically.

The focus, if I could say, is on clinical information. And that is information that would be obtained through these clinical questionnaires for up to a period of 20 years, as was discussed last November. The laboratory information that would be derived would be limited for up to 5 years.

So the emphasis is on clinical data that would be imputed into the centralized database for the majority of these patients with long term survival.

DR. MULLIGAN: I think a good example might be autoimmune disease. You list that as one of the things you'd look at. And that's a very clear case where a short term gene transfer could well -- and let's say it's a lytic kind and it goes away, and there's no trace of it, could well have long term effects. And that's not going to be dependent upon, really, very many characteristics of the vector.

DR. WILSON: If I might just clarify. Tier 2 is really designed with your points exactly in mind, and that captures all the other vectors that don't have those characteristics of integration and persistence. So, I think if you take into account tier 2, we've taken into consideration your point.

DR. MULLIGAN: So really the only issue is the 5 years of actual specimen collection, was that right?

CHAIRMAN SALOMON: This is really where I want to go next, and then sort of letting everybody just kind of follow their natural thing here, which is good, but what I wanted to do in a minute after Amy and Dr. Lawton have given their point, to go back and like just look at tier 1, and look at tier 2 and then look at tier 3 and get into this in a little more detail. Because I think a couple of us have some questions about the specifics here, and I think that's what they need to hear.

Amy.

DR. PATTERSON: Well first, I just wanted to offer NIH's commendations to FDA and the Committee for taking this issue up. But I wanted to underscore a couple of points and then address a question that I think was raised by Dr. Champlin about scientific user

community input into the design of these studies.

First of all, I think it's an obvious thing that deserves being stated that this must be an evolving strategy and the level of follow-up that's required over time will have to be titrated according to the data received.

And I think at your last meeting you very amply covered the points that this is a tremendous investment. It's a tremendous investment by scientists, by the sponsors, by the patients who volunteer to be research participants that once the study's over, they still give time and part of their life to be followed. Therefore, I think there needs to be a tremendous amount of that and much broader expert analysis into the types of clinical follow-up, how those studies are designed. Because to follow-up on Philippe's point that the detection of denovo cancer, neurologic or hematologic disorders that may be very rare events, that the design of those studies is going to be so critical. And my concern is that we don't end up 10/15 years down the road with very heterogenous studies that really the results are comparable and a tremendous amount of resources have been invested by all and we have no data for medical or scientific utility.

And, therefore, I think that I would urge that the process here be that these recommendations move forward, and NIH is very willing. I've talked to Dr. Siegel about this, we would like to hold a policy conference and a series of intensive workshops on this topic to get input from the scientific community, from the epidemiology community on how to appropriate structure studies that will give valid results.

CHAIRMAN SALOMON: Alison.

MS. LAWTON: Some of my comments kind of go along the lines.

I guess one of the things that I have a question on is around the database establishment. We've just heard from UNOS that basically we heard it's about $8 million worth to keep this database maintained. And so I do have a question around if we're going to ask the sponsors to make the commitment to this long-term collection of this data, do you have the funding, do you have that ready to be able to do this database? And what kind of commitment are we going to have on how that database is going to be put together so that the data that's collected can be analyzed and reviewed, and is useful? And as part of that I would also emphasize I think it's very important we always talk about risk benefit, and the

one thing we don't want to be just collecting safety information without understanding the different patient populations and some of the other aspects to put that into context for these gene therapies as far as the risk benefit.

I think that's it what I wanted to say.

CHAIRMAN SALOMON: I mean there's two directions that I think we need to go in in the next short period of time. One is to, of course, address a series of specific questions that Philippe and the FDA staff have put forward. And I thought a good way to begin to get at that, that at least I find easy to do, would be to sort of breakdown this tier system and look at tier 1, 2 and 3.

The other thing to do is to talk a little bit more about some of the practical implementation of a database system, which I understand that our UNOS colleagues have to leave at 10:30. So maybe just in interest to spend 10 or 15 minutes just sort of talking a little bit more about a specific implementation, and then if you will, I'll sort of take the Chairman's prerogative at some point to kind of cut that off and move toward a specific discussion of the questions and the tiers.

Is that reasonable for everybody?

So, just to focus a little bit on implementation of a database system, though I might have chosen to this in the adverse direction. How large do we think a database system for gene therapy would be now and in the relatively foreseeable future relative to the size of this UNOS system, which has been around for 12 years. We're throwing money around, like $8 million, as if that number is relevant to the cost of a gene therapy system. So I think we ought to start with considering how big do you think a gene therapy system would be? Would it be that big? Would it be bigger? Would it be smaller?

DR. NOGUCHI: Well, I think one of the considerations of that that would be good to hear is what about scaleability? Is there a concept that a smaller number of patients cost proportionately less? My guess is probably not depending on what you want to collect. I think for talking about 16,000 data elements, no matter how small or how big, part of the cost is going to be relatively constant. So that might be a good place to start.

MR. KECK: I think that the cost is directly related to, at least in the first year or so, the number of data elements you want to collect. We're currently actually building a system for a

private organization right now that is sort of similar to what you're talking about. It is for ventricular assist devices. And it has tiers of information. They are probably looking at anywhere from 1500 to 2000 individual cases worldwide per year. This would be a worldwide data collection system.

And they have a basic set of information that they get on all their patients that are participating in the system. They have tier 2 which relates to adverse events that are driven off of follow-ups that are pregenerated all along, which kicks off another form that is specific to that particular complication and get more information on that.

There's also adverse event reporting and prompting people to remember to report their adverse events.

Over long-term there is integration of this system with other databases. This particular entity has another database that we manage that they want integrated with this system, as well as integrated with the UNOS system for follow-up of those patients that get transplanted.

And so all of that is, I would say, over the next year going to cost probably half a million

dollars. And they're collecting right now 200 data elements throughout the whole system. The follow-up as time goes by is yet to be determined on how much that will cost because of the unsurety of the volume of patients. But to give you an idea of scaleability, that's the best example I can think of.

DR. CHAMPLIN: The toxicity collection is pretty straightforward. There is an NCI common toxicity criteria used for cancer treatment trials that's very detailed and could easily sort of be adopted to this purpose.

The efficacy fields they're a lot more controversial and complex and depend on the treatment and the objectives of a therapy. But the way the NMDP worked was to create the organization, get the relative investigators together to discuss just what fields do you want to collect both from an efficacy and toxicity perspective, and gradually build that database. And it was a big investment to get the computer system off the ground and work out the data entry system at the same time. But that's sort of the beginning of the program.

Since at this moment gene therapy is sort of a small field with relative small number of patients, UNOS is obviously dealing with a large

ongoing activity that won't be there immediately with gene therapy, although you will anticipate that over time and with the continued survival of patients that the number of individuals being followed and data collected will mushroom, but at the beginning the numbers will be relatively small. But you need to basically go through that process of getting the relevant investigators together to identify the critical fields that need to be followed for both efficacy and toxicity. But the toxicity part of it is pretty much standardized.

CHAIRMAN SALOMON: Michael and then Amy.

DR. O'FALLON: We've been talking about your cost, but there's an awful lot of hidden costs out there that are not part of your budgets. You got any sense of the proportions?

MR. KECK: Are you speaking to cost at the center?

DR. O'FALLON: Of course.

MR. KECK: I would hesitate to guess. We have such a range of sizes of centers and the number of forms that they get. We have centers that get thousands of forms that have been in existence for a long time and have a staff of 4 or 5 people that do nothing but fill out UNOS forms. And then we have

centers that might get a 100 a year and the clinical nurse fills them out. It ranges very dramatically.

I will say that --

CHAIRMAN SALOMON: We have a relatively small program and we have one data coordinator whose full-time job is filling out UNOS stuff.

MR. KECK: Although I do think that in terms of development of data systems, and I have come to strongly believe that electronic is the only sensible way to go. Paperback systems are just too costly and people have come to want to give information electronically. We ran a dual based on two parallel system of paper and electronic for a number of years. And I can tell you, it was extremely costly to have both. And the ongoing magnets of the electronic system, I think, is going to be cheaper and easier to change as time goes by.

DR. PATTERSON: I just wanted to follow-up with Dr. Champlin's point and give you a little update on some of the progress on the FDA and NIH collaboration on a gene transfer database.

Over the past several months the agencies have been in an intensive dialogue and have developed and almost finalized the system's requirements, the data structure from the feds' point of view in terms

of the federal review staff at FDA and in terms of NIH's needs in terms of being stewardship over public funds in this area in the RAC review.

The next step, and we're in the process right now of setting up a series of user groups where we will be meeting sequentially with members, representatives of patient communities, the ASGT, other scientific groups and industry to discern what their information needs are and also to discern burdens of reporting an what from a scientific and practical perspective they think are important considerations.

So, just wanted to give you that insight into what the current process is.

CHAIRMAN SALOMON: Can I ask of Philippe or Carolyn, and maybe Amy you can comment as well, we still haven't gotten the answer to my question, and that is what is the size of this program? I mean, how many patients do you have per year on gene therapy INDs?

DR. NOGUCHI: I don't think we necessarily have an ongoing accurate count of that date, because studies are in various stages and the reporting numbers of patients is also quite variable. The best estimate overall I think does come from OBA, perhaps.

CHAIRMAN SALOMON: Well, let me make a guess here. I mean, from the data we saw yesterday, maybe being generous, 150 INDs were in that review?

DR. NOGUCHI: Well, it's about 200 active ones.

CHAIRMAN SALOMON: Okay. 200 active. Okay. And that's good. I mean, that's close.

So 200 INDs. But in a gene therapy trial, these days at least, is relatively small. I mean 30/40 patients in a gene therapy trial is gigantic, right? I mean, most of these gene therapy trials are 5/10 patients. Again, I'm just testing. If I'm wrong, tell me. I'm just trying to come up with a number here in a second.

DR. KEEGAN: Well, it's true that the majority actually -- unfortunately I don't think we can give you a specific number. It's true the majority of the INDs are phase 1 and 2 trials; however, there are several phase 3 ongoing trials. There are probably at least 10 INDs that have as many as 4 in it and 5 active protocols in them.

So there are some very active programs. It's hard to generalize without going back and looking at the specific numbers.

DR. SIEGEL: And you don't want to exclude

those that are inactive or withdrawn. They have patients that require long-term follow-up. And there are certain types of things that we'd want to have in this database that were not within the scope of March 6th.

So, it's going to be hard to come up with an exact number. But if you're looking at ball parks, you know, you're looking at several hundred trials and thousands to tens of thousands of people at the present point of time and with a potential for great growth or for no growth, which is a little hard to predict.

CHAIRMAN SALOMON: Yes. I was just going to make a ballpark figure of about 4,000 to 5,000 patients, which is I think fairly generous. Because I mean that gives you a concept to what they're dealing with, which is a lot more. I mean, you've got 75,000 plus listed, plus they're following what? You said 200,000 some patients? A quarter of a million. 250,000..

So I just want to put some reality here. Now, Phil's point -- and that's not -- I think I'll stop there in the sense that the point of this Committee isn't to help you figure out how much it's going to cost. But I do want some reality check there

in terms of we can do this and it's not necessarily going to take $8 million a year, but you can't make a calculation like that.

DR. SIEGEL: On the other hand, and it's worth noting, that unlike, say, transplanting a heart if you have a gene therapy that treats a lung cancer or a breast cancer, you may have several thousand people in the study period and tens or hundreds of thousands or millions of people in the post-marketing periods. So the potential is different than that for solid organs.

CHAIRMAN SALOMON: No, no. If gene therapy takes off, Jay, this will be much bigger than organ transplantation. There's no question about it.

MS. LAWTON: Can I just ask, we do have another example that I'd like to ask about, and this is the xeno registry database that we've established for long-term follow-up of patients. And given the relative time periods here, you know, how does that compare and how are we doing on that compared to what we're now talking about doing for gene therapy, which I assume is much larger than the xeno database?

DR. NOGUCHI: We are in the process of completing the pilot stage and hoping sometime within the next fiscal year to actually be entering data into

that on a real time basis. There are several major differences between this and the gene therapy.

For the xeno database we have elements that would not be required for the human gene therapy in terms of we have a very extensive extra set of data fields for the animal; the animal production facilities, where they come for and an ability to link the particular animals from which organs, tissues and cells are derived to each individual patient. So, part of it is a little bit extra than what you'd see with gene therapy.

In terms of the safety data follow-up, we are restricting it at this point in time to those adverse events that we feel would be more related to infectious disease cause because that is our major concern with xeno transplantation. Above and beyond the usual adverse events in a clinical trial, it's the inadvertent spread of infectious diseases. So the scope of the adverse event reporting at this point in time is more limited and more specialized.

Some of the other aspects of it that have been put in are not implemented at this time are some of the ideas of being able to actually at a periodic time send out reminders to, in this case is could be either the physician or the organization or the

sponsor. Because it's not implemented yet there would be quite a bit more to do, but that idea has been built into it.

The projected number of patients this would follow at this point in time would be much more restricted, perhaps being generous, in the low to mid hundreds of patients.

CHAIRMAN SALOMON: Okay. I think we've sort of covered up until as far as I think we ought to be going in terms of the actual physical implementation of the database. So it's not off the table, first of all, if anyone has any last comments before I sort of segue back into the tier system, you're welcome to make those now.

MS. LAWTON: I guess I would just emphasize what I said earlier; that you know if you're looking for the sponsor's commitment for this long-term follow-up I think it's an absolutely critical component that has to be addressed with some level of urgency on how that database is going to be built, who it's made available to, how you search it, how you analyze you, how you provide that information.

CHAIRMAN SALOMON: What I'd like to do now is segue into the specific questions that Philippe and Carolyn and the rest of the FDA staff have posed to

us. But I'd like to do it is a little different than this question 1, 2, 3, 4, though I promise to get at them specifically.

I'd like to start with looking at table 1 and table 2 of the handouts, which I'm assuming everybody has. And ask everyone one to sort of pickup where Richard started in terms of the discussion of do we agree with -- I mean, what I would like to hear from the group is comments on the overall strategy of the tier system, but specifically if you wish to start with tier 1. I mean, just actually looking at the vector characteristics and the fact that participant follow-up past the first year is listed as none. Because that was kind of one of the issues that Richard brought up.

I mean, my feeling here is that it's a very important to help the FDA come up with a system that is flexible enough that it can be used for a long time and that provides something that the Committee is comfortable with in sort of an over-arching theory that gives sponsors and new investigators some flexibility to kind of slide into these. And that's a challenge. I mean, if we don't feel that that's possible, we owe it to the FDA to say no. You know, this isn't an organizational principle and we can't

use it. So, I think that's kind of where I'd like to end here with the idea of some sort of reassurance or not to the FDA that this is a good way of parsing it out.

Abbey.

MS. MEYERS: I don't understand the logic behind the stopping follow-up after one year on that lowest level. Can somebody explain it.

CHAIRMAN SALOMON: I mean, let's get to that. Let's talk about tier 1 then, unless there's anymore generic conversation, and then we'll get to your question, Abbey.

DR. SAUSVILLE: I think that to have this be based solely on the sort of modality or how it's delivered ex vivo as opposed to the nature of the gene deserves some thought. Because, I mean, it's well known that to pick up the oral immunity example, I mean a relatively brief strep throat can give a lifelong rheumatic fever and it's hypothesized that other elements can, for example, contribute to arthritis, etcetera.

So, one, I actually would feel uncomfortable about making this blanket exemption just in relation to how it's done. I think the investigator or the sponsor should justify why their

particular gene might be expected to not have this type of long-term consequences. And I can certainly imagine genes where that would be the case. But I can also imagine genes where it would not be the case.

CHAIRMAN SALOMON: I'd have to say that I agree completely, and I think that was what Richard was saying as well.

Again, if I'm not speaking for the Committee, but I really think that right now the public is not willing to accept any sort of gene therapy as having no responsibility to the sponsor for long-term follow-up after the first year.

DR. MULLIGAN: Yes. I think on the case that I would characterize as being the perfect case, one, would be an irradiated tumor vaccine. And definitely some of the thinking behind inducing an immune response is the risk of any autoimmune response because of a local concentration of something. And that is clearly the case where the cells will go away in a week or two and you'll note DNA persisting. So I would echo to have no follow-up of that as maybe not wise.

CHAIRMAN SALOMON: I think there's been a consensus on that.

DR. SIEGEL: To reiterate what I said

before, we have a lot of traditional drugs and biologicals that as needed, depending on their mechanism of action, we require long-term follow-up, collections off and data registries that exist well into the post-marketing period. And I think what we were focused on here are the specific needs related to vector class type and properties for follow-up, not those needs that might be related to the specific therapy and specific patient population. But we'd certainly agree that with any type of vector or even outside the field of gene therapy there are going to be certain types of follow-up necessary for certain types of trials that in some cases may extend to extended periods of time.

CHAIRMAN SALOMON: One of the limitations we've talked about before in the generic discussion is the tendency that you look at this and you go "no follow-up," and you go no you can't allow that. So I think that's what you're getting from the Committee right now.

DR. SIEGEL: I can't imagine a tumor vaccine trial, for example, where if you're treating a tumor and the patient is still alive at one year, you're going to stop following him in that trial. That's just not the way we do cancer trials.

CHAIRMAN SALOMON: Fine.

DR. SIEGEL: Or at least not the way we do most cancer trials.

CHAIRMAN SALOMON: So our only point is tier 1 has to have some element of long-term follow-up, that's all. That we don't think that right now in gene therapy the public's going to accept any tier --

DR. SIEGEL: As a routine, regardless of the nature of the vector or the trial, or whatever, that these patients -- regardless. And that being the 20 years of clinical follow-up. So basically tier 1 becomes tier 2.

MS. LAWTON: No. I understood that it's going to be based on all of the different components in that trial, that the patient population, the vector, everything else, the gene.

DR. SIEGEL: Right.

MS. LAWTON: And based on that you'll decide whether you need long-term follow-up. You're not automatically saying everybody has to have long-term follow-up, are you?

DR. SIEGEL: No, but I think that's what the Committee is saying, that everybody has to have that.

CHAIRMAN SALOMON: This is the problem I

have, again, with these generic discussions, and I've said this umpteen times. I mean if I can imagine that there should be -- if you can put some wording into it here, the problem I have is right now -- right now, not a few years from now with some experience under our belts. All we can deal with is right now. And right now I don't know under what circumstance any gene delivery experiment can be exempted from follow-up. And I don't know how I could defend not producing that sort of follow-up to the public.

Now, from a sponsor's point of view, whether as an investigator myself I know what I'm saying, you know it scars me -- we'll get into this -- to be committing to 20 year follow-up. And we'll have to talk about that in a minute, but I don't want to contaminate this discussion with that yet.

That's my point. If someone disagrees with me, then we need to get that table. But I just don't think we have the kind of information that could be presented to a group of science experts in gene therapy or gene delivery that would convince me that you don't need follow-up.

DR. SIEGEL: That I think will be, but I'd ask my staff to confirm this, except for retrovirus and mediated gene therapy, that would be radical

departure from what's been done over the last 5 to 10 years. And if that's in fact the recommendation of this Committee, we would be going back to large number of experiments. I'm not sure how much we can do that retrospectively. But I think -- well, I'll just leave it at that.

DR. NOGUCHI: Well, I think it may not be as radical as you think in the sense that what the proposal is on the table is that in addition to retroviral gene transfer studies, a large number of the others would have varying amounts of follow-up. And the specific --

DR. SIEGEL: Hey, that's the proposal we put on the table. Dr. Salomon, have you not said that for every patient receiving a gene therapy of any type, you think that 20 years of clinical follow-up should be obtained?

CHAIRMAN SALOMON: That's what I'm trying to say is the consensus of the Committee. And I've said that we should have discussion if that's not. I'm not trying to oversimplify it. That could be by postcards. And I'm not saying that they have to be in and have multiple tissue biopsies every year. But, yet.

DR. MULLIGAN: Yes. I think that what he

is saying was you want to separate the question of what the follow-up was from the discussion right now. So I don't think I would agree for a blanket 20 year follow-up for everything. But he was just saying let's defer the issue of the follow-up, but there should be.

MS. MEYERS: I think the main thing is that the patients have to know their responsibility when they sign that informed consent form. And that is that they are going to be expected to go back and see the same doctor, at least talk to him on the telephone or have his local GP cooperating with the investigator to give some type of follow-up, at least for the first 5 years. I mean, you've got to lay it out because the patient has to know what he's getting into.

Now, let's say 5 years down the road we have enough data to know that there isn't any problem from one type of vector, and you want to change the rules. That's fine, as long as the patient himself has committed to talking to the same doctor every year and giving his data.

DR. SAUSVILLE: Again, I reiterate my original point was that this as written here seems to be a modality sort of approach; ex vivo, plasmid, what

have you. I think to make it a blanket thing that there should be or should not be follow-up just on that basis. It should be reconsidered and the matter addressed by, perhaps, the sponsor and the investigator based on the biology of what they're manipulating. And I think that should enter into it somehow.

CHAIRMAN SALOMON: That's why I kept saying, I mean if we had a specific in front of us and we could engage in a specific discussion and you could convince us -- I mean not you, Ed, but the sponsor could convince us that they had data that showed that there was no reason to follow-up for 2 years, 5 years, 8 years, 10 years, I'm fine with that. I mean I'm science driven. But I was just saying, again, stuck with the generic I think that the message has to be that you can't exclude follow-up under tier 1, that there has to be some follow-up. That's all I'm trying to say.

DR. SIEGEL: I think you're missing the question here. The specific will always be the specific. Okay? We are discussing the generic. Okay? We're discussing saying if you're using this type of vector, you're going to do 5 years of specimen collection and 20 years; no matter what the specifics

of your protocol are.

And if what the Committee is saying is the FDA should just decide on each protocol how long the follow-up should be, we could do that. I'm not sure that's really the optimal way to do this.

If you're saying that we should decide, they can show us "Well, we think that this particular vector is safe enough, we don't need follow-up," then we'll make a vector-by-vector decision, well that's an interesting approach.

We are talking about generics and what we heard you say, and I guess we heard wrong, in November that there were some sorts of experiments such as these that were so low -- that the specific gene therapy type of concerns were so low -- yes, there are tumor vaccine concerns. We require follow-up on all tumor vaccine trials. We're always going to require, depending on the specific issues of a specific vector, the appropriate safety, but the specific risks of gene transfer we were told last time that certain types of products are so low that we didn't routinely need to require long-term follow-up based on the risks directly related to gene transfer.

And I think you're saying something different now, although I want to make sure that's

what you're saying.

CHAIRMAN SALOMON: I think we're saying something slightly different than -- I remember the discussion in November. It wasn't quite -- you know, you've come back again very appropriately now, and I congratulate Carolyn and Philippe for doing this. I mean, this is a really good way to focus discussion by offering something that I think would be very useful to the whole field, and that is when you're planning your studies you can say to yourself and your collaborators "Well, look, is this going to be tier 1, a tier 2, or a tier 3 sort of protocol or a vector, or whatever." And I think that's very useful. So we're trying to work with you.

But that's a little different than what we were talking about in November when we were just saying that in some instances where we didn't have any thought that there would be residual gene delivery detectable after several weeks, that that might not require the same degree of follow-up. And I think all we're doing is choking a little bit on the term none.

DR. CHAMPLIN: I don't think we had a tier 1 vector presented this morning. Are there any tier 1 products?

DR. SAUSVILLE: Well, you can imagine a

plasma that encodes MDR. I mean, that sounds pretty non-enorganic, none persisting. In fact, it is nonpersisting when people have done these experiments.

So I could probably live quite comfortably with not having a lot of follow-up on that. I could also imagine a vector that has B7 in the context of some antigen or other, and then I'd be real concerned about that in relation to long-term follow-up.

CHAIRMAN SALOMON: Richard and then Michael.

DR. MULLIGAN: Jay, I'm now getting confused because when you talk about the tumor vaccine you say well, of course, you know the FDA is going to make sure there's the appropriate follow-up, and that's obvious that's going to be the case. So what we're talking about here in that context is whether or not in a way the information that you're asking for ends up in a database, isn't in fact? Isn't that a way to look at it?

DR. SIEGEL: No, I don't think so. Let me state this problem as I understand it.

We will look at a vector that contains B7 and an antigen and determine the appropriate amount of follow-up for that or MDR, or whatever it is. Just as we look at a given drug and its potential adverse

effects and determine the appropriate amount.

What we're focused on here is that there are certain issues that have been raised in gene therapy that have led to specific concerns about long-term follow-up. Those are largely issues related to the nature -- to viral infection, to insertional mutagenesis, to specific activities that relate to use of virologic vectors and to gene transfer mechanisms. Those concerns are the types of concerns that led us initially into this area in requiring long-term follow-up for retroviral vectors, a requirement that's evolved over the years and that hasn't always yielded the quality of data we'd like, as was discussed a few months ago.

Further, we've realized that some of those concerns extend well beyond retroviral. And so we came to a belief that for retroviral vectors we're probably not targeting the right information well enough, and for other areas we're not collecting enough information.

But I think where the Committee is getting a little bit bogged down is, you know, if you give a treatment to a child, you may want ten years follow-up on it to see if they have normal growth and development; what happens during puberty.

If you treat cystic fibrosis or if you treat Alzheimer's Disease or cancer, the types of follow-up that are specific to that therapy and to that disease may vary tremendously. There's no notion here that patient follow-up is exempted. But I think if you're advising us that we should have patient follow-up that's suitable for the nature of what the gene product is going to be and that's suitable for what the patient population is going to be and for what their disease is, well of course. I think that we'll take that advice, that's what we do.

So then the question is those things aside. So those things aside, should we because it involved gene therapy say regardless you've got 20 years of clinical follow-up or 5 years of clinical follow-up?

CHAIRMAN SALOMON: Jay -- yes. So my comment I don't the Committee is getting bogged down. We've told you already several times that our feeling is that right now at this point, being sensitive to the way the public is looking at gene manipulations of any kind, that we don't think -- and again, I look to my --

DR. SIEGEL: Well, you've told me that several times. I think Ed said, for example, with

some inserts he wouldn't worry about that and with others he would; that's a different message I think.

CHAIRMAN SALOMON: Okay.

DR. CHAMPLIN: I think you might instead of saying the word exempted you could say protocol specific, which we all agree that pretty much what you're saying, that you need to do it on a case-by-case basis but it's hard to envision none ever applying.

DR. O'FALLON: Well, that's a great segue into my comment. The fact of the matter is I asked a question right after Philippe was done. Are we talking about what's happening while the protocols are underway or are we talking about what's happening in a general sense? And we keep getting them getting confused.

Protocols have to have follow-up in order to establish efficacy. Efficacy, not necessarily adverse effects, which is what we're primarily worried about here.

Every one of those protocols must be written in such a way that the FDA found them acceptable and when they come here for approval, they will have to have had adequate follow-up to have established efficacy that convinces us that the agent

is efficacious, or else it's not going to be approved.

So, we're not talking about the protocol specific follow-up that is necessary for the success of that protocol. We can't be.

DR. SIEGEL: We would include this safety follow-up within the protocol.

DR. O'FALLON: Well, that's fair enough. So we might say there is no safety follow-up necessary, but we certainly aren't saying there's no follow-up necessary to establish efficacy.

CHAIRMAN SALOMON: Michael, I just want to be clear. And in this case, you know, there has been times and it's okay, that the Committee doesn't have to have consensus. I actually think that's important.

I am saying that my opinion is that right now I don't believe that there's any gene delivery protocol that I can at least think of that I could do, give to a patient and then say that don't require any follow-up for safety. I'm just talking about efficacy.

DR. O'FALLON: Well, and how long is that minimal period of long-term follow-up that you're saying that they should require?

CHAIRMAN SALOMON: I was going to get to that next. But I thought it was -- we're having

enough trouble just getting across that. But I think that should be the next question: what we're talking about in follow-up.

DR. SIEGEL: What are you trying to follow-up for? Latent malignancies, latent diseases, latent neurologic, hematologic? Because we've tried to focus that follow-up on the particular risks, but you're saying there are particular risks you're concerned about that are there but just because it's gene therapy, independent of what cells and what vector and whatever, and so it's hard to know how long you follow-up for those --

CHAIRMAN SALOMON: We've got to take a biopsy of what the public is thinking about. I mean, this is a public who absolutely got hysterical when they found out that some genetically modified corn ended up in some tostitos, or whatever it was.

I mean, I respect that. I'm not making fun of it. That's the way the public is looking at this. And therefore, if we're trying to give you responsible advice, what's driving me is trying to sensitive to the way the public is looking at this field and looking to experts like myself to give them in terms of reassurance.

Personally I think that many of these

protocols after 5 or 10 years we'll look back and go "Boy, that was a lot of effort for nothing," and be thanking God that it was a lot of effort for nothing. But I think that that's what the public's expecting from us today, at least that's what's driving my comments right now.

DR. SAUSVILLE: I mean, obviously, you know we respect the interest, indeed, the demand of the public to have responsible follow-up.

I think what you're hearing here is some ambiguity in trying to chart a middle course between exactly that, because this is a gene therapy require, you know, follow-up ad infinitum, which I think plays more to the -- I would use the word -- hysterical aspects of worrying about a corn in tostitos versus-- I mean, I was reacting to the word exempted. I mean, and one interpretation of that is that actually a sponsor could choose a particular vector vehicle for an outcome because it would exempt them. And that I think would be wrong, actually.

I think that one needs to, and I return to, have the nature of the follow-up driven by the biology. Now what seems to have done is run into yes you always make demands for follow-up based on the biology of what you're trying to accomplish, and we

respect that. Okay.

So let's take off the table the types of follow-up that you would impart based on the nature of the protocol and try and come up with what I would hope would be middle ground generic consensus.

I mean, I agree with Dan. I think we're clear. I don't think we're --

DR. SIEGEL: I do want to say to Dan that maybe things will change after today. But it is important to note that much or most of gene therapy research has not had long-term or lifelong follow-up commitments. Those that have had it, as we discussed in November, have failed to achieve it in any meaningful way. And perhaps there should be more of a public outcry. It isn't there. And I think that as scientists we also have a responsibility to determine what is scientifically appropriate and to educate the public about what is scientifically appropriate. Because there's always more money you can spend collecting more data to provide reassurances, but if it's not useful, then it's not -- you know, you don't do it just because you --

CHAIRMAN SALOMON: Yes, I totally agree, Jay. I totally agree with that.

If I could choose what we talk about, this

wouldn't be the topic I'd like to talk about because I find it very uncomfortable because of the implications of it.

But I've said this before, there are groups in the public who have taken a position no gene therapy, and there are groups that no animal research and no this, and no this, and no this. But that's a minority. The majority of the public is willing to give us quite a bit of latitude to do these sort of cutting edge technologies. And that is based on a trust in us that we are going to do the proper follow-up, and that's what's -- again, just trying to state it a different way. I feel that that is a responsibility that we have.

MS. MEYERS: Jay, over 80 percent, my list calculation, of all gene therapy experiments since day one have been on cancer. And most of those people, of course, are dead. They've been dead a long time because gene therapy hasn't worked. So if you start that database today, you're going to have practically nobody in it.

But my long-term memory of this whole thing was that first little girl who went through the severe combined immune deficiency experiment and when that family moved into a new neighborhood, this girl

was known. Her family had gone public. Her face was in *Time* magazine. And the neighbors told their kids not to play with her because she had gene therapy and she might be contagious.

We've got to do something for the people who do survive to assure them that this whole thing is safe.

DR. SIEGEL: Well, I don't have any problem. Believe me. I mean, that's why I'm with the FDA. I believe in a public responsibility to ensure safety.

I'm simply saying that the amount of safety data we require should be based on scientific considerations. It should not be based on public expectations that we collect useless data. If we believe the data is not scientifically important to collect, we shouldn't say that we should collect it because the public expects us to collect it. That's the only point I want to make.

CHAIRMAN SALOMON: We agree with that, Jay.

MS. MEYERS: We understand. I think that public expectations are much more important before we lose this whole field.

CHAIRMAN SALOMON: We agree with that

concept. And there we get back to that there has to be within any of these sort of things enough flexibility that you can do your job, which you guys do well that part. I mean, detailing the system for a specific protocol.

DR. SIEGEL: It will be easy for us to ask everybody to collect everything on everybody for long term. And if they don't, to put them on clinical hold. That'll be easy to do for us to do our job.

This is not an issue of FDA resources. It's an issue of what's reasonable in order for science to progress.

CHAIRMAN SALOMON: We agree. And I think there's just a lot that still needs to be understood about gene therapy before I'm willing to say I recommended that you could exempt whole groups of vectors from follow-up.

So that's tier 1. One of the things that I wanted to point out, just a practical thing, in tier 1 is less than 2 weeks in vivo. I think that's probably a little bit too short. In fact, if you infuse T-cells, they can last a lot longer than 2 weeks. So I might say something like 6 or 8 weeks just to be a little more flexible within that coverage. A lot of cells survive longer or can be

detected by real sensitive PCR techniques. And even that you may find eventually has to be changed because of the cell's persistence.

DR. SIEGEL: If you say that's tier 1, I think -- you said you were going to come around to this issue of time. But if in fact there is a consensus of the Committee that for all gene therapy there should be clinical follow-up of at least a certain duration, I'd like to find out what that duration is and what the nature of that follow-up is.

CHAIRMAN SALOMON: All right.

DR. MULLIGAN: I have a radical suggestion.

CHAIRMAN SALOMON: Yes?

DR. MULLIGAN: Which is we move to that issue of the time, because everyone's real nervous about this.

CHAIRMAN SALOMON: That's what I wanted to do. So, Richard, why don't you make a comment on that? Let's talk about that.

I just wanted to make sure I remember to tell you 2 weeks was too short. That was a practical thing.

DR. MULLIGAN: Well, I'm not by no means an expert on this part of things, but just reading the