

Transcript

**Fifth Meeting of the  
Secretary's Advisory Committee on Xenotransplantation,  
U.S. Department of Health and Human Services**

Breakout Session: SACX Working Group on the State of the Science in Xenotransplantation  
Tuesday, February 4, 2003

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**DR. SYKES:** So I thought we would just go through the document in order and start with the introductory section. And I think what we should try to do with this section, you know, we talked in general terms yesterday about what should and shouldn't be included. I think right now we should try to come up with specifics about which points should be there and in which order.

**DR. ROTROSEN:** Before we do that, is there a general agreement that there will be an executive summary?

**DR. SYKES:** Yes.

**DR. ROTROSEN:** You know, that was mentioned yesterday, but not as emphatically as it should be. The chances that people high up in the Secretary's office are going to read this report are very low.

**DR. MICHAELS:** Right. Can I ask you to comment on how long an executive summary should be for the entire thing?

**DR. ROTROSEN:** Probably four to six pages.

**DR. SYKES:** I think what that will end up being is a confirmation of the bullet points in each section which we're also going to add to the sections that don't have ...

**DR. KASLOW:** I don't know whether the corollary question is does that influence in any way how long the total report is? So you think it doesn't make any difference?

**DR. ROTROSEN:** Yes.

**DR. SYKES:** Okay. So let's go through the introduction and try to come up with a consensus about which of these points should stay and what might need to be added and what might be taken out.

Just one point, a wording point in the very first sentence --

**DR. ALLAN:** Bob, you said you've re-done this whole section. Is that right?

**DR. MENDEZ:** Yes. Unfortunately I'm reading from another draft than the one that you have that I re-did that never got out to you.

**DR. ALLAN:** How long is it? Is it significantly shorter?

**DR. MENDEZ:** No. It's six pages.

**DR. ALLAN:** Okay.

**DR. SYKES:** What about the one you sent me on the weekend? It was slightly changed but it was generally the -- is that the one you're working on?

**DR. MENDEZ:** Right.

**DR. SYKES:** So the overall content is pretty much the same.

So in the first sentence we should make sure we refer to this as a report, not a paper or anything. That's just a minor thing. And I think I'll save my own specific wording suggestions for later and then pass that

on to you. So the first section, the burden of chronic and degenerative diseases, scope of the problem in the U.S., how do we feel about that as the first section, being the first section? Is that logical to everybody?

**DR. CHAPMAN:** Reading this whole report, my suggestion would be that you actually pull something out of your section, the scope of the problem, where you basically say this is what xenotransplantation is and here's how it looks, and put it right after this first introductory paragraph, and then go into what's now the introduction.

**DR. SYKES:** Yes, that we had already taken into account yesterday.

**DR. ALLAN:** And we should also summarize -- I mean, right now the intro is only directly related to the immunologic hurdles and those types of things. It doesn't include infectious disease. So I would suggest you put in a sentence or two in the intro, such as this report also describes...

**DR. SYKES:** It's right there in the first paragraph, John. And I'm not sure we want to add anything. In fact, I'm going to suggest subtracting, because there's a lot of redundancy here with the scope section.

**DR. SALOMON:** Yes, there's a lot of redundancy.

**DR. ROTROSEN:** The section that focuses on the examples of chronic diseases that lead to end stage organ failure --

**DR. MENDEZ:** We can pare it down a lot.

**DR. ROTROSEN:** It's very selective in the diseases you choose. You know, diabetes is a big one, and then you talk about, for the next one, polycystic kidney disease; unfortunately, it causes kidney failure. In a report like this, if that's what you want to do, we ought to cite numbers two and three before number four.

**DR. MENDEZ:** Yes, I believe that one in this particular instance.

**DR. ROTROSEN:** But kidney failure is only one issue when it comes to opportunities in xenotransplantation. If you want to cite these, then I think it would be better to be more comprehensive; limit it to just a few bullets to bring in many more diseases, but with very short one-line bullets.

**DR. CHAPMAN:** An alternative way to address that would be to just select examples that represent a larger problem.

**DR. KASLOW:** The compromise would be to do that, and then we'll have the one-line bullet for the others, the similar examples that you chose, the latter.

**DR. CHAPMAN:** I recently, for the first time in years, pulled out my Julia Childs Art of French Cooking and made a pot roast, and when I was reading this section, what she has you do is she has you putting in a zillion ingredients, and then she says simmer it until it's reduced to a third to concentrate the flavors. And those words kept coming back to me here.

Megan talked about what we should take out. I wasn't hit with a lot of concepts or points I thought should be taken out, but I thought to make this at the level of detail of the rest of the paper, we need to find a way to get an economy of wording that really condenses it down.

So I had a lot of comments that may or may not be good ways to do that, but I was trying to go through and say how can we rephrase this to keep it in this paragraph with really simple words. I don't think it's worth going through them individually. Maybe I can just hand them to you and you can figure them out.

**DR. SYKES:** But again, I think if they're going to be kept, it has to be made clear these are examples. And I think Dan's point is it is absolutely crucial that the section needs to be more comprehensive. I mean, we don't even mention cardiovascular disease in this introduction.

**DR. MENDEZ:** You mean on the burden of the problem, the scope of the problem?

**DR. SYKES:** Yes. It has to be a short, not detailed, but comprehensive introduction to the problem of chronic and degenerative diseases, so that means it has to include all. Not that you have to detail all, but it has to include all.

**DR. MENDEZ:** Just state all of them. If you do that, I think you would have to coalesce some of the sections. Because otherwise it actually gets bigger rather than smaller.

**DR. ROTROSEN:** One way to do it in a hierarchical structure would be to go to the database, look at the 80,000 patients on the waiting list, and say 10,000 are for this organ, 20,000 are for this. It gives you some magnitude of the problem and where the big issues are.

**DR. MENDEZ:** That's basically what we did, and we got a little bit too sterile. Somebody had mentioned that there were so many numbers, that that's what we did with the database, and I didn't know whether or not how many of those we should throw in. Bill thought we should put in one example, and I said why don't you put in two or three.

But we were actually just going to cross out a couple of them, and, just as an example, do diabetes and just mention cardiac. But we could elaborate and put one or two sentences on each one of them.

**DR. SYKES:** Well, I think one example is fine, but you should pick the biggest one, maybe, or the biggest two, if you want to have two.

But the other thing that needs to be pointed out is that if you do focus on the waiting list, that the waiting list in any case should be pointed out, that the waiting list is the tip of the iceberg; that there are so many more people who could be treated with transplantation if transplantation was available to the waiting list.

**DR. MICHAELS:** I think that that's a good way to do it and make that point, but I think the other point has to be that that's just for organs, and that xenotransplantation encompasses -- and then you could bring in the comment about Parkinson's.

**DR. MENDEZ:** Well, let's see. I guess the third point that we want to talk about, approaches to treating cellular transplantation, whole organ transplantation you could put in there first, assist devices, xeno assist devices. That's kind of done in the bridging technologies. It depends on how you want to collate it.

**DR. MICHAELS:** Actually, we're going to move the entire scope of xenotransplantation - not just that first paragraph, but the definitions - we're going to move that up front. Is that right?

**DR. SYKES:** The scope, where we describe all the different types of transplants. So much of what's written about these different types of transplants can be taken out here and taken for granted that people understand that. So, you know, mentioning your point about cellular transplants, there's already a context so you don't have to give a lot of explanation.

**DR. ALLAN:** What you're suggesting is merging the examples with the different approaches? Is that right, Megan?

**DR. SYKES:** Well, I think a comprehensive starting paragraph about the burden of chronic and degenerative diseases with mention of one or two examples of the biggest ones - and you can find out what those are by going to the waiting list for organ transplants and citing that - and then following that, pointing out that, number one, this waiting list doesn't include people who could benefit from cellular transplants, and number two, even the waiting list for organ transplants is only the tip of the iceberg, because so many more people can benefit from transplantation.

**DR. MENDEZ:** So you would state the 80,000 people who are waiting, and then you would selectively go down and say the types of people who are waiting die from heart disease, kidney disease, so on and so forth?

**DR. SYKES:** Not through all of them. I would start with the first sentence, the burden of chronic and degenerative disease, I think it is, and then the next sentence, the waiting list for organ transplantation currently includes 80,000 individuals; the largest number waiting for heart transplants have chronic congestive heart failure or whatever, and the largest number waiting for kidney transplants have diabetic and renal failure.

So just mention a couple of the major examples of what the causes of those diseases are, and then go to the fact that in addition, this list does not include people who could benefit from islet or neural tissue transplant, and furthermore, that many more people could benefit from organ transplants but they don't qualify for the waiting list yet because only those with the greatest needs make it.

**DR. SALOMON:** Following that, two quick things. One was in the second paragraph, when you talk about diabetes - which is fine, by the way, and the facts are good - but the point, however, is the emphasis is clearly on Type II diabetes, and I think the first -- you know, there's a million, million and a half juvenile onset diabetics, many of whom are young adults. I think that should come up front and then talk about Type II diabetes as the second one.

**DR. MENDEZ:** I wonder if we should even say Type I or Type II, maturity or --

**DR. SALOMON:** Yes. I mean, I'm okay with that blurring, but you haven't done that either. You're really talking about Type II diabetes, so the first thing I came up with was, well, that would be the first group that got transplants, probably.

**DR. MENDEZ:** Right. Exactly.

**DR. SALOMON:** But yes, if you want to do it that way, that would be another option.

The other thing I would point out is the recent statistics are that less people now are dying of an acute myocardial infarction, but they're rather dying of chronic congestive heart failure. So that the whole shift in the epidemiology of heart disease has been really major in the last decade, for all the reasons I think that we can guess at, and that actually hit the front page of the New York Times a couple of weeks ago.

So I think there the idea of a heart transplant serving even a larger population of patients destined to heart failure is kind of a dramatic point that could be made.

**DR. KASLOW:** I guess another point following on that first section, on page two, two paragraphs with

Parkinson's disease as the opening sentence, and then the rest of that paragraph and the following paragraph all deals with Alzheimer's disease. So I think you ought to consolidate and do one or the other and make the point more succinctly.

**DR. MENDEZ:** I think I'm just going to delete the whole thing about Alzheimer's disease.

**DR. KASLOW:** Yes, I think that's probably what I would do.

**DR. SYKES:** Okay. Any more suggestions on that part, or should we move on to the next section?

**DR. MENDEZ:** Let me just be clear, now. We're going to move your first part, the scope --

**DR. SYKES:** After your first paragraph.

**DR. MENDEZ:** No, right after the first paragraph.

**DR. SYKES:** So your readers will already know what xenotransplantation is and what types of xenotransplants this is.

**DR. CHAPMAN:** To me this is sort of an explanation of why they want us bothering to try xenotransplantation, this whole introduction.

**DR. SYKES:** In fact, we could even preface this section with something like that, why xenotransplantation being considered.

So after the section on the scope of xenotransplantation, just before going into the burden of chronic and degenerative diseases, you can have -- we can begin that header with a preamble sentence that says, why is xenotransplantation being considered.

**DR. SALOMON:** So what are you sticking up? I sort of like the idea of going from an introduction right into the burden of chronic and degenerative disease before talking about xeno.

**DR. MICHAELS:** But you don't know what xeno is.

**DR. CHAPMAN:** Then you tell them what is xenotransplantation and then you go into the burden of why --

**DR. SALOMON:** I guess I might have -- I mean, okay. If that's the feeling of the group, I can --

**DR. CHAPMAN:** Make your comments. What do you think?

**DR. SALOMON:** Well, my feeling here is xenotransplantation is one of several strategies to deal with the scope. And so if I was reading it and had no clue, I would rather know what the scope of the medical problems facing my people are, and then xenotransplantation could be put in -- as I read what xenotransplantation can do, I can relate back to what I just read as the scope. So I would favor this sort of an order rather than leading off with, we've already decided xenotransplantation is the cure for all these problems, so we'll tell you all about xeno and then here's the scope of the problems. I just think that's backwards.

**DR. MENDEZ:** I kind of do, too, now that I -- that makes sense.

**DR. CHAPMAN:** So you would move economic factors and different measures of productive years of life lost under the burden of chronic degenerative diseases, and then make an explicit heading like "approaches to addressing these problems" or something, and then go into disease prevention?

**DR. ROTROSEN:** I have trouble with a report that makes some probably lay educated person read one to two or maybe even two and a half pages before they can put this into the context of, why are you telling me about -- this report is about xenotransplantation. I need to tell people what that is and what the problem is it's going to solve before I tell them the details about the problem, two or three pages of details.

**DR. KASLOW:** But I think that the problem is that the scope --

**DR. MENDEZ:** Excuse me. Does that mean that you would put the scope of xenografts -- these definitions of solid organs in there?

**DR. ROTROSEN:** That should come right after the introduction, and then you can say there are alternatives.

**DR. KASLOW:** I have, again, I think a median approach to this, and that is I think you're right, you need to know what xenotransplantation is in a general sense, and one paragraph to do that. It may be a longer paragraph than what we have on page six as an introduction, but the four sections that follow are so scientifically detailed that it seems to me you're hitting awfully hard at the detail level --

**DR. ROTROSEN:** Oh, I agree with you.

**DR. KASLOW:** -- before you go. So what I would suggest is a paragraph introducing xenotransplantation as a prelude to the scope, and then go back to the detailed definitions later when you get to the science.

**DR. SALOMON:** And that's kind of what I was thinking. Your point is well taken. I also did not have in my mind when I made my comment that it would be two or three pages and then you would finally get to xeno. I think you're right. I mean, it is a report on the state of xeno science, so we want to make sure we don't lose that.

**DR. SYKES:** I'm sure we're going to be criticized. Because if we put in a short paragraph like that without the proper definition of what a xenotransplant is, without covering the whole scope of what xenotransplants are, then we're going to be criticized for starting our scientific report with an introduction to xenotransplantation which is really only a part of what xenotransplantation is. I think we either put the whole scope in or we keep the original format.

**DR. ALLAN:** What about putting in the definitions and then putting in the specifics on solid organ versus cellular versus whatever? Keep that in your section, and put the definition at the beginning. Put that up front.

**DR. SYKES:** But that's a confusing, detailed scientific definition.

**DR. ALLAN:** Well, you could put it almost like a footnote and say, this is described by the PHS.

**DR. MICHAELS:** Actually, you could take a combination of the very first paragraph and the paragraph on page six, and rather than going into the detail of what each one is, say, the different categories of xenotransplant include solid organs, cellular and tissue, extracorporeal, and exposure to animal-derived

feeder layers which will be described below. Then go back to the burden and make the whole description.

So we make it a longer paragraph and combine that with that short intro paragraph. So it's a bigger introduction, tells you what xeno is, and then we can go into the burden of chronic and degenerative disease and come back.

**DR. RICHMAN:** As a science writer, just to let you know that that's the approach you want to use, that you want to open up with something that's going to get the attention of your readers and then you want to make them a promise about what they're going to read in the remainder of the report. And then in the very end what you do is you summarize by reminding them about what you've told them, that you've mentioned your promise.

**DR. SYKES:** The first paragraph is just that. It says what it's going to be. So maybe you just need a first sentence saying what a xenotransplant is in that first introductory paragraph.

**DR. ALLAN:** It ends up being a couple of sentences, I think.

**DR. MENDEZ:** It has to be at least a couple of sentences.

**DR. ALLAN:** Yes. Just more in lay terms rather than the explicit definitions.

**DR. KASLOW:** And if you're worried about its apparent promotion of xeno as opposed to the others, you could put in another sentence or two about the others, and say that this is one of the more promising of several alternatives, and list the alternatives. I mean, this is not an advertisement, this is just a statement.

**DR. CHAPMAN:** This is a report on the state of science of xenotransplantation, so I don't think you have to worry about --

**DR. KASLOW:** Well, I was just responding to Megan's concern.

**DR. MENDEZ:** I think Tony has a good point here. That paragraph, that sentence under the informed consent of -- I think there's a whole box there that's pretty defined, if you want to put that that is the object of our group.

**DR. SYKES:** What I was saying before is that is not really a good opening sentence for the average reader, because it's a very scientific definition of xenotransplantation. Whatever people think is best is fine.

**DR. ALLAN:** The question I have is it's already defined in the first informed consent aspect. Are they going to read these two reports separately?

**DR. RICHMAN:** Yes, I think you have to assume that they are.

**DR. ALLAN:** And if they are, then you probably need to have it in this section.

**DR. SALOMON:** I think you need to do something like, in simple terms, xenotransplantation is the placement of organs or tissues derived from animals into human beings.

**DR. SYKES:** Well, that's not what it is.

**DR. SALOMON:** That's a simple statement. I'll add another phrase.

**DR. CHAPMAN:** How about this? The term xenotransplantation has been designated by the USPHS to apply to any procedure that involves the transplantation and implementation of...

**DR. SALOMON:** I wouldn't start that sentence off with -- what I was going to suggest is that following that you say, the PHS defines xenotransplantation in more detail as, and you put that sentence in as whole. And that way somebody as a layperson who isn't going to be obsessing about the fact that there are feeder layers on stem cells is going to get the idea that it's animals to humans. That's the key word here, right? That's the key concept.

**DR. ALLAN:** We're not PHS people, so we can get away with it. You guys worry about being absolutely correct, but we don't have to.

**DR. CHAPMAN:** But it's your report to the government, so you don't have to worry about it.

**DR. MENDEZ:** I think the science writer has the key. What do you think about that sentence as an initiation?

**DR. RICHMAN:** This first sentence?

**DR. MENDEZ:** The informed consent on the previous tabloid.

**DR. KASLOW:** Maybe we should ask her more generally, how much of the introduction should be what xenotransplantation is? How many sentences do we need to introduce it before we go to the scope of the problem?

**DR. RICHMAN:** Well, I think that the introduction could be longer than it is, and I think it needs to introduce the term in a shorter sentence than what you've got here. I think that that's a good description, but for your readership, it should be two sentences instead of one.

And I wouldn't be afraid of making the introduction perhaps three paragraphs, and the first paragraph a definition of what xenotransplantation is, the second paragraph maybe the scope, a small scope of the problem, how big the problem is, and then the final paragraph, the promise about what's to follow.

**DR. MENDEZ:** So you would cut it down to two paragraphs, the introduction?

**DR. RICHMAN:** No, I just mean the introduction to the introduction.

**DR. SALOMON:** Then go into your burden of chronic and degenerative diseases, scope of the problem.

**DR. RICHMAN:** And I think -- I have not seen what we would call the call-outs like this in other documents. It's very often in documents of this nature, but I think they're a good idea. But what you want them to do is reiterate what's in the body.

**DR. MENDEZ:** Well, we wouldn't put it as a call-out. I think that the idea would be to put it in the body of the introduction.

**DR. RICHMAN:** So you're asking is this a good introduction?

**DR. MENDEZ:** Right. To be added perhaps to what we have there.

**DR. CHAPMAN:** I want to read. I don't want to keep having to divert out to figure out.

**DR. RICHMAN:** But, you know, they did ask also for a glossary, so something like this could be in a glossary as well as written into the body of the document.

**DR. MENDEZ:** Well, we already have it here under the scope, the science of xenograft. The committee is going to explain in detail the definition of each of these different types of xenotransplantation where it is defined. So I think what I'm hearing from the group is that you just want to have a couple of sentences in the introductory paragraph stating from the beginning what it represents. And I think in my mind, that call-out, I think it's probably pretty good. Or something like that.

**DR. SYKES:** I think we're going to have to move on.

**DR. RICHMAN:** What I can do is help write the paragraphs. People can put down their best efforts and then we can work to polish it up.

**DR. MENDEZ:** We need a lot of polishing on the burden, because, as our chairman stated, after the first paragraph there, there will be an asterisk where there will be references. Now the references, how are we going to do references? Are we going to do it at the end of a section?

**DR. SYKES:** I think what we're going to have to do ultimately is compile the references at the end of the whole report. But for individual sections right now, what you can do is number them for your section and then have a list at the end, and then we can ultimately compile it.

**DR. MENDEZ:** Dan, on that second -- under the burden, do you want to change that paragraph in any way? I just wanted to reference it. Would you put anything else in it? Would you delete anything?

**DR. SYKES:** Well, I think we've talked about that already, about changing the structure of this section quite a bit. Right?

**DR. MENDEZ:** Yes. We're going to delete some of the aspects about diabetes and then go on down and add the other illnesses.

**DR. SYKES:** Yes. I thought we were going to start with a statement about how large the burden of chronic and degenerative diseases is, and then go to the waiting list as an example, and also use it to get an idea of the diseases that most often lead to a need for organ transplantation.

And so there give your specific examples of the commonest causes of renal failure leading to being on the transplant list and heart failure needing to be on the transplant list, and some numbers of that.

**DR. SALOMON:** And that's where you can make the point about the shift in the epidemiology of heart disease, for example, so that one can anticipate a growing pressure because of heart failure's growing numbers. And in terms of the diabetes, I would not cut anything, I would just blur the distinction between diabetes Type I and Type II, if you will, so that it's clear that there are a million and a half juvenile onset diabetics, and about 14 to 16 million Type II diabetics, that kind of thing.

**DR. SYKES:** I'm not sure that we want to get into too much detail on this.

**DR. SALOMON:** Or then just cut it out and talk about 16 million diabetics. I don't care.

**DR. ROTROSEN:** I would just say 16 million diabetics, a small percentage of whom may be candidates for xenotransplants. You don't want to overstate your case.

**DR. SALOMON:** I guess that's what I was getting at.

**DR. MENDEZ:** Well, I think we shouldn't understate it too much. What is going to be the treatment for diabetics, islets or xeno?

**DR. ROTROSEN:** I think if you transplant islets into a Type II diabetic, a majority of them are going to be continuing insulin resistant and have a failed transplant.

**DR. KASLOW:** I think a realistic estimate of what the treatment goal is, how many people you really think are going to benefit from it, whether it's Type I or Type II.

**DR. SYKES:** But diabetes is going to show up as the commonest cause of the SRD, right, so you can link that.

**DR. MENDEZ:** No, it isn't the most common.

**DR. SYKES:** So what's the commonest cause? I said end stage renal disease.

**DR. SALOMON:** That's correct. I think another way you could do it, then, to deal with Dan's good point, is you say there are 16 million diabetics, and say that about approximately two million would be potential candidates for an islet transplant, under our best estimate.

**DR. ROTROSEN:** I'm not even comfortable with that. I'm comfortable saying brittle diabetics are, but the lifelong prospects of immunosuppression are worse than daily insulin for most people.

**DR. MICHAELS:** Yes. I wouldn't put a number on it. Why don't we say some percentage of these, some of these patients may be.

**DR. CHAPMAN:** That's going to be a moving target, too. If pancreatic islet transplantation was at the stage where it was highly successful, there were minimal operative complications, and found a way to induce tolerance so that you didn't have immunosuppression, then you would be very liberal.

**DR. ROTROSEN:** Yes, but that's what we'll be writing 10 years from now.

**DR. CHAPMAN:** Right. Right. So that's another reason for not maybe going into so much detail.

**DR. ROTROSEN:** I wouldn't give a number.

**DR. MENDEZ:** How about stating something like there are 16 million diabetics in the United States; they comprise the primary group of individuals a waiting kidney transplantation.

**DR. ROTROSEN:** Yes.

**DR. CHAPMAN:** Or it's a primary disease leading to...

**DR. MICHAELS:** And a small percent of these may be possibly candidates for islets.

**DR. SYKES:** Exactly. And then a mention of the fact of -- are you done?

**DR. MENDEZ:** No. But go ahead.

**DR. SYKES:** That after you've brought in these major diseases coming from the waiting list, and then the fact that islet transplantation is another thing that doesn't affect the waiting list, then pointing out that the waiting list doesn't even include the majority of people; hence the huge organ failure, that many more people could benefit from transplantation.

**DR. MENDEZ:** This includes only a small percentage of those, actually, that could benefit.

**DR. SYKES:** So that's how that section will be distilled. Okay? Everyone happy with that? So can we move on?

So the next section is disease prevention, current approaches. I think it's the right length, I think it just needs to be a bit more pointed, maybe.

**DR. CHAPMAN:** Well, I thought this could perhaps be condensed as well.

**DR. ROTROSEN:** Yes, I thought these points could be made in other sections.

**DR. KASLOW:** Right.

**DR. ROTROSEN:** Just remove this section.

**DR. CHAPMAN:** I'm not sure what balance to strike here when doing why a mode of prevention is life-style changes to decrease obesity, which is a contributor to Type II diabetes and so on. But I'm also leery of overstating that, because the implication of many things I read is if we could just get everybody to eat right and exercise, nobody would have Type II diabetes. 70 percent of people over the age of 18 have Type II diabetes.

Now, yes, the advent of McDonald's and the decrease of having to walk when you want to go to town has contributed to that, made it worse, but there is clearly a genetic propensity that is way beyond -- I don't think if everyone in the tribe adopted Megan's life-style, they would lose weight. I know about Megan's life-style. We won't go into her diet.

So I think we can mention this as something that can contribute, but I think we want to be careful about the extent to which -- you know, it's like with brittle diabetics. Yes, you want to encourage them to be as rigorous as you can in their insulin control and their diet control, but the truth is there are some people who cannot be obsessive enough to keep their diabetes under control. And you don't want to leave the impression that these are all things that can easily be fixed if everybody just behaved in the right way.

**DR. MENDEZ:** Do you want to delete that particular paragraph?

**DR. MICHAELS:** Actually, I wouldn't delete it. I thought that particularly from our colleagues that are in the other room, that Alan Berger really brought up from the whole group - and this section is really coming from the whole group even though we're writing it - that they felt very strongly about keeping something in. So I think we can make the modifications that people have suggested, but I would keep it.

**DR. SYKES:** I agree with that. I think it's very important to make a nod to prevention and acknowledge our support of the approach, but also point out that it's not going to be a solution in the short-term.

**DR. KASLOW:** You could argue that it really ought to go at the beginning of the whole report, that this is what we ought to do first. But given that that isn't going to happen, we're still going to have a lot of chronic disease.

**DR. CHAPMAN:** And even if it happens, it will diminish the burden, but can't eliminate it.

**DR. LUBINIECKI:** Right. And it won't do anything to help the people who are not in end stage disease. They need something else besides diet management.

**DR. SALOMON:** Plus you've got to remind yourself, when I was in eighth grade, the President's Fitness Council was there. And I remember us running around and doing push-ups and all of that, and now I just had my significant birthday - we were joking about that yesterday - and we've got an epidemic of Type II diabetes. I mean, come on, guys. We need to acknowledge the importance here, but let's be realistic.

**DR. MENDEZ:** I thought we dampened it down a little bit with the third sentence. It says, "However, even the optimists about the ability to change human character acknowledge the disease group will continue to be established."

**DR. SYKES:** That's good. And so it's probably focusing again only on one disease rather than all the other obesity-related complications. So I think you should broaden that a little bit. Not delete it, but just broaden it to include other complications besides obesity.

I do think the header here could help to focus this section better, to put it in context, the header where it says, "Disease Prevention, Current Approaches." I think it should change to be something like "How Much Can We Accomplish by Disease Prevention," or something that just puts it into the context of the report.

**DR. ROTROSEN:** The last sentence -- this paragraph, I think it's fine to talk about prevention, but at the end of it you talk about therapies, talking about better medications. And I just think we should be clear about it. Maybe it should be prevention and disease treatment.

**DR. MENDEZ:** Disease management?

**DR. ROTROSEN:** Yes. And give equal weight to the life-style, behavioral choices, and the prospects for -- or the lack of prospects for better medications eliminating disease.

**DR. MENDEZ:** So you would delete that sentence or you would add to it?

**DR. ROTROSEN:** No, I would change the heading from Disease to Prevention and Treatment.

**DR. SYKES:** That broadens it quite a bit, though.

**DR. ALLAN:** That's okay.

**DR. SYKES:** You want disease prevention and treatment?

**DR. ROTROSEN:** I think we need to say that medical treatments are not going to eliminate the need for surgical treatments.

**DR. CHAPMAN:** Have the treatment and have the first thing what you're saying, and then going into xenotransplantation attempts to develop treatments.

**DR. ROTROSEN:** But they're surgical treatments, not medical treatments. I think prevention of medical treatments is in one.

**DR. KASLOW:** What she's talking about is conventional medical intervention.

**DR. MENDEZ:** So what would you title that paragraph, Prevention?

**DR. ALLAN:** I would say Disease Prevention and Management, and then that way it would include other things besides just treatment.

**DR. SYKES:** How much can be accomplished with current approaches to disease prevention and medical management.

**DR. ALLAN:** Well, he's saying that in the text, but I wouldn't bias right in the beginning. In other words, let the reader --

**DR. SYKES:** I didn't bias, I just asked the question.

**DR. SALOMON:** Bias is the failure of prevention

**DR. ROTROSEN:** Alternatives to transplantation.

**DR. SYKES:** They're not alternatives.

**DR. ROTROSEN:** Well, they're complementary.

**DR. MENDEZ:** Change to --

**DR. SALOMON:** Prevention and medical management, which is what I think Megan --

**DR. SYKES:** Okay. Can we avoid transplantation with prevention and medical management? There's an unbiased question for you.

**DR. ALLAN:** It's not going to be in the title.

**DR. SYKES:** Why not?

**DR. MICHAELS:** Just make it a subheading.

**DR. SYKES:** Well, the paragraph has to be in context.

**DR. MENDEZ:** It does kind of stick out a little bit.

**DR. CHAPMAN:** You could put it in as a working header, and then at the end when you're looking at the whole document, maybe you don't need such a big heading.

**DR. MENDEZ:** What would you put in there?

**DR. SYKES:** Can the need for transplantation be avoided with disease prevention and medical management.

**DR. ALLAN:** Or something like that.

**DR. MENDEZ:** And the need for transplantation.

**DR. SWINDLE:** I want to point out something procedurally. We've got less than an hour to go, we're not through page two of a 27-page document, and I suggest that we shift gears and quit going sentence by sentence and go over the broad points of the major topics. These are not broad points to me. The broad points could be done in 15 minutes in each section, and then assign people to rewrite their sections and send them back out for review. And that's the only way we're going to get through this in 45 minutes.

**DR. SYKES:** Okay. Xenotransplantation strategies, approaches to treating human disease. Here I think you have way too much detail.

**DR. MENDEZ:** Well, we cut out on the one that you have on page two, the second sentence; page three, the first sentence except for Parkinson's disease.

**DR. SYKES:** Okay. Well, we'll have to see what you've got.

**DR. MENDEZ:** The fourth sentence, all of that discussion, all of that section, in fact, deleted all of that.

**DR. KASLOW:** Do you think you've cut it in half?

**DR. MENDEZ:** Yes. 50 percent.

**DR. KASLOW:** Then let's go ahead and see what they did.

**DR. MENDEZ:** And then on the whole organ, we deleted paragraphs three and four.

**DR. KASLOW:** Let's just see what they've got and then move on.

**DR. MENDEZ:** Then on page four we deleted half of the first paragraph and all of the second paragraph.

**DR. ALLAN:** This is the bridging?

**DR. MENDEZ:** Yes.

**DR. SYKES:** Yes, I thought there was some redundancy in having heart and assist devices in that section and then having it again in the next section.

**DR. MENDEZ:** So delete all of that paragraph and half of the first paragraph.

**DR. SYKES:** Okay. And then content-wise, I think it is important to point out some of the limitations - and I think you said this yesterday - and you recognize that it's overly enthusiastic about the --

**DR. MENDEZ:** Right. Very much so. Then the entire parallel of alternate strategies to gene therapy, stem cell and artificial, Bill wanted to delete that entire section.

**DR. SYKES:** No, it's very important to mention the alternatives, but I think what is missing is it doesn't give the reader a sense of where these technologies are in relation to xenotransplantation. And the

cloning and stem cell transplantation are in very early stages, they're exciting, but we really don't know what the intentions are.

**DR. KASLOW:** I wonder if strategically, to diffuse the whole stem cell issue, if it ought to come linked to the other conventional medical therapy. I mean, wouldn't it make sense to summarize all of the alternatives to xeno in the same kind of place, and then you don't highlight stem cell?

**DR. MICHAELS:** I thought that what we're discussing is actually under those --

**DR. KASLOW:** Well, then, I'm missing where this heading for xenotransplantation strategies comes in between them.

**DR. SYKES:** Well, the section that we discussed earlier was not on the alternatives to xenotransplantation, it was alternatives to transplantation. It was a voiding transplantation. So this is specifically alternatives to xenotransplantation.

**DR. ROTROSEN:** And the other section focused on currently applied alternatives, whereas these are...

**DR. KASLOW:** No, that's fine. It's just that the way this is organized now - maybe I'm missing the reorganization that took place - is that in between this disease prevention paragraph and all the other stuff is xenotransplantation.

**DR. SYKES:** There's a leak there.

**CAROLYN WILSON:** Actually, more than that, there's also the bold heading --

**DR. KASLOW:** Right. Of course. But I'm just saying we're separating those two things when I think they're all part of the same issue, which is what are the alternatives, past, present, and future.

**DR. MICHAELS:** Right. I misspoke as well. I think that you're absolutely right, the xenotransplantation strategies should come after the alternatives.

**DR. MENDEZ:** So that should go after the disease prevention and management, and then stick in there alternate -- I would --

**DR. SYKES:** Can I step back just a minute? So we have a section on avoiding the need for transplantation, period; not just xeno, just transplantation. So the next step is we've acknowledged in that paragraph that we can't meet the need, there's still a big need, then we go to transplantation in a general sense.

And here it would actually make sense to point out in a very succinct way the limitation in organ and cell availability, or at least to -- since you've already done that, refer back to the point that has already been made; therefore, we need to consider alternatives to human cell and organ transplantation. These are the alternatives. And there are three, there's xenotransplantation, there's artificial organs, and there's --

**DR. SALOMON:** Four. Gene therapy and stem cells.

**DR. KASLOW:** Gee, I didn't quite see it that way. To me it's human versus animals, and all the other stuff is human and xeno is animals.

**DR. CHAPMAN:** So do the humans first?

**DR. KASLOW:** Yes. Exactly.

**DR. SALOMON:** I don't think I would contradict what Megan just said.

**DR. KASLOW:** Okay. It's just an order. It's just what --

**DR. SALOMON:** Well, I was thinking the same thing, Dick, is what is the order. Logically, to me, in the context of a xenotransplantation document, we ought to go -- I like the idea. I think we owe it to the world to go to prevention and medical management, so I'm happy with that. But the next step shouldn't be starting to talk about stem cell and gene therapy. I think then you go to right to xenotransplantation, and then when you're done with xeno, you say, well, we're not selling you xeno. There's also gene therapy, stem cell transplantation...

**DR. KASLOW:** Okay. As long as the transitions and the headings are clear without the examples.

**DR. CHAPMAN:** Here are the limitations of those fields to date.

**DR. MENDEZ:** So you would -- well, actually, I thought we did that. You go to xenotransplant strategies, and the thing is, in xenotransplant strategies, cellular transplant would use stem cells and clone cells and bio mechanical devices to --

**DR. MICHAELS:** Actually, I think it should be transplant strategies. Right?

**DR. SYKES:** So disease prevention, you can't avoid the need for transplants. So now we have transplantation, and then you say, we've already said there aren't enough human transplants; therefore, we have other alternatives.

**DR. CHAPMAN:** Another way to conceptualize it is you've talked about efforts at disease prevention and disease management, which is what medical therapy is, and the limitations of those, and then you say, what is the approach to curative attempts? Well, the present approach to curative attempts is the mechanical alternative, which is not really a cure, or a transplantation, which is...

**DR. ALLAN:** Current versus future.

**DR. KASLOW:** As long as the sequence is logical and the transitions are smooth, I don't think it matters a whole lot. So that's the message.

**DR. MENDEZ:** What was suggested, and I think that's what we did, was that after avoidance of transplantation, that paragraph, then we came to xenotransplant strategies approaching the issues, then we did cellular and whole organ transplantation. I guess we could add a paragraph on the...

**DR. SYKES:** It's just that the headings and the sentences don't conceptually link.

**DR. MENDEZ:** Then after that we went on to the bridging technologies. In other words, is there something being missed in the xeno strategies?

**DR. SYKES:** There's no conceptual framework given to the reader here, that the logic of choosing these headings, where you have them, is not there. And there needs to be a conceptual logic that ties everything together, and we've discussed a couple of ways that you can do that.

**DR. CHAPMAN:** So maybe the way to do this at this point, as Michael suggested, is to let them take all these suggestions, do a revision, and then circulate it. And then at that point people can give their individual -- that may be a more productive stage at which to put in specific comments because you bring out this framework by changing the heading this way or whatever.

**DR. SALOMON:** Yes, I agree with that. Without getting caught up in detail, I just had a general question about a style approach here. It gets kind of into something that we talked about yesterday, and that is how do we bridge a scientifically rigorous discussion with one that is also more accessible to people who don't have a scientific background?

I was thinking one strategy - I just want to try this out - would be to make every heading a question, because that really -- and put it in plain terms, like how do you do a void transplantation. Bridging technologies at organ end stages could be what are our options when organs fail. Put at least a question for every section that are in lay terms.

**DR. MENDEZ:** Instead of saying parallel --

**DR. KASLOW:** I would say potentially a subheading, a general thing, and then in parentheses the subject --

**DR. SALOMON:** And then the question. I like that, too.

**DR. CHAPMAN:** On these sections, the interim summaries I thought were really good, and in the discussion yesterday, what I came away with from this was leaving the text at the level it's written, where Megan says we're talking to the scientist and the physician without patronizing them, but putting these interim summary things in lay language I thought was a good compromise on that. And the interim summaries are helpful to the physicians and the scientists, but also that's where you can rephrase your conclusions in lay language.

**DR. MENDEZ:** Megan, can I just get back to the point you wanted to make. You said of bridging technologies as alternate strategies to resume transplantation, you do want to leave that in, the stem cell, gene therapy, artificial organs?

**DR. SYKES:** Yes.

**DR. MENDEZ:** And that should go after the discussion of the approach to xenotransplantation?

**DR. SYKES:** I think it could go before or after. I think it's a little easier to do it after, because you've already by then presented xenotransplantation, and so you have something to compare the stage of development of these other technologies to. I would find that easier.

**DR. MENDEZ:** So on that alternate strategies, the gene therapy and stem cell, we're going to leave this in and not delete it, just try to narrow it down a little bit.

**DR. ALLAN:** And also maybe more specific instances. As Eda said, don't just say stem cell, say embryonic adult stem cell technologies.

**DR. SYKES:** And say that these are still in the early stages.

**DR. MENDEZ:** Right. Embryonic stage.

**DR. KASLOW:** The economic and differential measures of productive life and so on, are you going to

leave that pretty much intact or have you done that bench editing on that?

**DR. MENDEZ:** The third paragraph was deleted. Some people thought that we shouldn't say that --

**DR. KASLOW:** What I was going to suggest is that if you could cut this maybe close to half, the whole two sections, economic and so on, you might think about putting that back up with the burden as well. Because it's disease burden, economic burden, and all together.

**DR. MENDEZ:** We were actually going to delete the last three paragraphs -- the last two paragraphs of it.

**DR. KASLOW:** So you're getting it down to size enough that it would fit back there without taking up too much space.

**DR. SYKES:** People aren't using their microphones.

**DR. LUBINIECKI:** Can I make a suggestion? As we discussed briefly yesterday, perhaps it may be worth considering under the economic section to not only talk a little bit about cost to develop xeno, but also value created by developing xeno, and make a comparison to that. I would be happy to work with you on that. Because I think in a world of limited resources, the Secretary and everybody else is always wondering what he should put his money on. And I think if it's possible to say something objective about the likely cost and the likely value created, there would be perhaps some...

**DR. ALLAN:** What you're saying is to add the xeno into this section? Because right now the xeno is not in the economic factors here as worth considering. So you've only considered other strategies --

**DR. MENDEZ:** We didn't guesstimate the cost to develop xeno, no. The value added in the first paragraph that you saw - just as an example in diabetes, indirect costs were under a billion dollars a year - the health care benefits of those with diabetes versus those without diabetes. So we give some examples of that. The same thing with the kidney, we gave examples of that.

**DR. ALLAN:** But that's not within this section, that's distributed?

**DR. MENDEZ:** No, that's in the different measures of productive life. I think probably that heading should just be deleted and it should be under economic factors.

**DR. LUBINIECKI:** Maybe I could send you some e-mails and we could talk about a few ideas .

**DR. MENDEZ:** Yes, please. That would be great.

**DR. MICHAELS:** We can't do the science part until -- do you want to wait until Megan comes back?

**DR. ALLAN:** Let's just delete the science part since she's not here.

**DR. MICHAELS:** So I think the major point that we all agreed upon yesterday was just to put in some bullets to help the reader who might not be as scientifically knowledgeable in this area.

**DR. CHAPMAN:** I think all the other sections should adopt what that section does. I think that was really...

**DR. KASLOW:** And Robyn said she put a glossary together - that is, the terms that she didn't

understand - and we'll have to fill in the glossary.

**DR. SYKES:** You'll help us with the glossary?

**DR. RICHMAN:** Absolutely.

**DR. ALLAN:** Because I think it would be a help for -- people have stated in the other sections that the science is a little bit too tough for them. I think getting their input is a good thing, because in the end it will make it clearer. And I don't know whether you want to sort of interface that or not. But it's not just Robyn, it's several members who have said that they've had difficulty reading that section.

**DR. MICHAELS:** Well, I certainly think we should take everyone's opinion, but Robyn specifically volunteered to tell us what they were.

**DR. SYKES:** But I don't think we want to take out information. And I'm just afraid that to put all the information in lay terms with all these details, it would produce a --

**DR. CHAPMAN:** I think between adding a glossary and putting in those intermittent summaries and making sure the summary statements are in lay language, then you can address that problem without having to delete the scientific content, I think.

**DR. SYKES:** Okay.

**DR. SALOMON:** Megan, did we agree to just extensively edit, or I would actually just say delete, some of this verbiage on page 18? Is that it? Yes, page 18, the second paragraph on that -- I really don't think we need to get in to these kind of things. I mean, the Secretary isn't going to pick up the phone and go, yes, you're right, and call the head of the NIH and put more grants in or something like that. I don't think that's what we ought to be doing. He's also not going to get on the phone and talk to McClellan and tell him to make the FDA go easier, either.

**DR. SYKES:** Well, I must say, I'm not entirely comfortable with the paragraph, but I don't agree that it should be just thrown out. My discomfort has always been with the statement that a proof of principle or accomplishment is needed. I think from what we heard yesterday and people's enthusiasm based on that, and there's no single proof of principle there, but there are advances that encourage people. And so I think that just proves this idea that there's substantial proof of principle.

**DR. KASLOW:** Yes. At the time we wrote this, of course, we didn't know about this, and so we were hoping for some sort of, quote, breakthrough. And I think that's kind of what we were hinting at here, that somebody needed to say, wow, we really can do this. And we don't agree anymore six months later, so...

**DR. SYKES:** So we can take out that first half of that paragraph, but I think Dan's suggestion is more that we're encouraging the government to put in more money. We've had this discussion before.

**DR. KASLOW:** Maybe we ought to let the rest of our colleagues tell us, since we three have been around this.

**DR. ALLAN:** I think that I agree more with Dan on this, in that it's not -- I think it is within our purview to suggest this, and maybe it could be done in a more broad approach rather than a specific, we need more funding from the government. I mean, I know you've tried to work with this to make it less demanding, and I know you've done that because it reads better than I think when we first started talking about it, but

I agree that if you don't take it out, that it should be more, I don't know how to say it, less direct.

In other words, instead of just saying, while the government is not necessarily obliged, the public -- I mean, you're getting kind of specific in terms of reagents and information is proprietary, but I think that's okay.

**DR. SYKES:** So is it too condensed, perhaps, with not enough explanation why those particular things are chosen?

**DR. ALLAN:** I'm stuck.

**DR. KASLOW:** These seem pretty explicit to me.

**DR. SYKES:** Well, I don't know.

**DR. KASLOW:** Not explicit in terms of what you do, but what they are. What does it mean to help a scientist change career paths? I mean, that seems like an example that's clear-cut.

**DR. SYKES:** I don't know if it's obvious to anyone why we would want scientists to change career paths. I think that needs some explanation.

**DR. ALLAN:** I would suggest that you -- I mean, the thing is, you can do this without, like, "While the government is not necessarily obliged to infuse large sums of money into the discipline." let's get rid of that. Because you're being sort of apologetic. Just get rid of that and just say there needs to be some mechanisms associated with this field. You know what I'm saying? Instead of just directly asking for money.

**DR. KASLOW:** Carolyn, from the outside? Or from the inside, I should say.

**DR. WILSON:** I just want to give a general comment on Dan's reaction about not putting in recommendations of what HHS should do, because as an HHS representative - and Louisa and Dan, correct me if you're not in agreement with this statement - I think that you're writing a report to HHS. You're making recommendations of what you think needs to be done in this field, be it more government investment to enhance the research development. I don't think that's an inappropriate recommendation for this committee to make.

**DR. CHAPMAN:** HHS may or may not accept it.

**DR. WILSON:** Right. You may not give that particular recommendation, but you shouldn't hold yourself back from saying, oh, we can't tell HHS what to do. I think that's why you're an advisory committee to work with HHS.

**DR. KASLOW:** That was the gist of that sentence, to balance the fact that it wasn't going to be the government exclusively, but clearly there were roles. And then we defined what we thought were those roles.

**DR. SALOMON:** Just so I'm clear, I'm okay with some version of this, Megan, because it doesn't have to be so black and white. I'm just saying that I'm not comfortable that our big recommendation here should be to increase the government's responsibility for making xenotransplantation go forward. I think if xenotransplantation is going to go forward, it's going to have to involve a significant investment by venture capital, biotechnology, and large pharma, and I just think the government is maybe an easy group

to ask for more money from, but I don't necessarily believe that. My own feeling here is that I don't think we ought to be demanding more money from the government.

**DR. ROTROSEN:** Well, I agree with what's just been said. As I read this, the quality of the document on the state of the science is very good. You know, it's more than good, it's excellent. But where this falls short of most government type reports like this, or advisory reports, is you're not really making too many recommendations. And you're not -- you know, the recommendations ought to be in call-out boxes or bolded, these are our recommendations.

And they don't necessarily have to be recommendations for government research support. They could, I'm not objecting to that, but they could be -- you know, if you look at what's going on in bio defenses, the Secretary is pressuring the industry to partner with government. There's lots of things that the Secretary can do using the loophole that he has.

**DR. CHAPMAN:** Well, one suggestion I would make in the recommendations is if one of your recommendations is that the government should infuse more financial support, I would suggest that you first, in your own minds, delineate why that support should come from the government, and then delineate that in your recommendation.

In general, I mean, my thought is when the public has a stake in something being unbiased or publicly available or in the public domain, then the best underwriter is usually the government, because that belongs to the people as opposed to an industry, where it belongs to academics who maybe patent it or whatever operating with non- government funds.

If you can't make a case that what you feel should be underwritten financially is something which the public has a stake in having in the public domain, then I would say it's not appropriate to ask the government to underwrite it; you should be pressed as having alternative sources of funding.

**DR. SYKES:** The statement is made that the public has a high stake, but what I'm hearing from your comments is the case for why government should put money into this has not been well made here. And we've discussed the case; I believe there is a strong case. I think the words are there in this section, but I think it's not coming through.

But the case is, number one, sharing of proprietary reagents. And it's just not going to happen. And xenotransplantation is going to require many technologies combined, and companies won't do that on their own.

Number two, investment in biotechnology is way down, and there's a lot of discouragement, and if we wait for that to fund this, it's never going to happen. It's going to die. You heard those words yesterday.

Number three, the public has a huge stake in this enterprise, and that in itself is a justification for the government to put money in.

**DR. SALOMON:** I guess just to be clear, it's not that the government can't prime the pump. What I'm objecting to is how this reads is that the government is the one on the line right now. And they're not. And just because venture capital is down doesn't mean the government has to come up and support it. Because the companies aren't giving up anything. What you're doing is you're asking the government to be a venture capitalist, because what everybody does in this field is take their NIH funds, get a certain amount done, and then go fund the company.

**DR. SYKES:** People are obligated to share what they generate with NIH funds. That's the whole point.

**DR. SALOMON:** But what I'm saying is that then take the bigger picture. There ought to be a lot of things. The government could prime the pump to a specific -- as one group. The other thing is that the biotech companies need to begin to make even available what the hell they have.

**DR. SYKES:** You can't tell them to do that.

**DR. SALOMON:** You can't tell them to do that. Exactly. But you can put into place a call to them, given all this great public stake that we've so eloquently -- or you can just bark off and say the companies can do whatever they want; this is America, and all we'll do is the government will make up all the difference. Just write me a blank check. And that's not how it's going to be.

**DR. SYKES:** Well, Dan, you're asking the impossible. I mean, Robin Pearson has been going around for the last two years trying to do this, and as far as I can tell, he hasn't gotten anywhere. It just isn't possible.

**DR. KASLOW:** Do what, Megan?

**DR. SYKES:** To get companies to share their proprietary technology. They're just not going to do it. They've invested money in obtaining the technology, and from their point of view, there's absolutely no value in sharing it.

**DR. SALOMON:** So one of the things that the government could do if they want to bring money into this area is deal with product liability issues, which is what is chilling the pharma companies.

**DR. LUBINIECKI:** I think it might be -- rather than trying to focus on the bigger picture, to try and focus it on the proof of principle concept. I really think that is useful. Big companies and large investors and biotech companies will be more than happy, once the principle is proven, to put their own money at risk. But until the principle is proven, given the failure rate, given the high risk, it's going to be hard to get the people, especially when they don't control all the pieces, to want to put their own money into this.

And so I think having the government or some other non-industry group somehow pony up the money for the proof of principle is a good idea, and I think if we all agree, then I think we can recommend it. I also think that the last sentence asking that the regulatory hurdles and the safety guidelines be relaxed really should be removed.

**DR. KASLOW:** Yes, negotiating paths meant simply helping them --

**DR. ROTROSEN:** It sounds like getting around them.

**DR. KASLOW:** I know it does. But we meant simply helping them deal with it.

**DR. SALOMON:** I like the idea of -- if you can convince me that the government could invest in a focused way on proof of principle, I like that. And at the same time the government should also be involved in fostering anything that they can do to create partnerships between the industry and academia to move the field forward, and to recognize that there are major barriers.

And an example would be product liability issues. I can tell you, for example, within the last two weeks I had a discussion with a major pharma about xenotransplantation risks, and they're reluctant to get into it - and they're a big pocket player - because they're worried that 20 years later someone is going to blame xenotransplantation for -- you know, it would be the asbestos of biotechnology, and we're all aware of

that.

**DR. SYKES:** Do you have a suggestion for how the government could deal with that?

**DR. SALOMON:** Yes. I think that this is something that's really critical at the level of laws. I mean, there are now legislation moving through Congress committees, for example, to look at malpractice issues, liability and malpractice, which had doctors on strike in Ohio and Pennsylvania --

**DR. KASLOW:** -- on the level of how the government indemnifies the company.

**DR. ALLAN:** Not always in a good way.

So let me suggest something here. The second to last paragraph there is all about saying why industry is not going to cut it, biotech is not going to cut it, all these other things. Instead of doing that, which is more on the lines of what Dan is talking about, let's make it more objective and say, okay, obviously we need to have input from these different sources and there are some shortcomings at this point. And really I think what you guys could probably do is sit down by e-mail and hash out how you would like to see it done in terms of bullet form.

Because really what we're discussing now is really what we want in the document, right, and so it's basically evolving as we're talking. So instead of just saying it has to be this way or we need to have this in here, it's evolving and it should continue to evolve. I don't know if it will by e-mail, and it works better here because it starts to get clearer about what we really want in here. Instead of this or this or that or that, it tends to get -- so I would like to see -- you know, maybe you guys could work on it.

**DR. SWINDLE:** I think the issue is of such magnitude that it would require a whole committee vote on whether -- no, seriously. I mean, it's a major magnitude issue as to whether you're going to ask the Secretary to funnel government funding into a specific research program. And I think the entire committee has to bring that to a vote.

**DR. ALLAN:** It's also how you present it. The thing is, is that I don't think there's anybody at this table who can say that we need some government input on reagent repository. I think that's probably a no-brainer. If you're saying we need to fund whole organ experiment transplants, you know, in pig to primate for X, Y, and Z, to fund that whole field, I think then you're going to start having problems.

So all I'm saying is, is you can hash out what it is you really would like to see, and then you can have discussion about what -- we can have a whole committee discussion on how people feel about each one of those points. So we can just more direct it. Instead of saying the government should put more money into it, what are we talking about?

**DR. SYKES:** I would like to ask for a chance to work with this section. Because I think that we have talked about those things, specifically what we want to ask for, and I think the problem is it's just not coming through here. And I would just like to see if we could put something together that would convince people. And I think our recommendations do need to have more meat to them, but they need to have the weight of an argument behind them.

**DR. ALLAN:** Okay.

**DR. KASLOW:** That's fine.

**DR. CHAPMAN:** I've been assuming at this point that everybody here will have written comments on

these drafts that will be handed back to whoever is doing these sections, that we're sort of beyond the point where the individual people assigned to one section are responsible for taking it forward.

If that's not the way people are operating, maybe we should. I mean, telling the people who have already worked on this to go back to their e-mails and look through it and hash it out further, maybe it's time for other people to put in their written perceptions of how this should be going to help the original authors move forward.

**DR. ALLAN:** It would be helpful. To help that, I agree with you.

**DR. SYKES:** We all have written comments on all the sections, I'm sure. How should we do that? I've given my written comments on your section right to you, John, but I think for the bigger issues, on written comments, they should probably be distributed to all of us. Dan, yours are electronic?

**DR. ROTROSEN:** I have electronic from NID staff, but what I have here is Mary's handwritten compilation of all of the HHS representatives.

**DR. GROESCH:** No, it's the institutes. We have a group of institute liaisons within NIH and we asked for comments.

**DR. SYKES:** I mean, it would be great if these could get into an electronic format and then you could distribute it to all of us. I think it's really important for all of us to see all of these comments.

**DR. LUBINIECKI:** I think some of us have each other's e-mail addresses, but I don't know that we have everybody's.

**DR. GROESCH:** Yes, I'll redistribute the list.

**DR. SYKES:** And I should point out, we have asked for comments on this section quite a long time from the entire working group, and it was distributed electronically.

**DR. KASLOW:** We skipped over about nine pages of science to get to that last paragraph. I wonder if there were other things that needed a group discussion before we leave the whole --

**DR. ALLAN:** I'm just wondering in terms of all of that discussion, how your bullets are going to look. Because most of it is just descriptive, saying that this is what is available, or this is what it is, cellular, it's this, it's that, it's this. It's mostly just educational materials; it doesn't really tell us exactly what it is that you're specifically recommending or what it is that -- how that fits with -- do you see what I'm saying? Most of that is informational, which is not -- I think it's good, I'm just wondering if you need a paragraph at the end of each one that says, okay, what does that mean.

**DR. KASLOW:** Right. Right. What you're saying is, okay, as a result of this, what does that mean and what do we do?

**DR. ALLAN:** Yes, for each.

**DR. SALOMON:** I mean, I think that the theme is clear, it's just that when this was written and Megan and I took different pieces of it, we weren't thinking about, well, we need to recommend this and we need to recommend that. I think everybody is loud and clear that what we need now is to finish the job, which is to put in the recommendations. And I think that's what we'll do.

**DR. SYKES:** But are we now putting them at the end of each section?

**DR. KASLOW:** Well, I think they were suggesting the infectious disease section, at each end they have "in summary." and so it would be a combination of what have we learned and what do we do now.

**DR. ALLAN:** In each one of these sections. If it's applicable.

**DR. KASLOW:** I like that. I think that's reasonable.

**DR. ALLAN:** Because it forces you more to say, okay, I've just given this information, what is -- you know...

**DR. KASLOW:** What's the significance of it.

**DR. SALOMON:** I think the two things we want to accomplish at the end -- I mean, I thought the main thing that we wanted to accomplish at the end of each section was to restate the key points in lay language, but without calling it lay language to insult anyone, but just say an interim summary. But do things like say, hyperacute rejection, which is really just the destruction of the organ by circulating antibodies, something like that.

**DR. ALLAN:** I think beyond that, I think you want to say, okay, so you present hyperacute rejection and these different forms of rejection, and maybe at the end of that section you say -- you know, the bullets are, well, in the future we can see that most of the problems will be at this end, or, you know, it's your area. Something like that.

**DR. SALOMON:** Right. I like that.

**DR. SYKES:** I would think that the whole summary would not be on hyperacute rejection, but on the immunologic hurdles, so you would say the immediate rejection problem has been solved, but some antibodies cause a bigger problem, and even if that's solved, we expect that other components...

**DR. KASLOW:** I think that you can even reserve the summary to the end of each bolded section, so you've got four or five summaries.

**DR. ALLAN:** Right.

**DR. SALOMON:** I think the key question, then, is the recommendations, I would think, but this is just a thought, would be in one section at the end.

**DR. ALLAN:** Yes.

**DR. KASLOW:** Whatever works.

**DR. SALOMON:** Yes. Exactly.

**DR. SYKES:** So when we expand that last section, that last paragraph, we'll make it a separate recommendation.

**DR. MENDEZ:** Megan, I thought it was excellent, the whole thing was excellent. There are two areas that I would possibly delete because they were a little bit redundant, and that was on page 17, the first paragraph there, and then the other one is on page 13, the last paragraph also you had also stated on page

eight. And so it might be that you ought to think about that.

**DR. KASLOW:** Which piece on eight was repeated later? Where later is it repeated?

**DR. MENDEZ:** 13, the last paragraph. And then --

**DR. SYKES:** I'm not understanding. So the transgenic approach that's already been mentioned?

**DR. MENDEZ:** No. No, that's good. The very last little paragraph, the last five lines.

**DR. SYKES:** It's all about transgenic...

**DR. KASLOW:** "these studies have demonstrated," he says is repeating something on page eight, which is where?

**DR. MENDEZ:** On hyperacute rejection. No, maybe it's only in the first sentence.

**DR. SYKES:** Well, it's a little repetitious.

**DR. MENDEZ:** On the advances on page 17, just that one first paragraph, whatever you think is necessary.

**DR. SYKES:** Well, we can reword that first sentence.

**DR. MENDEZ:** It gets to the point where we start that second paragraph.

**DR. SYKES:** Okay. Can we move on to the infectious disease section? Our time is really more than up.

**DR. ALLAN:** Maybe we should just go until 11:30, we need another 10 minutes, at least.

**DR. MICHAELS:** 11:35. I want to get to the infectious disease part, because I feel that it's all over the place. But it's not what I remembered. But that could be that I just missed the last one and missed it, but I don't think it flows in the right order and I think we have to reorganize it. It left out what exogenous and endogenous explanations were. It's just -- I'm embarrassed to see it since I was part of it, but I don't remember -- the sections that I had thought were in aren't there, so I don't know what precisely happened.

**DR. ALLAN:** I think I know what happened. I mean, I went back to the original draft from the July, and I didn't have your part of the write-up because you had it handwritten.

**DR. MICHAELS:** No, I e-mailed it.

**DR. ALLAN:** Because I didn't have it, so I'm just trying to go back to memory why that's missing in the introduction section. I think it's because either I couldn't find it or I didn't have it, and I thought it would be put in since we didn't have it in there. I'm going to go back and put in whatever paragraphs are missing in that intro section, then we can discuss that again. So I didn't take out anything because I didn't think it was worthwhile, I just --

**DR. KASLOW:** You made it sound like there's an order that has changed, too. It's not just what's missing, but you didn't like the order.

**DR. MICHAELS:** Well, I was thinking that we start -- PERV sort of comes in the middle somewhere,

but there's nowhere that gives an explanation as to what exogenous and endogenous --

**DR. ALLAN:** That was in the intro .

**DR. MICHAELS:** Oh, that was. Okay. Thank you. Maybe that was it.

**DR. SYKES:** But it doesn't flow. Conceptually it doesn't flow. And it doesn't end the section with the bottom line, which is we need to -- there are these types of infections; you can deal with them in this way, and so this must be done. Or for the PERV section, these strategies, but there's certainly no --

**DR. KASLOW:** Was there an outline that you were working with that has changed, or could we see that again? Would that be helpful, or should we just work with what we have?

**DR. ALLAN:** That was the outline. It changed a little bit in terms of the heading, what they said, but the outline was pretty much...

**DR. MICHAELS:** Right. The outline was an introduction that gave a definition of exogenous and endogenous viruses, and talked about the difference between a cute infection that would be easily recognized in both a source or in a patient receiving a transplant, then went on to discuss the types of exogenous microbes. And then I think we did the endogenous ones, and then the mechanisms of preventing them through the husbandry techniques and through the monitoring and through the need for the monitoring as well as the diagnostic procedures in the animals up front to help with the husbandry. Is that what you recall?

**DR. ALLAN:** We have that in here.

**DR. SYKES:** What Marian is saying is that that's a framework. The endogenous versus the exogenous, that's a framework. Not just something that is mentioned in the intro, but it should be the framework for the organization of the report. And I agree.

And I think with the exogenous, you should then divide that into known and unknown, because the way of dealing with those is different. We know how to deal with known, we don't know how to deal with unknown.

**DR. SALOMON:** I like what Megan just said. That's a nice organizational principle. But I actually didn't think this section was quite as bad as it's sounding here. I thought it read pretty well. I mean, you could do some things like just make sure that you do your summary bullet points for every section, because I think everyone agreed that was really a great idea, but I thought when you -- I mean, if you look at just the headings for a minute and not all the details, they cover about what needs to get covered. And Megan's points are well taken and should be incorporated, notwithstanding --

**DR. SYKES:** Dan, you're a well informed reader --

**DR. SALOMON:** Right. And I could be missing something.

**DR. SYKES:** -- and what I'm afraid of is that the uninformed reader will not come a way from this with a picture of what we do and don't know how to deal with.

**DR. ALLAN:** I think we can take care of alot of that in the interim.

**DR. MICHAELS:** Yes, I think you're right.

**DR. ALLAN:** I think once you see the intro, hopefully once you see the intro, it will flow better. And, in fact, I think what you're suggesting is we could introduce the different sections a little differently and add sentences such that it keys you in from exogenous to endogenous. Is that what you're asking?

**DR. MENDEZ:** Yes, known and unknown.

**DR. LUBINIECKI:** There was also a point that was made yesterday that would be very useful, and that is to link the risks and organize it that way to the control steps, so there's an outcome, a clear picture of what you do about what.

**DR. KASLOW:** So instead of having a whole section on controlled infectious diseases, you would actually incorporate the control into each of the sections --

**DR. LUBINIECKI:** Yes.

**DR. KASLOW:** Well, can you? You can.

**DR. CHAPMAN:** You may also be able to do that without reorganizing the whole body by the use of headings, where you have parallel headings; here's the risk, and down here in this section here's the control for that risk kind of thing.

**DR. ALLAN:** What we decided in the meeting yesterday was to merge the section on porcine infections as potential pathogens and diagnostics and control all enveloped into one. So instead of sprinkling control throughout this whole thing, it will be mostly in the framework of this particular heading, if that works for people.

**DR. MICHAELS:** And then I think we should probably add in, which we did not have it here because of the time, the concept of being able to eradicate endogenous viruses.

And then the other part that we were missing that I took a way from yesterday's meeting, that we should at least put in a paragraph or a section about the fact that other source animals might be used, and while the specific microbes will be different, the framework would be the same. Is that what all the people recall?

**DR. SWINDLE:** Yes, I understood that somewhat, because we're going to leave this pretty wide open. Because you have all the aquatic species and everything else, it's a physical impossibility to put all that in there. Are we saying that if you put in a paragraph that other species are used, the principles of looking at their health status and quality control should be the same framework, and just leave it like that without going into anything specific?

**DR. ALLAN:** And put it in an intro. I would put it as an intro to that porcine infectious agents, say, we understand that that there are other source animals that have -- that we're going to be -- since the swine model is the one that's at the forefront, you should also understand that the principles involved in protecting or looking at infectious disease agents for this would also be applicable to other species.

**DR. SYKES:** Well, the principles, yes. But what this discussion is bringing up in my mind is that, in fact, we have a lot less information about these other species, and so what we're really saying - and I think it should be said as a recommendation - is that if other species are going to be used, there's an awful lot of work that's going to need to be done to get it to where we are now with the pig.

But then another aspect is should we make recommendations about different types of xenotransplants? Because, as you know, there are already xenotransplants done where mouse feeder cell layers are the source of the xenotransplant, and do we really think that the same amount of work needs to be done on that basis, the same amount of work that needs to be done in understanding the potential of murine pathogens as is now being done with the pig. I think we need to state a sample.

**DR. CHAPMAN:** It may need more work, because there's some data to suggest that endogenous retrovirus (inaudible). But I think you can encompass that in this framework, because whether you're talking about tilapia fish or you're talking about goats or you're talking about pigs or you're talking about mouse feeder layers, the word and phrase may change but the principle is the same. One is control the source of the cells; you know, purpose bred breeding may not apply to mouse feeder layers, but know where these came from and have documented for several generations back the potential for introduction of infections. Do the science to explore the body of endogenous and exogenous agents currently in the PERV or feeder layer, put in the control efforts to exclude those that are excludable.

I think that you have to think a little bit about the wording, but the principles apply where you're talking about purpose bred pigs, you're talking about mouse feeder layers, or you're talking about some other source of living tissue from non- animal sources to humans.

**DR. SYKES:** They do, but I think what we're getting towards is the existing guidelines and whether they're adequate. I mean, is there more work to do on mouse feeder layers? Is there more work to do on (inaudible)? Are we being perhaps too lax about these things, or is the opposite true? Are we really satisfied?

**DR. LUBINIECKI:** On that point, I think there's now probably at least a decade if not two decades worth of experience on the guidelines of those cells and other cells that look like those cells that are characterized in the same way. And I would like to hear your opinion, Carolyn, but mine is that the existing frameworks look like they work pretty well.

**DR. WILSON:** Right. Well, to clarify, we're really talking about two different types of murine feeder layers. There's the Epicel-based product, which you've heard about a couple of times, which is using an established murine cell NIH 3T3, which is essentially used as a master cell, and the guideline says things like the points to consider for characterization of signs that have been used to assess signs used to produce biotech type products for, as you mentioned, 20 years.

So that's sort of one category of murine feeder layer. But when we're talking about the embryonic stem cells, those feeder layers more often than not are actually primary cultures of murine embryonic cells, where I think then you do want to take a step back and think about that source animal where those cells are coming from and have that information as well.

And the question you're asking, Megan, is whether or not the current guidelines would cover that, and I think that's a valid question for you-all to consider.

**DR. LUBINIECKI:** Well, the current guidelines always do sort of waffle on primary cells because they're sort of intermediate between the characterized bank cell situation and the intact animal situation. And I think we can state it, that the answer to the question is unknowable, whether it's adequate or not.

**DR. CHAPMAN:** So the recommendations, those need to be reviewed as to their adequacy or not.

**DR. LUBINIECKI:** I think we'll have to review it as we get data that says we should review it again, but short of that, I just don't know what else could be done.

**DR. SALOMON:** Yes, I'm sort of sympathetic to what Louisa said, in that I'm sitting here and I can't think of any really big gap here where the general principles aren't applicable. And what I've gone back to is the discussion - Carolyn, I think you were there - when we presented epice1 a couple of Bermac's ago, and it was a very comfortable discussion. It wasn't any big deal. We basically used these guidelines, and it was a very comfortable discussion. I thought the company felt we were being reasonable, they got the points that they deserved because they have a beautifully characterized master cell named the NIH 3T3. We did suggest to them that they need -- and they had done some retroviral transfer studies, albeit they had used older technology than some of the new PCR technology, and we suggested that in a subsequent submission they should update their technology, which they agreed to do. And I don't know how those recommendations from the Bermac eventually got into print.

So I would stick with the fact that -- I think the primary answer is that we're covering the basics in a good enough framework that when specific projects get stuck in front of us, that they're okay. I mean, that's my current thinking.

**DR. SYKES:** Carolyn just said that she thought more work would be needed when cells from primary that have been growing on primary feeder cells were transplanted. Not that we're there yet, but shouldn't we make a recommendation about that?

**DR. SALOMON:** I guess what I'm saying is that more work that would be needed would be to follow the guidelines that are already there. But I totally agree with you, more work would be needed. And I think what I have heard as being potentially valuable for the report is just a paragraph saying -- you know, kind of looking ahead, there are going to be other kinds of...

And I think the other thing Megan said is also true, and that is if suddenly someone wanted to use bovine pancreas, which isn't totally crazy, or goat, well, we don't know the PERV that's in bovine, but we know they have endogenous retroviruses. And like John and probably Dick will tell us, two or three of them already. Then we would have to characterize them and we would have to test them out, so there is a lot more work. But it is worth mentioning. But it would be the same principles.

**DR. LUBINIECKI:** The principles are the same, but there are some very big practical differences, and that is that the primary cells are being used for manufacturing at the same time in parallel they're being characterized. And because of the nature of the cells, frequently you can't get multiple passages out of them, and therefore you can't get the power of the kinds of characterization tests you can for a bank cell.

So I don't know that we want to spend pages going into all this detail. Primary cells are always going to be a black box. They've been a black box for 50 years, and they're always going to be a black box, in part.

**DR. SALOMON:** Right. And I think that's actually well stated in the sense that we shouldn't be taking on problems that nobody else has solved or been able to. I mean, what's different or unique for xeno? That's the part that we ought to deal with. And I don't see it.

**DR. WILSON:** I was just going to say that in that regard it's like the pig situation, where even when they have cultured cells, again we don't have a lot of time to characterize them. So that's why we asked for all that upstream information in the guidelines about the husbandry and the herd screening and the animal screening and so on, and that the mouse situation would fall into that category.

**DR. ALLAN:** My suggestion is that we have a separate section on other source animal tissues and whatever, and we just briefly discuss, like, tilapia, and the basic principles for these things are common,

but that there are individual characteristics for each that needs to be addressed, including each has their own infectious diseases that need to have further research. And I think we just leave it at that.

**DR. SALOMON:** Yes. And that primary cells have their own problems that are unique to primary cells, for the reasons we already stated.

**DR. ALLAN:** Yes, we can do that.

So we brought this up a little bit. We need to finish this, but the other thing we need to bring up is there's the regulatory guidance type information, that basically we didn't address that. There's a couple of sentences that say they're fine, but we never really talked about them and have never really gone through them. So I don't think we should be putting in anything regulatory at this point until we've actually had a discussion on this.

Now, I don't know how to do that, because we're basically asking whether we need to have a regulatory guidance part or even a discussion. Because in the charter for the SACX is review guidances and regulatory types of things, and we haven't included that.

**DR. SWINDLE:** But we're going to do that. Wasn't that one of the things we said yesterday?

**DR. ALLAN:** Well, that we need to have.

**DR. SWINDLE:** That we're going to have a session on that. My recollection of this section was we wanted to list the documents that we were using to make these recommendations and say that the recommendations in those documents was okay for this particular issue.

**DR. ALLAN:** I'm not sure that it's okay, though.

**DR. KASLOW:** That's what you said here, "No new regulatory guidance," after you list them, "is recommended at this time. The present regulatory environment seems comprehensive and addresses known risks that the current clinical trials occurring under..."

**DR. ALLAN:** But we've never discussed that.

**DR. KASLOW:** That's what I'm saying. If you haven't discussed it, you better be careful about saying that.

**DR. SWINDLE:** But we're going to have to address that at a session. On the basis of known knowledge based upon hearing all these trials and everything for the past two years, I haven't heard any problems, and so I had no problem making that statement because I haven't heard of a problem.

**DR. ALLAN:** The issue is has anybody read all the documents that FDA has put out and CDC has put out and scrutinized them and said, yes, I like this. We haven't discussed that.

**DR. LUBINIECKI:** We haven't discussed it, but I assure you, I've read every word of it.

**DR. KASLOW:** I think we heard about a potential problem this morning, and that is the whole issue of what do we do now that there are actually people who have had xenotransplants coming into the country or appearing on our doorstep or physicians' offices for which there are no guidelines?

**DR. MICHAELS:** This is slightly just to take that one step further. Some of the things that have been

discussed in the larger group context about people who have undergone xenotransplantation who are not agreeing to lifelong follow-up, which is probably the case at this point, and if they are asymptomatic, I have to say I have a great deal of concern with the discussions that were beginning to come out in terms of saying that the public -- that we would be asking the Public Health Service to have stronger abilities to quarantine or to force them to have blood work obtained if they're asymptomatic and not proving to be a disease risk, when this is still -- I mean, the hypothesis is there. We all believe that there's an infectious disease risk, potential risk, but this has not been proven.

**DR. CHAPMAN:** In a local situation, not in every --

**DR. MICHAELS:** This has not been proven, and maybe this is a discussion for the whole group.

**DR. KASLOW:** My problem, though, and I mentioned it to Robyn, I think they're going to be addressing it, the public health laws address symptomatic infection, and the problem --

**DR. CHAPMAN:** That poses an immediate risk.

**DR. KASLOW:** Right. Which makes it even more restrictive. Because the fact is, we may be talking about an infection that has a 10 or a 20 or a 30-year incubation period before most people are going to get infected symptomatically -- I mean, are going to express symptoms. And I think to suggest that just because we're dealing with asymptomatic infection, doesn't relieve us of the problem. The question is whether the infection is capable of producing symptoms, not whether it's producing symptoms now.

So we sure wouldn't want to -- I mean, the AIDS epidemic is a perfect example as a parallel. We conceivably wouldn't know about the occurrence of an infection for four or five years, until the first person developed symptoms, if the disease had a 20-year incubation period.

**DR. MICHAELS:** But at this point in time, without further data to prove that there was an epidemic - not potential, but that there was a true disease that was able to be transmitted - I would be uncomfortable -- I would want us to be able to encourage and develop every mechanism to have every xenotransplant recipient remain in surveillance for their life, and for surveillance not only for syndromes, but to bank serum, cells, et cetera. Not even just for having syndromes, but to continue to give of their tissues and bodily fluids for archival purposes and for periodic surveillance. But I would be uncomfortable having regulations -- or asking the government to have a regulation where we would force them to do that.

**DR. CHAPMAN:** It gets pretty touchy when you're talking about restricting -- you know, putting legal restrictions on people based on our concern that they may hypothetically have an infection that the most concerned people think might be a one in a million chance, and you're going to constrain everyone on the basis. But I do think -- this seems to be an area where there needs to be some thought about what should be -- what recommendations should be going out to physicians who are seeing these patients.

**DR. ALLAN:** I think this isn't an area that we're going to get into in this document today. You're talking about surveillance and regulation together, and that's something that we haven't really tackled. And I think we're going to have to tackle it, but it's not going to --

**DR. KASLOW:** It's going to be in the whole group.

**DR. ALLAN:** It's not going to go in this report. And I don't know how to deal with that, because if we're going to try and finalize this report without having anything on surveillance or regulations --

**DR. CHAPMAN:** John, it might go into the report in some general format, like this is an area that the

PHS should consider trying to work with multinational health oriented organizations such as WHO to try to develop some guidance for how to deal with these issues that transcend national borders, or something like that.

**DR. ALLAN:** I would even go farther and suggest that this is for SACX to tackle in the future. Because we haven't really discussed it, so we're just sort of talking off the tops of our heads, to some degree. I mean, many of the people are very well informed, but in general, it may take some discussions further.

**DR. SALOMON:** There's another critical point here just in that. Until we really could say that we have scientific methods to absolutely, unequivocally monitor these patients, I think we have to be very cautious also about what it is we demand of them.

**DR. SYKES:** Are we wrapping up?

**DR. CHAPMAN:** So the agreement on this is that we will put our comments into the Word document and send them to Mary to be distribute to the whole group?

**DR. SYKES:** Right. And if there are any handwritten, you can fax them to Mary and she'll fax them around. Everyone hear that? So everybody, please either e-mail or fax all your comments to Mary and then she'll distribute them to the rest of the working group.

(Proceedings adjourned.)