public group comes up with the money to do that? Is that, in fact, what you're suggesting? Okay.

CHAIRMAN SALOMON: You got me there.

I think until--I think we're looking at--we're talking about what is long-term follow-up, right? And I'm saying that the principle that I think the committee is agreeing is that long-term follow-up is really just knowing whether the patient's healthy, whether they've had--you know, the key issues of pregnancy, malignancy, autoimmune disease, neurologic disorder, and any other unexpected diseases. You need follow-up on those patients long term.

DR. MILLER: I mean, the sponsor's required--I mean, I think it's clear that the sponsor, whoever is doing the therapy, is required to follow up the patient. I disagree that it's in the public requirement to get the scientists together to figure out how to use that data. You know, as an academic community, generally the people who are going to be doing these gene therapies, I think that it's through the grant mechanism and the volunteer--you know, it should be something like the IBMTR. The reason UNOS can be some--a registry of scientific or a group of people who are doing gene therapy, get together and say we're going to pool our data, because I don't think that that--I don't think that there's a mechanism as well to really do that.

Now, the reason UNOS works so well is because they

can monitor the number of kidneys and transferring back and forth, and, you know, it's been legislated because there's a product that goes back and--I mean, in some way there's, you know, interstate and--isn't that what brought it up because there's interstate and a sharing of organs that can be--are a resource that has limits, where compared to this, where anybody can--who has a product can--can expand to fulfill the--to fulfill the need. So I think it's very, very different. I think it's up to the scientists to figure out how to use the data, but it's required in each individual to follow their patients because that's good clinical practice.

CHAIRMAN SALOMON: So there's two kinds of databases. I just want to clarify one thing. There are databases that have come up where groups of scientists have got together because they're interested in an area like the International Bone Marrow Transplant Registry, I think is a database like that, or the North American Pediatric Transplant Registry. I'm not referring to that.

In UNOS, actually the driving thing has been Medicare reimbursement for organ transplants, not interstate commerce, necessarily.

DR. SAUSVILLE: So, I mean, one point of difference that might exist, again, is--I mean, this field is so new and lots of things are going--lots of people are doing lots of different things, and I'm--I would be

concerned that the survival of the relevant population may outlast the survival of the companies and academic affiliations of the investigators doing these things. So, to me, that's one reason or could be construed as one reason as why--and, again, I look to our colleagues at FDA or my colleague at NIH and say everyone said there's a desirability to create some type of database. We agree that it, you know, might not be public in the sense of a publicly grazeable database as a first cut. I think whether it's funded as a line item from NIH or FDA as part of their appropriation or through a tax, ultimately, of currently acting companies to have ultimately a user's fee, someone's going to have to pay for this. And I don't think it's going to productively arise from expecting voluntary sorts of--people who write grants for these things.

DR. GORDON: I think one way to tie in these sort of parallel issues of a database and what sort of follow-up should be needed is--but I always thought of the database being envisioned for gene therapy as an adverse events database in many respects, not the only thing but certainly one of the most important things.

I think one thing I would glean from this discussion is that long-term follow-up is more likely to be recommended to be observational in nature than interventional in nature, and that there is already an onus

on sponsors to report adverse events. Long-term follow-up could be tailored to indicate that anything adverse that occurs to the patient down the road would be an observational process that would be then a reportable event to the database. The only disadvantage of that is if the patient is cured, that wouldn't be an adverse event. And, therefore, I'm not sure how to gather that information.

Personally, I think if we get into this discussion of how to pay for this, we're going to get absolutely nowhere, because I'm sure that we're not going to figure it out, who's going to pay for it.

CHAIRMAN SALOMON: I think the--that's fair, and I think that's what I was resisting earlier in the day. I don't want to get into who's going to pay for it. But what I was putting on the table for discussion--and we are discussing it--is what this long-term follow-up will constitute. Is this going to be something that each individual protocol will devolve back to the sponsors? And I think we've heard multiple lines of reasoning why that's not a good long-term strategy. And, therefore, I think what we need to consider if we're advising the NIH and the FDA on what long-term follow-up should be, I guess my point then, looking for feedback, is that we need to change the paradigm. It needs to move from sponsor/investigator-oriented long-term follow-up to more of a follow-up such as-

-again, I exemplify by UNOS as a long-term follow-up of anyone who gets a bone--gets gene therapy trial. And that follow-up is the responsibility of some government or a group of governmental agencies.

DR. SIEGEL: Of course, these are very different situations here. We're talking about products under commercial development. In UNOS we're not. UNOS has certain enforcement--not enforcement powers, but obviously there's strong incentives to be a player with UNOS.

But, you know, I would like to terminate this discussion, not because I don't think it's important but because I firmly believe that there's a fundamental presumption in current policy that if a sponsor sponsors and proposes a clinical trial, that they are responsible for collecting the safety data. We can discuss the merits and the efficiencies of having a government essentially subsidize that and do that other ways, and, in fact, there's a lot of reasons why that's a good idea. And I think there's a lot of discussion as to how best to do that.

But I think that what we have to--we have to address now what information to collect, how to collect it, under the assumption that until something else exists, it's going to be collected by the sponsor. And while further discussions need to be--need to occur about what else should exist, I think that in the interest of time and the issues

we need to face immediately, I'd like to focus more on where we're going at the present time.

CHAIRMAN SALOMON: I guess my response--yeah, my response, Jay, is fine, but you guys started this off with a litany of reasons why sponsors are having trouble complying, investigators moving, companies going out of business, cost of a database, grants that only last five years; and yet when we tell you that, yes, maybe the response to what you introduced as the issues was to change the paradigm, your response is, well, that's not what we're here to talk about. So I'm just putting it in context.

Dr. Anderson--

DR. SIEGEL: That's right and that's fair, although I would note that those issues are on the table for any of a number of reasons. It's important for the--if you look at the last part of Question 3, the issue is, okay, given all of those factors, given the fact that we know that even under the best paradigm we're not going to collect this information, should we just--is it unsafe to continue the research? Because one can assume that if you can't collect on 100 percent of patients, you shouldn't do the research, or maybe the goal is to collect as much as possible and get a database, and maybe if you get 50 percent or 70 percent, it's every bit as good a database as 100 percent, in which case--and maybe you can improve that with techniques such as

postcards, in which case, you know, it isn't--or it isn't so critical an issue or maybe the risks are smaller.

So there are many issues on the table, but--and that's one--the one you keep coming back to is one of them, but it's just not one we're going to solve today, so I'd rather focus on those that we are going to try to solve, although I don't think--having said that, I should qualify that and say I'm not suspecting that we're going to solve this issue today. What I see as a way we're probably going to move forward is integrating your advice to try to develop a somewhat more specific current approach and return perhaps to the RAC or to this committee, either way, supplemented with others, for further discussion and further input on that, and evolve as we move along.

CHAIRMAN SALOMON: Okay. So let's accept that, you know, guidance from--

DR. CHAMPLIN: I have one quick comment. There are sort of two levels of questions. There's one product-related. Is the individual product safe or unsafe? And then there's the generic. Is gene therapy safe or unsafe? And a much broader scale where it's not one company's responsibility but more of a societal or professional responsibility of the field.

And so a sort of tandem approach of the company having intense follow-up for maybe some period of time like

five years, and then some registry function that would look at long-term generic risks, maybe picking up after five years of follow-up for individual patients.

DR. SAUSVILLE: Yeah, I would echo that, because even with the way the reporting requirements are constructed for drugs, I mean, you report adverse events that are expected at one level or another, or unexpected. You sort of divide the world into that. Long term is sort of beyond unexpected. You're by definition sort of collecting things in an observational sort of way that are unexpected to the second power, but, nonetheless, by the nature of this therapy is called for, I think, at some level. And that's the--that's what I'm seeing as a tension between what is reasonably expected of a sponsor and might then might devolve to somebody else.

CHAIRMAN SALOMON: French and then Amy.

DR. ANDERSON: I wanted to add one other thing on the record. Several times you folks have talked about the scientists in the field, investigators in the field. Well, what about the scientists and investigators in gene therapy? And that is the American Society for Gene Therapy.

Since I'm Chairman of the Government Affairs Committee and this is a government affair, I suppose I can speak for the society, and Xandra is also here and there are other people here.

We have discussed at the board of directors for the society this very issue a number of times, and the American Society for Gene Therapy is absolutely in favor of long-term follow-up. It's absolutely in favor of a database. It will cooperate in every way possible. But we have no way to do it ourselves.

And so I just wanted to put on the record that the society of investigators in this field is very supportive and will cooperate in every way possible, but we can't do it.

DR. PATTERSON: I was wondering if it might be helpful to FDA if the discussion focused a bit on distinguishing between active surveillance and passive surveillance, and began to break out, for instance, for integrating or replication-competent vector systems what type of active surveillance would be appropriate during the first five years, and then to what extent and how would the passive surveillance in the subsequent 20 years be done, what types of questions.

CHAIRMAN SALOMON: So, I mean, let's take that. So we all agree that there's a very active surveillance for the first year that we're not going to get into. So let's talk about what we think is the level of surveillance for a vector that--for a gene therapy trial that fulfills the principles we articulated in the first part of the

discussion, from year one to year five. What should be the responsibility of the sponsors, Jay, during that four-year period?

DR. NOGUCHI: With respect, I'm not sure that that discussion is necessarily the focus here. We do have on the record for retroviruses what we expect. It's active for the first year and yearly thereafter. It could be up to five years. I'm concerned that without a lot of preparatory work, I wouldn't want to raise the bar higher without a lot of discussion and more surveillance of what would be the scientific issues. In some of these areas we simply don't know. Herpes, we only have two protocols ongoing.

So I would just say while I appreciate Amy's concern there, I think that the level of the active surveillance is not something we--I don't think we want to really go there here. We are concerned about the more general long-term follow-up.

CHAIRMAN SALOMON: Okay. So help me here. Now I'm a little off. What is it--I mean, one thing I'm thinking of is that we basically are done. We've answered your questions. I think that there is very little sympathy from the committee for anything more than after the first year, I think, than passive follow-up. Passive, maybe that's not the right word, actually. I don't like that word. Follow-up that would require, you know, sort of a

series of epidemiological questions being answered and recorded in a database. That's what I think everybody's been very clear about today.

DR. SIEGEL: Actually, I heard some committee members suggest a more active follow-up, and I thought you were going there, through up to five years may be appropriate, depending on the protocol, in terms of--

CHAIRMAN SALOMON: Well, I was going there.

DR. BREAKEFIELD: That's kind of the consensus I got, that maybe for five years of active follow-up and then have some kind of more passive follow-up after that. I would say--I'm not sure--and I think the FDA has really dealt with sort of integrating vector in the context of retrovirus vectors, but I'm not sure we've really dealt with replication-competent vectors and whether we're really even now monitoring shedding well enough over that--potential shedding over that period, because you can't in an animal model, given the tropisms of these viruses, ever know in an animal model what that virus is going to do in the human body. You have to accumulate that data. I mean, hopefully it will be negative, but there's no other way to get the data.

DR. SIEGEL: Shedding of which virus? I missed that.

DR. BREAKEFIELD: For instance, if you take a

replication-competent virus like an adenovirus that now has an altered surface marker that potentially will change its tropism or has now one of its essential genes under a promoter that's for a particular, you know, human tissue, you just don't know what it's going to do. You don't know whether it's going to replicate. You don't know whether, you know, it's going to find a little niche where it's a little bit immune isolated and now it can replicate and be passed. So I think we need to find that out.

DR. SIEGEL: Is there a specific concern, though, if such a virus were not replicating or not being shed at six months, a year, two years, that it might be at five years other than for, say, a herpesvirus?

DR. BREAKEFIELD: Well, I think that--I mean, basically you would decrease the frequency of monitoring, but there is the chance of kind of like a smoldering infection that it might at some point--because as the virus keeps replicating, it keeps accumulating mutations and it changes its properties, so there's a chance that you would have a very low level and then suddenly, boom, something new would pop out from that reservoir of actively replicating virus in a different tissue.

DR. GORDON: Yeah, I'd highlight the word observational more than passive, if you're looking for a word. But, again, one has to look at the practicality of

follow-up after a year and the active sort of follow-up. That is, are we going to draw fluids from the person? Are we going to biopsy the person or even bring them in for a physical exam? And I appreciate what Xandra is saying, but I think one of the messages I take from that is that we really don't know what to expect. It's very difficult from my point of view for us to devise a monitoring protocol that will cover us for everything that we don't expect. I mean, we have to--

CHAIRMAN SALOMON: If you take that, then I think one of the things that I'm trying to anticipate where Phil wanted us to go is over the next--from year one to year five, if we don't know the answer to your question, then maybe one of the things we ought to expect is a yearly physical and archiving of blood and/or appropriate tissues, depending on the type of protocol.

DR. GORDON: Right. I'm just saying that I feel a little bit--while I'd like to see that happen, I feel a little bit less zealous about it than perhaps you do.

DR. BREAKEFIELD: Well, there are certain standards for monitoring viral shedding. You know, I wouldn't say we have to invent anything. We just go to standard, you know, monitors of viral shedding, which can occur in different body fluids, which aren't that difficult to obtain, even.

CHAIRMAN SALOMON: I think that the issue here for me is that I think what we need to advise the FDA on in terms of the committee's opinion is how--you know, during this period of time, from year one to year five, how much should be demanded of the sponsor within reason. And those are--this part of the discussion avoids a lot of the issues, you know, of what happens at seven and ten years when grants run out, et cetera, et cetera.

So within five years, I would put on the table that it's very appropriate given that this is brand-new therapy, that there are many things that we don't know. You pointed out viral shedding. We've pointed out the possibility of integration events, reactivation of viruses that might be latent, unusual clinical events, antibodies that might develop, so-called inhibitors, et cetera, all of these things.

I can't imagine any reasonable gene therapy protocol that isn't going to accept the onus of at least yearly contact with the patient via the PI or one of his or her designees. And at that point, you know--so that I think is--that's what I'm putting on the table that we should expect of any sponsor, in that five years, at least yearly interaction with the patient and archiving of appropriate tissues, and that would be appropriate to the vector. I mean, if there's an issue of shedding, then you do saliva or

vaginal secretions or whatever is appropriate.

So I'm putting that on the table for--

DR. GORDON: What I'm trying to say is that this all sounds fine to me, but to me, five years is an arbitrary amount of time. I mean, we don't know that after five years we don't need to worry about it, and I don't think we should here be suggesting that we stop at five years because grants typically run five years. I mean, this is a medical/biological question. It's not an administrative question.

CHAIRMAN SALOMON: We accepted the onus early on of being practical, so I don't buy that that we can't put a five-year thing on it. Secondly, you got to have some time frame. The public doesn't want to hear that we discussed it and we said, well, just sort of we'd follow them but we're not really sure how long. I mean, you've got to say something, and it will all be arbitrary, we agree, right? But--

DR. SAUSVILLE: And, clearly, if new data emerges in the five years to sort of influence your thinking, you might extend it. I mean, you know--but, clearly if we don't see anything at the end of five years, it's hard to make the case that you should build a superstructure or require sponsors to look beyond that, I think.

DR. GORDON: Well, I guess what I'm trying to say is that I could make an argument for a year in the sense

that if something occurred in the patient that could be defined as an adverse event, it would immediately be very thoroughly characterized, and that would be a more sensitive way of finding them than looking at random, searching the innocent to find the guilty, as it were. But, I mean, it's obviously, as you say, arbitrary. I mean, I have no logical reason for objecting to five years.

CHAIRMAN SALOMON: Make it three years. I mean, you know...

DR. MILLER: Well, then in your protocol you justify why it's not, and if the protocol then goes through--I mean, you--I mean, this should be the standard for which it's a reasonable assumption, but that if you want to diverge from that assumption, you just have to justify why your protocol doesn't require that, and if you provide enough information that the FDA will say yes, you can go ahead and push that protocol through, your IND is accepted, then you follow--as long as you follow what's written in your protocol, or at least attempt to--I mean, one of the things about this is that if then you can--sponsors can go back and put in their patients' consent forms. The expectation is that you're supposed to be followed for five years. The patients are told up front.

Now, they can, just like with anything else, decide two years down the road that they hate Baltimore and

never want to come back and see us again. But everybody who comes to transplant is told up front, at least in our center, that the expectation included in our consent form that they're followed up for five years, but, you know--and I think that's something that we--that should be strived for, and there's some guidance from that standpoint. But the patient can always refuse, but, you know, at least you're striving for that.

CHAIRMAN SALOMON: We also have plenty of examples where we follow patients that have left our transplant program, and you call the nephrologist up and, you know, (?) , and you tell him, you know, this is what I want to know, what's the renal function, you know, how are they doing, do they have a bunch of skin cancers. So even then I think if the responsibility is in a finite period of time, a five-year period, and that's demanded of the investigator, I think that those are things that could be reasonably and practically dealt with.

Now, that doesn't deal with the fact that two years after the protocol's over the PI leaves, but, I mean, I can't solve everything.

DR. SIEGEL: Are you suggesting for this sort of approach for five years of clinical follow-up for all gene therapy protocols or based on some of the factors that was discussed before?

CHAIRMAN SALOMON: I was just putting something on the table so it could be commented on, but I guess what I'm saying is, yes, and then as--I think taking Carole's point of view, that if a specific investigator has an argument that's compelling to the FDA's review group, that they only need a year follow-up or three years follow-up, then you should have the latitude to do that for a given study, but at least it gives you some sort of general guideline.

French?

DR. ANDERSON: This is one of the few things I disagree with. In principle, Carole, of course, the investigator can argue only to go three years, but the reality, that's not going to happen. IRBs are not going to look kindly if the FDA and everybody else expect it to go five years, and you say, "Well, I only want to go three years." The lawyers and the institution are not going to let you do it. I mean, you're going to have to do it.

So our job is to struggle exactly like we're doing and to say one year, absolutely, no question; five years, after five years, I think it's pretty clear now, postcards.

Now, what is the category between one and five years? It requires more intense. And we were starting to get at that, replicating, integrating and so on, and I think we've got to come out--you know, we've got to bite the bullet and do it and provide it, so that when, say, if

you're talking about a plasmid, you don't have to have as intense from the one to five years.

CHAIRMAN SALOMON: As I was arguing then, we use the principles we articulated earlier. If you fulfill those principles, you got five years of follow-up. If you don't and it's gray, you know, then you make your argument for how long the follow-up is.

DR. ANDERSON: But I think the issue is from the one to five years, maybe for something which, you know, an irradiated dendritic cell, which has a plasmid in it--I mean, ex vivo--that instead of a intense for five years, that could be an intense for three years. But if there's some way we can give the FDA advice on that.

DR. SAUSVILLE: That gets back to tailoring it to the expected biology of the issue, and that's something that really is going to have to be judged on a case-by-case basis, but I think the general principles that we've articulated, I mean, as you say, would pass the test being applied to most things that you could conceive of.

DR. SIEGEL: I think that this has been an extremely useful discussion, notwithstanding some people's feeling, perhaps, that we haven't gotten anywhere. I think we have a--there's a general sense that, I think this is an important notion, the notion of dividing long-term follow-up into that which needs to be accomplished with direct patient

contact and that which can be accomplished through less direct--through postcards and phone calls, and that hopefully--and that latter can in fact--can and should be focused not on anything that might happen to the patient, so that everyone who gets a heart attack when they turn 65 is going to be in the database, but should focus on those issues that are of scientific concern, as I've said many--heard many say.

And that both the intense personal--direct contact, as well as the follow-up, be triggered by scientific issues, and I think we can work with that to devise a scheme, which as I said, that we will undoubtedly want to--won't be able to devise a highly specific scheme, because, you know, there's new vectors and new issues arising all the time, and I think it would be inappropriate to try to apply rules to fluid concepts, but propose some general approaches that we can then come back, as I said, here, and/or RAC for further discussion, make sure we're in the right direction.

CHAIRMAN SALOMON: I think as a general principle from what, at least trying to summarize what the Committee's told you this morning, is that we've tried to be as pragmatic as possible, yet everyone around the table still sees a number of practical issues that have not been solved here yet, right? And I don't think we need to go back over

those again, and that's, of course, the problem that we can't solve this morning.

There is an issue of monies, but at the moment, if you at least can define things as reasonably as we have, then you could potentially incorporate those sort of costs into NIH grant funding, and certainly the sponsors can deal with that. I think when you start talking about these numbers that got thrown around this morning, where it's $500,000 a year to do the database follow-up, that makes me want to get out of my research job and take a database job.

[Laughter.]

CHAIRMAN SALOMON: I don't know how many--I can't get my head around why it would cost that much. And I think we have to just be--I think that maybe part of the issues that the FDA has to deal with--and I don't think that's for the Committee--but I think that one of the sense of the community is that if you make the reporting so onerous that it costs $500,000 a year to do follow-up, then really, you've not been responsible to the field either, and I think that's something you want to make sure that you're being as practical as we're trying to be.

Lastly, I think it's really clear that the Committee is assuming that after five years, that there will be some form of long-term follow-up, and as I now would personally go back to making sure it remains on the record,

that I think that long-term follow-up from five years on is societal and not as much any longer the sponsor's responsibility. And I say that because I don't think it's that practical after five years. But you made your point, that also conflicts with a basic principle of the FDA's, holding the sponsors responsible.

DR. SIEGEL: I think I agree with what you said. I would add, so there's no confusion, as you and others have used the word "pragmatism" here, that it shouldn't be fully misconstrued. It means two things. There's the issue that French raised, that at some point you get--you have to draw a line somewhere on the curve, and there is some information--there's always some information which you could get for additional expenditure which is of some value, but of so little value that it's just not the right place to put your resources. And that's a point well taken, and it's true.

But I do want to highlight, before we leave this, as we talk about pragmatism in this context, there's another issue which I raised which Dr. O'Fallon mentioned, which is that, you know, if you go for--well, what our experience has showed us and what we know, and what epidemiologists know is that if you go for everything you want, you can wind up with nothing. You wind up--you know, every time somebody gets a cold, you get so much into a database at such a low

reliability level, that you just can't tell anything useful. Whereas if you target what you want in a reasonable way of where you think the most likely information is and a reasonable way of getting it, then you stand a much better chance of getting the type of information that you need.

CHAIRMAN SALOMON: And my point is exactly, and that's why I was saying that the FDA then has to deal with the fact that its reporting requirements are not so onerous that it costs a half a million dollars a year to follow ten patients--100 patients. Still, I'll still take that job.

[Laughter.]

DR. GORDON: I wanted to make one additional, small seconding of Dr. Miller's comments in the context of pragmatism. And I think one of the things we want to do in follow-up is, of course, forestall adverse events and protect people, as well as the general public, and of course, that's what we want to do. It's not possible to completely cover every base there. I would disagree that we cannot survive another death in gene therapy. I would say that we not only can, but we will survive another death in gene therapy if there is one, because of the imperative of the therapy. We're dealing with people who have nowhere else to turn, and we're dealing with potentially tremendously powerful technology for even better treatments of diseases for which there already is an approach of one

sort or another.

Therefore, I think worked into this notion of pragmatism in follow-up, must be the notion that we understand that we can't get every piece of information that in retrospect we feel that we should have had, that there's going to be--the system isn't going to be perfect, but that there is a great imperative for proceeding.

DR. SIEGEL: I'm assuming that that answers our final question for this session, the concerns regarding long-term safety of integrating vectors sufficient to warrant stopping such research until these issues can be better addressed. But there's not a sentiment here that until we have a better mechanism implemented or whatever, that we stop this research.

CHAIRMAN SALOMON: I think it's disappointing that we don't have a--I think that, speaking for myself, I think it's disappointing that we don't have a better mechanism in place after over ten years of this, but I don't think that's an issue in terms of going forward. I think the imperative I agree with is to go forward.

DR. SIEGEL: I would just like to comment on that though, that I think--I think it was Dr. Champlin made a very important remark, which is there are the risks of a specific therapy and the risks of a class of therapy. And databases are most useful for risks of a class of therapy,

because the IND process is well designed for the risk of an individual therapy, and I think--I would say, first of all, if you look at the experience of the last ten years, there's barely emerging a class of therapies, in that there just haven't been more than a handful of trials with anything that could be classed together as a class of therapies, and I believe that--and I firmly believe that our systems in the FDA of having reviewers who are working with related therapies discuss things and share ideas and share information, given the size of what we've seen and the number of protocols in any one type of vector or one type of class of therapy, have been reasonably functional to accomplish that, although one might hope and project that growth in this field would be such that that may change.

CHAIRMAN SALOMON: I'd like to bring the morning session to a close. I think all of this served well to summarize things, but before we absolutely close, I want to ask is there anyone else on the Committee or at the table who would feel that we haven't adequately summarized it or they have an additional comment? I think these are very important issues, and I think we got consensus on a number of them, but I think there's still some issues out there. So any other comments? I don't see anyone jumping. Amy, specifically? Phil, did you get what you wanted out of that? Carole? Okay.

It's almost 11:25. Can we take a 15-minute break, and then we'll be back and start the second session. Thank you.

[Recess.]

CHAIRMAN SALOMON: I apologize for being a little bit later. I got to talking to Dr. Siegel and Noguchi about some of the controversial issues and didn't check out, so I apologize to everybody.

So this is the last session, Session IV of the meeting. And these now carry over into one aspect of long-term follow-up, and that's the issue of germline transmission. So just in the interest of time, I'd like to get right on with it. So what I'm going to try and do is finish at 1:30, which is an hour and a half from now. So if we can maybe make the presentations quick and to the point, and then we'll get into the discussion, and that way everybody gets what they want.

So, Mercedes Serabian is going to give the FDA introduction.

MS. SERABIAN: My talk is kind of a lead-in, if you will, to the next talk after mine, which is specifically regarding germline transmission of a product that Chiron has.

What I want to do is present a brief overview of basically at this point CBER's recommendations for current

performance of preclinical biodistribution studies.

Okay. Basically, first, what is a biodistribution study? They're preclinical animal studies that are designed to determine the distribution of vector to sites others than the intended therapeutic site.

So, obviously, then you want to know what are the goals of the study? What are you trying to look for? What are you trying to achieve? Well, first of all, there's mainly two issues. First there's evaluation of the potential dissemination of a vector to the germline, and that's obviously the assay of gonadal tissue. Second is the evaluation of potential distribution of the vector to non-target tissues, and this can be gained from information such as potential target organs for toxicity studies. And it's important to try to determine the kinetics of the vector transduction and persistence in these studies.

Okay. Now, one way to address these goals is obviously by assaying the PCR--excuse me--DNA-PCR. And both issues can be addressed in the same preclinical study as we discussed yesterday, either using normal intact animals or even possibly the use of animal models of disease. And that's an important point I think.

The March 12, 1999 RAC meeting centered--one of the discussion points centered around the issue of gonadal distribution. Basically one of the conclusions they came to

at that meeting was that the risk of foreign gene transfer to germ cells on future progeny was perceived to be low, and this was the acceptance by those present in context of somatic cell gene therapies.

And again, some of the results from this meeting is that evaluation of biodistribution to the gonads--and this is important--may not be needed prior to all Phase I clinical trials. The consent form in this case then should address the issue whether there's a lack of data in that you have not done preclinical studies yet, or the unknown risk, which is always the case, I think.

What I did--and I divided this into two slides, because it was a bit on one--but this is a sample informed consent form. And again, I stress the word "sample", just as an idea as to what would go into an informed consent form.

"Risks associated with treatment in this study could cause permanent genetic changes in some of your sperm (men) or eggs (women). These changes could be neutral or may eventually cause abnormalities. Some of these changes could lead to miscarriage or abnormalities in your future children. Other changes may have no apparent effects but could still be passed on to future generations."

And to continue with that, "The likelihood of such outcomes is currently unknown." And there are certain

scenarios you could put in there, such as: "Studies to estimate the likelihood of such effects have not been done in animals or humans."

"Some studies (animals/humans) have been performed, but the information available does not allow estimation of the likelihood of such effects."

Or "Conclusive data regarding these potential effects in animals and humans are not yet available."

So, obviously, then one question that comes up is when can you postpone performing these biodistribution studies? Several scenarios that one could think of would be, first of all, if you have a previously defined vector, which would be previous experience with a similar vector, similar route of administration, formulation and schedule. One example give here--and there's many others--is adeno type 5 vectors.

Another thing would be if a transgene product is innocuous if expressed ectopically, or if the size of the vector is not excessively different.

And when in some cases do you need to perform biodistribution studies prior to Phase I trials? New class of vector, a vector that we've had little or no experience with--and again, these are just some examples, and this will change, obviously, as time goes on: AAV, lentivirus and other vectors; there's a change in the formulation such as

the lipid carrier; if there's a change to intentional systemic route of administration with an established vector, or a change in the route of administration; if the transgene has the potential to induce toxicity if it's aberrantly expressed in non-target organs.

And this is, again, I stress the word, sample. A regulatory letter that maybe would go out for studies that have not performed biodistribution in animals at this point would say something like: "The present submission does not contain data that demonstrate the extent to which this vector is able to disseminate out of the injection site and distribute to gonadal tissues. These data are necessary to determine the risk of inadvertent gene transfer to the germ cells, which may result in genetic changes in subsequent progeny."

I apologize for the small print, but I was just trying to get it on a slide.

"In the course of development of your product, you will be required to obtain these data and provide them to the Agency for review and comment. Data may be obtained either from biodistribution studies in animals, analysis of clinical samples, or from a combination of preclinical and clinical sample analyses. Clinical data should be derived from peripheral blood cells and semen samples during the treatment and follow-up periods for the clinical trial, and

from gonadal tissues (primarily ova) obtained at autopsy from consenting patients. We will require that these data be provided in a timely fashion so that the results may be used to guide further development and optimization of your product as a therapeutic agent."

Last but not least, "Please update the Agency on the status of these studies at the time of each annual report."

Well, so now the next question is, okay, we're talking about biodistribution studies. Well, how do you design a study, what do you do? What needs to be entailed in the study?

Well, first of all--and we heard discussion yesterday--species selection is important, and notice I stress here that non-human primates is not always needed. The next thing, animal gender. Could be male and/or female, and this would reflect a patient population, such as hemophilia, for example. Animal numbers are a crucial point, and I state here 3 to 5 per sex per group minimum, definitely minimum. Use of smaller animals such as rodents, obviously, allows for inclusion of larger numbers.

Dose selection, important issue. You're going to include the appropriate controls. You're going to include a maximally feasible and clinically relevant dose level. You want to be able to establish, to maximize exposure, and then

you're going to do a lower dose to establish a no-effect level, no observable adverse effect level, which we went over yesterday what that meant. I'm not going to get into that. For vector presence in the target tissue, so you want to see a dose response basically.

And then ROA or route of administration for short. And, obviously, this should mimic the intended clinical route of administration to the greatest extent possible. And it's important to note that worse-case scenario may not adequately represent the risk. It's your intended clinical route which is of primary importance.

When do you kill these animals? When do you sacrifice them? When do you sample tissues? Well, there's certain time points that we suggest in order to appropriately evaluate the kinetics of the vector persistence, as well as the transduction peak. Early, at the time of peak vector transduction or expression, and again, it depends on your particular vector. Later, to be determined by intended clinical route, and even later still, in order to determine the clearance of signal from the gonads and the non-target organs.

So you kill these animals. Well, you need to sample them. What tissues do you take? Well, this is a recommended list. It's by no means all-inclusive. It's just strictly a minimal recommended list. Initially,

peripheral blood, gonads, injection site, at a minimum need to be obtained. Highly-perfused organs for determination of toxicity. Some of them I've listed here: brain, liver, lung, kidneys, heart, spleen, et cetera, okay, major organs.

Then there's other tissues, and that's based on the toxicology or pathology of your transgene. For example, interferon, bone marrow. You know, you need to know your product. And it could be based on the route of administration. If you're giving sub-cu or IM, you could be taking additional tissues, so it's important.

Okay. I'm not going into specifics on the detection assay, other than just to say that the methodology should detect a sequence of vector that's unique to that product, and that the methodology should be appropriate to adequately detect vector sequence.

And what's important is that tissue samples from preclinical animal studies--you should also have, obviously, a methodology that works for clinical samples during--that you obtain during the clinical trial.

And on the NIH website, at the RAC discussion on March 12, 1999, Dr. Steve Bauer, who spoke yesterday, went through a bit of detail as to recommended methodology for PCR assays, such as sensitivity, spiking, et cetera. So I'm not going to go into detail on that, because it's out there, and you can also--he nicely volunteered that he is

physically here, so if you've got specific questions, you can ask him.

Okay. So briefly then, in summary, biodistribution studies are designed to evaluate vector dissemination out of the injected site in both gonadal and other non-target tissues. The current method right now is DNA-PCR analysis. And these studies are not always required prior to initiation of Phase I trials. It depends on previously defined vectors, the clinical context, and obviously, you know, your data will be required during the course of product development.

And last but not least, I found this slide, and I thought it was appropriate for the lead-in for the next study. It says, "Hey, was I supposed to wear a tie?" So you always have that one that you're worried about.

[Laughter.]

MS. SERABIAN: So I guess we just continue on then with the next presentation to keep moving, Debbie. Okay.

CHAIRMAN SALOMON: The next speaker is Dr. Deborah Hurst from Chiron. She's going to talk about the use of germline transduction after direct injection of retroviral vectors. And again, as yesterday, we--I know I speak for the FDA in appreciating that willingness of sponsors to step forward with real data, because it's very important, and to share it with us.

And I also point out that I will follow the same guidelines as yesterday, that once the discussion gets started, your specific protocol is not, you know, going to necessarily be on target.

DR. HURST: Okay. I'm grateful to hear that.

You've already introduced me. I'm Deborah Hurst. I'm director of clinical development at Chiron, Corporation. I'm in charge of the Phase I retroviral vector trial in hemophilia. I'd like to thank the FDA for inviting us to present our data on yet another difficult issue facing this Committee.

I'm going to first very briefly review Chiron's history of retroviral vectors in the clinic and the rationale for the current use of retroviral vector for the hemophilia indication, then review our preclinical data on germline transduction that was used to support the progression to the Phase I study in the clinic, then present data from the clinical trial, which is ongoing, and finally, a proposal for follow-up based on our protocol.

Chiron began using retroviral vectors in the clinic in 1993, first by ex vivo transduction techniques for cancer, and then in 1994, moving to direct tissue injection, intratumor or IM injections for cancer and immunotherapy for HIV. A total of 250 subjects received this direct injection of vector, and this formed basically the safety basis for

proceeding to an intravenous vector for the current hemophilia study.

Now, patients who received repeated IM injections over a period of up to 18 months, also had semen testing on a previous protocol. 104 subjects actually were tested by a PCR assay with single-copy sensitivity, and all samples were negative in this past study.

Moving now to hemophilia, the choice of the retroviral vector was based on the well-known property of stable integration with a potential for long-term expression of the expressed protein, and in addition, retroviral vector's excellent safety record in the clinic since 1990 in over 1,000 patients. In addition, transduction with the Chiron retroviral vector for Factor VIII resulted in therapeutic Factor VIII levels measured in preclinical models. So even though transduction rates can be low with retroviral vector, in hemophilia, of course, even a 2 to 5 percent increase in protein expression can make a tremendous difference in a clinical course, and so this vector was successful in the preclinical models in showing efficacy.

Finally, the decision to go with intravenous delivery was based, of course, on the fact that this was non-invasive. Basically, it's administered through a 25-gauge needle in a hand vein, so it's no more invasive than a patient's regular Factor VIII concentrate infusions, and

this avoids the increased risk and cost of surgical procedures in this patient population, as well as avoids possible risk related to delivering high concentrations of vector particles directly to the liver in a population that has underlying liver dysfunction.

Finally, Factor VIII can be expressed in multiple tissues, so delivery via a peripheral IV injection, which of course may go anywhere in the body, may be appropriate for Factor VIII. We know that because this is a secreted protein, which is unstable unless it binds to von Willebrand's factor in the blood, that any cell expressing Factor VIII needs to have direct access to the bloodstream.

The retroviral vector Chiron developed was derived from a Moloney Murine leukemia virus that was amphotropic and replication deficient, and carries the gene for a B-domain deleted form of Human Factor VIII. There were two novel features of this vector. It was produced in a human cell line to render it human complement-resistant, and prolong the half life in circulation. And also, it was manufactured at a high titer, 10^8 to 10^9 transduction units per ml, so that a large number of particles could be delivered in a relatively small volume of IV infusion. In fact, the volumes have ranged from 23 mils to 40 mils in the doses given to date in the clinic.

Now, any systemic administration of retroviral

vector, of course, raises the question of--and the concern about biolocalization, so extensive preclinical studies were carried out in 122 rabbits and 4 hemophilic dogs that had received intravenous vector. Tissue samples were obtained at various time points after infusion, early time points to get--at peak transduction and later time points for steady state. And a PCR assay was used, which was validated for single-copy sensitivity. Multiple replicates were tested, 1 microgram per DNA per replicate, the equivalent of 150,000 diploid genome equivalents per replicate. So the sensitivity was basically the detection of 1 cell out of 150,000.

And for frequency analysis of PCR signals standards, statistical assumptions were made, that the reactions were independent of each other, and that sampling was representative of the vector distribution in the specimen.

Results of this study are summarized here. Basically, the highest signal was seen consistently in liver and spleen, and this was seen in 4 out of 4 replicates in PCR studies, and this persisted as long as the animals were followed or out as long as two years.

There was also high signal initially in bone marrow and peripheral blood mononuclear cells. However, this signal declined and was essentially gone after 70 days

in rabbits.

The brain showed no PCR signals, and other tissue showed intermittent, threshold low-level signals. These tissues included lung, thymus, kidney, lymph node and testes.

Now, of course, actually seeing even a very low-frequency signal in gonadal tissue raised a red flag, and resulted in additional studies. These were done in a collection from semen samples. We tested 2 available hemophilic dogs at 6 months and 2 years, and semen samples were negative in these animals. In addition, an extensive rabbit semen analysis study was done, which I'm going to describe in a minute.

But first I want to review a little bit more about the testicular localization data, because actually this is the data that allowed us to go forward into the Phase I study in fertile individuals. And these data were presented at the March '99 RAC meeting.

Basically, this figure shows the probability of a transduced cell in rabbit testes over a period of time. There are four time points tested: 4 days, 15 days, 90 days, which would be following a cycle of spermatogenesis in rabbits, and then 2 years to represent long-term steady state. And notice the signal was higher at first and then declined very quickly to practically undetectable levels

over time. And probably the most important thing to point out is that even initially, the highest point was still a probability of only 0.00005 or 10^{-5} of finding one cell in the testes that was transduced with vector genome.

The semen analysis study was designed together with the FDA to look at the tissue that was of course our direct concern, sperm cells, and this was carried out in adult male rabbits who were treated with intravenous Factor VIII at clinically relevant doses that showed therapeutic Human Factor VIII levels in the blood, and also gave a positive PCR signal in the testes.

The semen samples were collected weekly for PCR testing, and the duration of the study was 21 weeks in order to span multiple cycles of spermatogenesis.

For each sample 20 replicates were tested, 10 replicates at each of 2 primer sets, and no positive semen samples were confirmed in this study. There was a low incidence of sporadic unconfirmed signals that was actually higher in the control animals, 1 in 800, compared to the treated animals, 3 in over 4,000 replicates tested. So the false positive PCR rate for this assay was about 0.08 percent, which was certainly considered acceptable, and in fact, lower than published rates from other labs.

The PCR results then, in rabbit testes and semen, confirmed that the risk of any germline transmission event

was extremely low, and testes, after one cycle spermatogenesis or 90 days, the risk of any single rabbit testes cell containing the vector genome with 99 percent confidence, was 1 in 709,000 cells. And in semen, all samples were negative throughout weekly testing over multiple cycles of spermatogenesis.

So our conclusion from the preclinical work was that a positive PCR signal for vector genome in the gonadal tissue was not associated with transduced sperm cells in the semen.

Moving then to the Phase I study. Again, this study actually started on the basis of the frequency of signal found in testicular tissue and the rabbit semen study concluded, as the patients were dosed with a lower dose from the study. It was a single-treatment study design dose escalation with end points of safety and circulating Factor VIII levels. Subjects were adult men with severe Hemophilia A. Informed consent required barrier contraception for the study period, and an indefinite period thereafter if semen samples were positive, and extensive information regarding the possible risk of inadvertent germline transmission and the implications thereof.

Now, semen test points include a baseline, and then weeks 2, 6, 9, 11, 17, 29 and 53, plus additional samples would be obtained in case of any positive result,

and the study's duration was one year.

Currently 12 subjects have been on study for at least 3 months, and 4 dose levels have been administered, with 3 subjects receiving each dose level. Infusions have been well tolerated, and all subjects are alive in their usual states of health.

Semen PCR results are available from 11 subjects through week 17, 8 subjects through week 29, and 3 subjects through week 53 at the end of study.

The clinical PCR assay consists of testing of 10 one-microgram DNA replicates per sample, again, with a validated single-copy sensitivity, for a detection rate of 1 in 300,000 haploid cells, 1 in 300,000 sperm cells.

The assay procedures were designed, again, in consultation with the FDA to minimize common sources of contamination leading the false positives.

And collections were scheduled to maximize the chance of detecting transduced sperm. The schedule was based on our model spermatogenesis. First we assumed that germ cells that were accessible to blood-borne retroviral vector must be both dividing, and also on the blood side of the Sertoli-cell barrier, otherwise known as, quote, "blood testes barrier." And this would be then proliferating differentiating spermatogonia of which there would be many rapidly dividing cells, and then some smaller number of

dividing stem cells. This would mean that spermatocytes, spermatids and spermatozoa were not accessible to transduction, these later-stage germ cells.

The timing of the transduced sperm in semen was predictable, timing of appearance, based on the time required for maturation from transduced precursor cells, and this can be calculated out to be a period between 49 to 92 days after vector infusion, but equivalent of out study weeks 8 to 14.

This is a timeline just showing the semen sample time points on a timeline, which also shows the first possible appearance of semen in semen of transduced sperm, and the last expected sperm in semen from the first cycle of spermatogenesis. And the darker bar indicates the time of expected peak appearance of a transduced sperm.

Sample collection points were planned so that two samples would be collected during this peak period. In addition, in case our model assumptions were perhaps not right, and also to collect additional information, we have two samples before this period, a sample after what would be the expected washout period, and additional samples, which aren't shown on this slide, at week 29 and 53. And, of course, per protocol, additional samples are obtained following any positive test result until three consecutive samples test negative.

Results to date have been obtained on 63 semen samples tested from 11 subjects. 61 have been negative. We've had 1 positive in 1 out of 10 replicates tested, and 1 indeterminate with contamination suspected.

Our positive sample occurred in a subject who was treated at a dose 4, which is the highest dose that's been completed to date. It occurred after two previous subjects had received the same dose and had had negative samples through this period, the first 18 weeks. At week--the positive sample occurred at week 9, which, as you can see, would be early in the time of highest risk of transduced sperm possibly appearing in semen. Following this, two samples were obtained also in the risk period, and these were both negative, and two additional samples since the period have also been obtained in addition, and these were negative as well. And the samples prior to the risk period were negative. So the patient has had only the single sample with the 1 out of 10 replicates positive, and all the rest have been negative.

So, what's the interpretation of this result? Well, there are several possible interpretations. First, it's possible that the signal is coming from a non-sperm cell, some somatic cell. The semen contains granulocytes, macrophages, lymphocytes, epithelial cells, in addition to sperm. And we know that the subject's peripheral blood

mononuclear cells are PCR-positive for vector in 4 out of 4 replicates throughout this period.

Also, despite efforts to reduce the chance of test contamination, in any very sensitive PCR assay test, contamination can't be ruled out.

And, finally, of course, the signal could be coming from a sperm that was produced from a transduced differentiating spermatogonia. The signal's low frequency, detected during the first cycle of spermatogenesis, and repeat samples were negative. So again, this all supports an interpretation that probably this was a late-stage differentiating spermatogonia that was transduced, which was on a one-way path to developing into sperm and would not be a source of continuing bursts of sperm production.

We went on to perform a frequency analysis to better define the risk of possible germline transmission, assuming that the signal was in sperm cells, looking at the three subjects who had received dose level 4.

First we looked at pool data from all time points measured, and see an instance of 1 positive out of 109 replicates, for a probability of any 1 sperm cell being transduced of 1 in 57 million, or 99 percent confidence bound probability of 1 in 8.6 million.

We then looked only at the data from the high-risk period, in other words, the study weeks 9 and 11 samples.

And this would give an incidence of 1 out of 70 positive replicates for a probability of a sperm cell being transduced of 1 in 21 million, or a 99 percent confidence bound probability of 1 in 3.1 million.

In summary then, with 99 percent confidence, the worse-case frequency of a transduced sperm in our study data so far to date is 1 in 3 to 9 million cells, or a probability of 0.0000003, which is 10^{-7}. No positive samples have been detected after the first cycle of spermatogenesis, again, providing no evidence of a sperm cell transduction or a continuing event, continuing release of transduced sperm.

Our conclusions then are that current human data in semen is consistent with preclinical data, supporting the fact that the probability of the germline cell being transduced is very low, and the probability of inadvertent germline transmission with this retroviral genome at the current dose is remote.

Now, FDA's current policy is to place a clinical trial on hold if there's any positive PCR signal, regardless of its intensity. However, with risk levels as low as were presented here, we think that the approach is unwarranted, and that in such cases the trial should be allowed to continue while further investigation is conducted.

Features are built into the trial which are

sufficient to prevent safety issues. For instance, all subjects are required to use barrier contraception, and all are advised in the informed consent about possible risks and implication of germ cell transduction events.

On the other hand, a clinical hold would be appropriate if the subject's PCR signal were stronger, if multiple patients showed positive signals, or if timing of a signal suggested a continuing event based on the biology of spermatogenesis.

For follow-up of individuals with positive testing, our recommendations would follow the current protocol. Repeat tests should be obtained as soon as possible, and if three tests were negative over a period of 3 months, which would represent another cycle of spermatogenesis, and negative following the routine testing schedule to the study end at one year, then no additional extra semen collection would be required.

If repeat tests are positive or sporadically positive after the first three months and to study end, a situation which we haven't encountered yet, then, of course, one would ideally like to perform a cell fractionation procedure in order to test sperm and other cells in the semen, and determine once and for all whether sperm cells are in fact the source of the signal.

However, there are technical difficulties in

performing a fractionation which would be pure enough to be accurate and provide a reliable conclusion because of the sensitivity of the PCR assay. In our research, we basically couldn't find that there was a technique that was workable on frozen semen samples. One would need to use fresh semen and use probably a dual technique of sperm swim-up technique, centrifugation, coupled with a discontinuous percol [ph] gradient, and in that way, get a close to pure sperm separation.

But because, as I said, we had one single sample of a very low-frequency in a frozen sample, and so we were unable to perform, even attempt to perform any study such as this. But in a person who had repeated positivity, you would certainly want to do the best you could and see if you could accomplish this.

Following this, however, if it was possible not to completely rule out the possibility of a sperm being transduced, one would estimate the risk of germline transmission based on signal frequency, and then provide genetic counseling to the individual regarding possible outcomes of conception and reproductive alternatives. If the conclusion of the risk calculation was similar to the risk that was identified in our study to date, in other words, very low, then it's highly unlikely that there would be any effect on reproductive decision making based on these

data.

Okay. I'd like to thank you, and be glad to try to answer any questions.

[Applause.]

CHAIRMAN SALOMON: Thank you very much. So we have one hour to go into this. Are there any questions specifically to Dr. Hurst to clarify anything she's presented, or should we go on to--

DR. BREAKEFIELD: I just have one question. When the FDA does put it on hold, what do you do in the interim? Do you do--

DR. HURST: Well, getting additional semen samples on the patients.

CHAIRMAN SALOMON: Okay. I think it's probably good that we don't have a whole lot of questions, because again, we didn't want to put your particular protocol under examination. I don't think that's the intention here. Thank you.

Okay. This one is--this is easy, right? No, just kidding. So the questions to the Committee are two, and I have, unfortunately, about six or seven different issues though that I've put down in my own notes. So, we'll see where this goes.

So the first question is: if semen positivity is identified in patients in a clinical trial, our current

approach is to place a clinical hold on the study until it is determined that semen positivity is transient, at which time the trial may be resumed. Please discuss whether this approach is appropriate.

In cases where a positive PCR signal is observed in patient semen samples, discuss methods to determine the cell source for the positive signal, in situ hybridization, fractionation of the sperm, et cetera.

French?

DR. ANDERSON: Well, the issue of inadvertent germline transfer has been, of course, with gene therapy from the very beginning. It is an issue that I particularly have to deal with because we are developing protocols for in utero gene transfer, where germline is at even greater issue, and therefore, we've had to deal with these issues in some detail.

I'm pretty certain, in fact, I'm pretty positive, that we are the only program that has actually obtained an animal--in this case, sheep--this is with Ishna [ph], then Johnny--where the semen was positive, and we were able to fractionate and show that it's not in the sperm, it's in the semen itself, the non-sperm portion. And all of that has been published and was at the RAC's in utero gene therapy policy conference and so on.

This study that was done by Chiron--it's a

beautiful study--there have been a number of other studies. In addition, we have the description of Hank [ph] Kazazian at the March '99--Hank, by the way, is right upstairs at an HLVI meeting right now. And so I wonder if--I have to say one other thing in preface. I'm very much aware of the political issues, the social pressures that are on all of us because of the issue of germline, and this has prevented, at least at the RAC--how can I put it appropriately without upsetting our RAC members here--a really rational discussion of the issues.

And I'm very much aware of the issues. When our in utero came out, I had lots of hate mail, death threats and so on, because of it would appear that we were going to do intentional germline gene transfer, so I'm aware of the political issues.

But I really wonder if with all the data that is now available, if we aren't getting pretty high up on this patient safety versus cost, and we're starting to put so much money into studies that hone down, it's not really 3,100,000 sperm, it's actually 2,845,000 sperm? I mean, every piece of data says, "This is really, really rare."

I've talked with two pathologists in two different institutions at two different times, who tried to specialize in pathology of the reproductive system, and their feeling was based on the presence of--and so on, and specifically

retroviral vectors, that the chances of a retroviral vector actually getting into the sperm is extremely rare. That's what all the data says.

So I just put out on the table--I'm aware that politically we have to keep doing this, and we'll keep doing our studies, but I really think we're way up on that curve and we're doing an awful lot of posturing about an issue that is really pretty minor.

CHAIRMAN SALOMON: Okay. Well, I think, number one, we'll take on French's challenge that we have a rational discussion here, as opposed to other groups.

[Laughter.]

CHAIRMAN SALOMON: But you guys can hold me to that one later. I'm already in trouble. I know that.

Anyway, so I think that there--I think, French, you've done a good job of sort of setting the stage here. The question that's on the table though, you did confuse it a little bit, in that one question, which we should talk about, is how much we should demand as proof that we're not getting transmission to the germline, but that's not what the first question was.

The first question was: if we could demonstrate that sperm were indeed positive, regardless of all the semen--no, no, no, no--I know--but I'm saying that if semen positivity is identified in a clinical trial, they put it on

hold. And the FDA wants us, I think, to go either tell them, "Yes, that's great; any time semen's positive, put it on hold." Or whether we should break it down and say, "If semen is positive, you don't put it on hold unless you can demonstrate that the sperm is positive." So that's kind of the way I see the first question. So I'd like to make sure that we focus on that, and not all these more complicated things that French put on the table about, you know, if it was positive, but it was only in 1 in 8 million sperm, what the impact of that would be. I don't mind getting to that later, but that's not what I want to discuss first.

So, Dr. Gordon, and then Xandra.

DR. GORDON: I think I was probably invited to this meeting because of my background in this field.

I think what we have to consider here is--you can call it political if you want to--but the fact is that the insertion of new genetic elements into the germline has with it special characteristics, which I think makes it incumbent upon anybody regulating to do their utmost to make sure it doesn't happen. I think it is intuitively improbable, but I also think that a 1 in 1,000 event will certainly occur if you do the procedure 1,000 times. There's also the problem of vector proliferation and diversification. And so, while we may think this or that with retrovirus vectors that we use today, we don't really know what we're in for down the

road as vectors diversify.

So I would say that it is reasonable to put a study on clinical hold if semen is positive, pending a more close examination of exactly what cells have it, and sperm fractionation, while it was sort of thought of as maybe imperfect in the previous discussion, really is pretty good. It is true you run the risk that it will also be positive because of an occasional white cell in there after discontinuous percol gradients, but reality is that it's a reasonable thing to go forward to do while a study is on hold. It's not that difficult to hold a study for a period of time.

CHAIRMAN SALOMON: Okay. That's very clear. Xandra?

DR. BREAKEFIELD: Yeah, I just wanted to add also, that I think there is a lot of data, and maybe at certain doses and certain routes, maybe it shouldn't be required, but I think in this example of this type of case, where you're going suddenly intravenous, which hasn't been done before, and you're starting to escalate, and then you're looking at a situation where you say--well, I forgot exactly--we're on the highest dose, but let's say 1 out of 3 people on the highest dose had it, I think you do need to pause and consider, because you're in a different--it's not the database you have. You're escalating dose, you're

changing route, and you have a small number of people within that category that you're evaluating.

CHAIRMAN SALOMON: So, I don't want to put words in your mouth, but you also are supporting the idea that if in the conduct of a trial, the semen is positive, then you hold the trial until they investigate what's positive in the semen?

DR. BREAKEFIELD: I would say certainly in a trial like this where there's a novel route and a dose escalation. On the other hand, if it's a route that's been done extensively and there's a lot of semen data already available and they've been negative, I'm not sure that I would--and there was one positive, I think I'd be more--I don't know what it means to put on hold to a company, but I'd be more inclined to think it's maybe an--if there's a lot of data out there, and depending how serious it is, when you say you put it on hold, it sounds like oh my gosh, you know--

CHAIRMAN SALOMON: Well, Xandra--

DR. BREAKEFIELD: That's what I ask, what happens when you put it on hold? Is it like put in limbo for a year, or can they do something to get out of hold?

DR. WEISS: Sure. It's not necessarily a permanent hold. It depends on what the issues are, and we usually outline what it would take to get off hold, and that

just depends on how long those additional data take to come to the FDA.

CHAIRMAN SALOMON: So I think, Xandra, one of the things you said was, if you are monitoring semen samples and it's positive, what to do? And then you sort of began to segue into another question, would be, when do you demand in a protocol that you monitor semen samples? Which I don't think is irrelevant, but I think there's two things there.

So we're still basically--I still want to just come to at least one clear piece on this first question, because I think this is a big issue for the FDA, and I want to be responsive. So do we so far agree that if you're monitoring semen samples--we're not talking yet about which situations you should monitor--but if you are monitoring it and one is positive, should put it on hold?

DR. TORBETT: If it's an ex vivo kind of therapy, for example, T-cell therapy, put the cells in, there is a risk of getting T-cells in the semen. And under that criteria, without paying attention to say categories, then that would be considered on hold.

CHAIRMAN SALOMON: Okay. Well, I mean, I guess that's a point of saying if you were doing--I guess there we're kind of getting into what kind of a trial needs to have semen samples monitored.

DR. TORBETT: I guess so. Yeah, exactly. you

have to look at the biology of the system and also what kind of trials are being done. It doesn't make sense to me if it's a T-cell therapy trial, for example, independent of RCR, that if you see positive cells in the semen, you would say, "Gee, perhaps we should put this trial on hold." And I would submit that perhaps this isn't--you know, this would be considered different than injecting it IV or in the brain or wherever.

CHAIRMAN SALOMON: Point made. It's a good point. But I think that again the point here is, if the FDA agreed to be monitoring the semen samples, you know you could argue that now as being a study that didn't need semen samples monitored, and we could talk about that in a second, but still, if semen samples are being monitored, and one's positive, then the trial goes on hold. Is that--I mean, again, is there a consensus on that?

DR. NOGUCHI: Well, a couple of clarifications. We do not require semen analysis for ex vivo transduced cells, one. And the second is the question is just slightly different, because it describes a situation where there's a positive sample, and on the next sampling or somewhere down the line on sampling, the sample no longer is positive. So that's all we're asking. Is it appropriate to call a halt, look for further samples, and then take them off hold if it becomes negative?

The second question is really trying to focus on what are the current methodologies for us to go further and distinguish between transduction of cells and just carrier vector.

CHAIRMAN SALOMON: Well, let me follow up on that then. So if we would agree that if in the course of a study, a semen sample is positive, I won't know what the sample is going to be a week from now, so you're going to put the trial on hold, unless someone on the Committee wants to argue that that's not appropriate.

Then we can talk about whether--you know, how many negative samples after that you should have before you take the trial off hold, right?

DR. ANDERSON: Having said my piece, but if nobody is going to respond to that, then I feel compelled to respond.

I can understand that the FDA still wants to be in that position and the Committee still wants to be in a position to say if there's a positive semen sample, put it on hold. But that's a whole different category of clinical hold than everything else you do. You put on clinical hold when there is a real problem. And having what all the data says will turn out to be a minor incident, and even if 1 in 100 sperm samples is a positive, one can then go on protection so that one doesn't go on and have a pregnancy

and so on. But I'll simply raise this so it's on the record. I know if we'd vote for it, I'd vote to say go on, put it on hold and so on, because politically you sort of have to do that. But it really doesn't make sense. There isn't any danger for the patient. There isn't any danger anywhere around. It isn't a patient safety issue. It is simply that it is--until we get more information, it's nicer to do.

DR. SIEGEL: Just as a clarification on the first part, our reasons for hold--one of our reasons for hold is significant and unreasonable risk, but another reason for hold is insufficient information to assess risk. So one could make a reasonable determination that if you had a positive semen, and you yet had follow-ups or fractionation, you don't know if you do have something that's in the sperm cell, you don't know if you have something that's going to persist for years or just be transient for days or weeks, that that in a sense raises you to an--

And one other point about this that probably ought to be considered in the mix, is if you don't stop a trial at this point, you are in a somewhat awkward position regarding consent of new patients that you enroll. As good clinical practices creates an obligation to inform patients of any information that might influence their willingness to be in a trial. So now you're in the awkward situation of saying,

"Well, somebody's had this in their sperm, but it may well be artifact, false positive"--I mean, in their semen--"it may not be in the sperm at all, and it may be something that lasts a week, but we don't know yet." So it's something to think about as the option if you still continue enrolling in a setting that you have to figure out what to tell the next patient that comes into the study.

CHAIRMAN SALOMON: Good point. Dick?

DR. CHAMPLIN: I'm just wondering if this is an overreaction. I mean, what's the worse-case scenario if you put--a normal Factor VIII somehow got into a sperm? I mean, it's a situation where even if that was passed on, would not produce disease. So it strikes me as a sort of paranoid, worse-view situation of a non-event. And clearly, any patient going on a study like this should not be having children in the middle of the study. We use a lot of drugs routinely that we know is teratogenic, and we get consent of patients not to have children while they're receiving thalidomide, for example, as a therapy for a variety of immunologic conditions. So, that should be part of the consent process.

And the tradeoff, I would think, curing hemophilia, would certainly be a major positive in terms of a benefit, and we're talking about a theoretical risk that could be minimized by an agreement not to have children in

the course of the trial.

DR. NOGUCHI: Of course, that assumes that the hemophilia gene is properly expressed when integrated and so forth. So I think that the question of potentially curing your offspring is highly speculative at this time, and you could get exactly the opposite--

DR. CHAMPLIN: I wasn't saying it was a way to cure your offspring, but I would say the likelihood of even if it was somehow passed on, it would not produce a disease. You know, you could envision there would be genes that would be dangerous. I mean, you put an oncogene in--

DR. SIEGEL: I mean, I don't--I concur in general that we're talking about extremely low-level theoretical risks, but it's non-zero. Even a normal gene can insert in an area under abnormal regulation, so that it's expression is pathogenic, or certainly can insert in an area where it's mutagenic, and even if it's not disease forming, it raises other issues that need some consideration. So I think we can agree we're talking very small risks, but not--

DR. ANDERSON: You want to bring up Hank Kazazian with him, or I will--

DR. GORDON: I don't think we should go on the record as saying anything relating to if the gene goes through, it will probably be okay anyway, because I don't think the public is very likely to accept that probably true

statement.

But I just want to give you an example of how--first of all, my intuition runs the same as those who have talked. But let me just say that if you have a CMV P-53 gene that you're putting into somebody for a reason, let's say they have a liver malignancy, you may do a wonderful job of helping that malignancy in the liver. If that is transmitted to the germline and P-53 is expressed ubiquitously throughout a developing embryo, I think it could be highly teratogenic, and could be a pregnancy disaster. Furthermore, we all know that the people who say they're not going to conceive for an assumed period of time, do, and it's a matter of the profile of this type of anomaly that we're dealing with.

So my recommendation would be that if a positive semen sample is detected--and this takes into account not retroviruses with Factor VIII, but let's face it, we're looking at a huge variety of vectors and genes down the road--that you're put on hold for one cycle of spermatogenesis, pending repeat cycles, but that that hold could be removed if sperm fractionation in the interim determined that it was not in sperm.

CHAIRMAN SALOMON: French?

DR. ANDERSON: Jay, the FDA put on the RAC agenda, back in March '99, this issue, and you remember that Hank

Kazazian was brought in--I might have the numbers a little bit off--but it was something like the number of active retrotransposons [ph] present in the germline tissue was such--if the numbers aren't exactly right, they're close--that a couple would need to have something like seven children in order to have a mutation caused by a retrotransposon, and they'd have to have something like 6 million children in order to have a mutation caused by a retrovirus.

Now, so, your statement, although correct, is quantitative, orders of magnitude or from what happens naturally all the time.

DR. SIEGEL: No, I don't think so, because I said we were talking about very rare events. I'm not sure how that could be orders of magnitude higher than anything. It depends on what "rare" means. But basically, I was simply trying to say what Dr. Gordon said much more eloquently than I did, simply that we can't call it zero. But I concur that we're talking--

DR. BREAKEFIELD: Let me also add--just according with what Jon Gordon said--that it's one thing to do just random mutagenesis, and I think that's going on all the time. It's another thing to take in a very strong promoter or some gene that can have biologic consequences and was expressed in the wrong tissue.

CHAIRMAN SALOMON: I think basically I think we can say as a consensus, that we agree that if a semen sample is positive--now, that's providing that a trial was designed with semen sampling as part of its demand--is positive, then it is appropriate to put things on hold until we do what we'll discuss next. And that is, analyze what is positive. And I think what I hear as an underlying principle to the whole thing is essentially a deal that is--to the public--that we will not use gene therapy at the moment now, at least within our ability, to inadvertently transfer anything into the germline, regardless of our decision process about how significant it is, how likely it is, that it seems to be sort of a deal we're making to go forward, that we're not going to do this at this point.

I think, is everyone comfortable with that as sort of a consensus?

DR. GORDON: I just want to say one other thing as a way of arguing with Dr. Anderson there. It's not that I disagree with a single fact he says, but I can just not view the scenario of a semen sample being positive, and then somebody saying, "Well, go ahead. Go ahead and do what you want", and then have to face the consequences of that later, however remote those consequences might be. I mean, it just wouldn't make any sense to the consumer advocate if that approach were taken.

DR. ANDERSON: I agree. I agree, Jon.

CHAIRMAN SALOMON: I think that's fair. And the other thing that I would say to French would be, in his experience with current retroviral vectors, we also can make these kind of calculations that you might need 6 million children. I wasn't present for those kind of calculations, but that even exceeds the wildest dream of any group I know of for having children.

But essentially, we also have admitted already, several times in the discussion, that we don't--that this is all such a changing target, that we're all working toward these hybrid vectors, et cetera. So I think that if we're advising on general principles for FDA regulation, I think we should be very cautious, rather than say, "Well, you know, I know what it's like for retrovirus."

Okay. So then--

DR. CHAMPLIN: I wonder if the test should be different. If semen is--if you're going to give systemic treatment, the semen is likely to be involved passively in that process, and some more direct sperm test should be selected.

CHAIRMAN SALOMON: Let's go there. That's exactly where we should go now. So what--do we agree that we should be monitoring semen? And I'd like to point out that if we do, then one of the questions I want to ask everyone is:

then, to me, if you want to be intellectually consistent, that means that none of these trials should be done in women.

[Laughter.]

DR. MILLER: A surrogate marker. I mean, it says surrogate marker. I mean, you use what you can have. I mean, I don't think you--

CHAIRMAN SALOMON: Well, wait a minute. Now I'm having a problem, because, I mean--this is one of my notes here--but if you tell me that we have--we just went through this whole thing. I don't want to repeat myself. This principle is we're not going to, you know, as a deal with the public, allow inadvertent transmission to the germline, but you tell me--and we're going to monitor the males in the trial, but you can't monitor the females. And so, why shouldn't we say that females then shouldn't be allowed into these kind of trials until a point at which you can confirm through enough data that it isn't being transmitted into the germline? I mean, I'm just trying to be--

DR. ANDERSON: Okay. There is a scientific answer to that, and that is, a number of mitotic events occurring in the female is so much less the number of mitotic events occurring in the male, that the risk factor is whatever it is, 7 orders of magnitude or 8 orders of magnitude or something.

DR. GORDON: I'd like to speak to the female a bit. First of all, I was quite taken aback, and I must say, a little bit put off by the notion that women of reproductive age would be denied gene therapy because of--they have to wait till they were in menopause or something like that. The ovary is quite a bit different than the testes. The primordial oocyte in a primordial--the primary oocyte in the primordial follicle is the most accessible of all of those cells, but even that cell is very difficult to access. It's surrounded totally by theca cells which are very tightly opposed. The minute the oocyte starts to develop, the zona pellucida develops. It's almost impossible to get compounds across the zona pellucida. The egg does not divide. One of them is ovulated every month, and that is out of 400,000 that sit in the ovary.

Now, that doesn't mean that there's no risk, and I think that if the FDA told a woman to not conceive during the period of gene therapy, that might be a good idea, but I think if they told her to not conceive ever again in her life because a primordial oocyte, infected when she was 20, might be ovulated when she was 40, would be unfair to women.

I do think though that in conjunction with this inability to be formal about the woman, as we can with the man, that we need provocative animal-testing systems for these vectors to know what their real potential is for

getting them into the egg.

And I'd like to take just one more minute to describe examples of that that we're doing in our lab. For example, we have adenoviruses that express Lac-Z [ph]. Sometimes people have found animal ovaries to be positive during somatic gene therapy. We have said to ourselves, "If that's a rare event that we could get it into an egg, let's make it less rare." So we put 10 billion adenoviruses into a mouse ovary, injected it directly in, looked for Lac-Z. Couldn't even get the virus into the ovarian follicle. The follicles are in fact surrounded by blue stain from Lac-Z. You can actually see where the eggs are because they're not stained. We then took 1,500 eggs out of mice, removed the zona, so in the rare circumstance of a naked egg, exposed them to 10^8 adenoviruses for an hour, fertilized them, saw no evidence of entry.

Now, these are studies which are different from "Let's make a sheep, and then if it has a few lambs, check them." Now, these are looking at a few cells out of hundreds of thousands, but if you are looking at the very same cells that are exposed to the vector to see whether or not they've taken it up, it's far more sensitive. And I think one of the things we could recommend to the FDA is they look aggressively towards designing test paradigms for each new vector that comes along that will really look at

this, but I know I'm opposed to barring women who are dreadfully ill from undergoing gene therapy or from conceiving for the rest of their lives because they underwent it.

DR. MILLER: Underscoring the need for long-term follow-up.

CHAIRMAN SALOMON: Okay. Well, that was great. I mean, that is a very good scientific answer to my query about whether it was intellectually consistent to a lot of the women in the trial, so the question--

DR. SIEGEL: Now the question should be whether we should allow men.

[Laughter.]

CHAIRMAN SALOMON: So the recommendation here would be that in any trial, as it's moved forward with new vectors, new class of vectors, hybrid vectors, that there should be definitely some sort of germline transmission experimental work, and that should be part of the submission for the trial. I think that's a very clear kind of recommendation.

DR. GORDON: Can I just add one other detail here, which hasn't made it to the RAC yet or to the FDA's--this venue yet. And that is women who undergo assisted reproduction. The number of women who undergo assisted reproduction, in vitro fertilization, is rising every year.

There were 40,000 cycles of IVF done in the US and Canada last year about. An increasing number of these involved violating the integrity of the zona pellucida, which is a major barrier exogenous vector access. Sperm injection now takes place in a very large percentage of women. When embryos are biopsied for pre-implantation diagnosis, the zona is opened. Women over the age of 38, every women over the age of 38 in my in vitro program, has the zona opened because it helps the embryo hatch to implant, and it gives a very slight percentage of increase of pregnancy rates.

These women who undergo assisted reproduction are at exceptional risk for exogenous DNA integration; embryos are very permissive for being infected, they like to integrate things, as Rudy Inish [ph] will tell you about retroviruses, and I think that this is a category where I think the FDA should advise a sponsor to tell a women not to undertake assisted reproductive technologies during the time of gene therapy. This risk would pass quickly, but it is a significant risk if it is undertaken during the time of gene therapy.

CHAIRMAN SALOMON: Would you think that then if the husband or the significant other, I should say, was a male--was the male, and was undergoing the gene therapy, that artificial insemination shouldn't be done during the period of gene therapy?

DR. GORDON: Well, not only artificial insemination, but now that we're thinking about this, if a man was contributing sperm to an assisted reproduction procedure, which artificial insemination would not qualify because the zona's intact there. But suppose a man was giving his sperm for sperm injection or so-called ICZ [ph], what's already been demonstrated in mice, you have about a 30 percent gene transfer rate if you mix sperm heads with DNA and inject them. And that's a very reliable investigator. So, I think that men who would contribute to an assisted reproduction procedure should be advised not to do that during a time of gene therapy.

CHAIRMAN SALOMON: So the next question I have down as a note is, we need to talk about how you should tell--how you should separate--how you should analyze a positive semen sample now.

But one question I wanted to ask sort of as lead-in to that, is if you have a replication competent virus in the semen, and even if it's not in the sperm, and you have sexual relations, does that mean that you can't transmit it in the uterus to the developing eggs? In other words, is proving that it's not in the sperm, yet it is in the semen, an argument that, you know, you should not put the trial on hold and it should go on?

DR. GORDON: My answer to that would be it would

be okay for the trial to go on, because there's no evidence that DNA-carrying or nucleic-containing agents in raw semen, can make their way into the oocyte during the process of normal fertilization and early development. It's actually rather an interesting point because the embryo has to get out of the zona to implant, where you'd think it would be susceptible, but the fact is that vertical transmission in viremic people is not a documented phenomenon to my knowledge.

CHAIRMAN SALOMON: Okay. So if we have a positive semen sample, I think the next issue--question two is: what should be done to analyze a positive semen sample?

DR. GORDON: Again, I would propose that the clinical study be put on hold for one cycle of spermatogenesis, which is several weeks time--I don't know the exact numbers of days in humans; I work more with mice--during which time fractionation could be done. Discontinuous percol gradients are very good at enriching for pure sperm, and I think if a repeat study is done with a discontinuous percol gradient--don't forget, you can always get another sample the next day; depending on the age of the man, you might have to wait a few days. I mean, I don't know, but whatever--

[Laughter.]

DR. GORDON: You get another sample, and you know,

you can PCR a fractionated sample in discontinuous percol gradients or swim-ups. Both work well, though the discontinuous percol gradient works better. It's not difficult to do, by the way. And if that were negative, I would say take the study off hold and let them go forward.

CHAIRMAN SALOMON: So let's say you were--just to play--I think--let me stop here. There's two ways we could go here. We could spend a little more time talking about, you know, should you do in situ hybridization, should you do flow cytometry, should you do discontinuous percol gradient? I'm not really certain that's very fruitful, but I don't mind going that direction.

The other direction would be, you know, the way I would see another question here would be, if you were doing a trial, and you had one semen sample was positive, and then one sperm rotation later which--did you say it was 90 days was the period of time in the human, Dr. Hurst?

DR. HURST: Well, that will be completely through the washout period, yes.

CHAIRMAN SALOMON: Yes. So, let's say in a 90-day period of time you would now be negative. One question I would have is, how many times do you allow that to go through before you put the trial on hold for multiple--for a longer period of time? So in other words, so you find out whether it's 1 patient in 10 or 5 patients in 10?

DR. CHAMPLIN: What if it's 1 patient in 100, and you have one positive; would you put the entire study on hold or just that one patient?

CHAIRMAN SALOMON: No, I guess I was just--no, I'm not trying to make it more complicated. I'm actually trying to say that if--you know, one thing I have sympathy for is if a semen sample comes up positive, you put the trial on hold until it turns out to be negative. That's okay, because if it never turns out to be negative, then we have to think about what we do next, right? If it turns out to be negative, the only question I was now asking would be, okay, fine. Obviously, we'd agree to allow the trial to go on, but how many times would that happen in a trial before you'd have to say the trial really needs to be reevaluated? In other words, after ten patients came up positive and 90 days later were negative, does that mean the FDA should look at that again, or do you just repeat that for a hundred times, which of course, would drive the sponsor crazy and likely the FDA crazy.

DR. CHAMPLIN: But if the definitive test is the sperm analysis, and you can do that the next day after your positive test, you should probably just go to that definitive test before doing anything.

DR. SIEGEL: I guess the question is--is the question you're asking, well, what if it's in the sperm but

transient? Does that mean you just should stop the research, or does that mean you just should make sure people are aware and take extra care?

CHAIRMAN SALOMON: Well, I was just--I mean, at some point it's easy to say if one's positive, you stop and you get it in 90 days. I was suggesting that the next thing that could happen, it seems to me, is that if every other patient this was happening to, and then I was just saying do you want to--I mean, shouldn't we maybe then--

DR. SIEGEL: Right. But Richard's pointing out that, I guess, that you could--it could be in the sperm, and I think in the paradigm you said that was suggested, we might then--the sponsor might then do discontinuous percol, and if they had another positive specimen and it was clear that all the positivity was not in the sperm, was in other cells in the semen, they might move ahead. So in which case you don't have to wait 90 days. You just know you've got something in the leukocytes. But what if it--I was wondering if your question was, so what if they--if whether if they do that and it is in the sperm, is transient expression in the sperm acceptable? Or are you simply saying, what if they can't find that out?

CHAIRMAN SALOMON: I guess I was just thinking of--here's a scenario. These guys are doing this trial. A patient comes along on Tuesday positive in the semen. Put

the trial on hold. We already said we agreed with that. And now the trial is on hold. 90 days go by or 30 days go by, and it's now demonstrated that the semen is negative, and further testing shows that the sperm were never positive. It was a leukocyte in the semen. Now it's Thursday. Another patient comes up semen positive. I mean, how many times are you going to put the trial on hold until you finally say that, hey, we know what's happening here, so stop putting the trial on hold for a positive semen sample.

DR. SAUSVILLE: I mean, at one level--I mean, this is similar to the familiar grading sort of system for adverse events. I mean, clearly, if you document with reliability that it's the white cells that are the problem, and we've agreed that it's--that's something we basically live with, I think probably stopping it a few times to establish that is reasonable, but once you've reached the ends that statisticians are familiar, telling us that that's what it is, I have no problem going forward.

Now, on the other hand, if you do document that it's actually in the sperm, okay, unexpectedly, I guess, then I mean, that's sort of the way we've defined the terms of this discussion. That's sort of a like a grade 3 societal adverse event, and if you do it with any degree of frequency, that's--then the trial has failed, and that's a problem.

CHAIRMAN SALOMON: So let's take now two possibilities, just for point of discussion. So the first possibility is that how many times can the semen be positive and we demonstrate that it's in the semen but not in the sperm, before we tell--before we relax and say it's not an issue that we have to worry about for the rest of the trial?

And then the second issue is, how many times--if the sperm is positive, is that the end of the trial?

DR. NOGUCHI: Well, we need to add some practicality, reality in here. The occurrence of this event is rare to the point that you may only have one semen sample, that the next time you sample the same patient it's negative, but you don't have enough to do any fractionation. You only have enough to do a PCR reaction or maybe a repeat PCR reaction, because they're doing 10 to 20 samples at a time, replicates.

So you may be in a situation where let's say out of a dozen people, three of them come down with one positive event at some point during the course. You may never be able to answer the second question, that is, is it in the semen or the sperm?

DR. GORDON: I would propose that if a semen sample is positive, there's no number of times that would make me relax, but on the other--that should be taken in the context of what Phil said. You're not going to--with the

current generation of vectors and administration procedures, you're not going to come up with a very high number of positive people. But let me also say, to get another sample and fractionate it, we're talking about 72 hours. I mean, it's not difficult to do a procedure with fractionation.

DR. NOGUCHI: That's correct, but it may not have a positive signal.

DR. GORDON: I would say that if it didn't have a positive signal on repeat with fractionation, that you take the study off hold.

CHAIRMAN SALOMON: I guess what Phil's saying is, if I understand right, is that these are relatively low frequency events, and so that if you wanted to be--am I following you--so if you wanted to be really careful, to wait 72 hours or whatever, and get another semen sample and it's negative, isn't necessarily when you should take the sample on hold. You maybe need multiple negatives before you could convince yourself that it would be negative.

Then that's in addition to what I was saying, is how many patients can have semen samples that are positive before you relax? And I guess then part of it is how many semen samples should be positive that you prove are not in sperm before you relax and say it will never be in sperm and stop putting the trial on hold.

DR. SAUSVILLE: But doesn't this equally address

how confident you are that you're positive? I mean, you know, we're giving lots of weight to one test that may be by PCR, and depending on who's doing the assay, and what travel to the lab, the--you know, this gets sort of very complicated from a statistical point of view, right?

DR. NOGUCHI: I was not trying to put words in anybody's mouth, but merely to point out it is a rare event. The sample is limited. We may not be able to, on any given sample, do both PCR and do any fractionation or in situ. So part of the question is: when have we discharged to the best of our ability at the current level of technology, our best attempts at ascertaining what does this mean?

DR. SIEGEL: I guess there's--in response to your question, there's no number of events of it occurring where it's somewhere other than in the sperm that's going to tell you that, that there's no possibility that it's in the sperm. But what might happen, I suppose, if you were to study a population where leukocytosis in the semen is high, perhaps because of the nature of the population or the disease, and with a vector where there's a high level of transduction of leukocytes, then you might have a trial where you're going to anticipate a more than rare event, and when you start seeing it, you might ask, is it pragmatic to put the trial on hold in an event that you expect to occur in half the patients and not to be a risk, but simply the

transduced leukocytes occurring in the semen like as expected. And I'm not sure we're facing that situation yet, is what Phil's saying, but we probably can use some common sense when we do.

CHAIRMAN SALOMON: I mean, another way to deal with it would be not to test semen, but rather to test sperm. So, I mean would it be--does anyone want to comment on that? I mean, if it's not that difficult to separate the sperm for these kinds of trials--I mean we're talking about 100 patients at a time--would it be reasonable then to separate the sperm, do the PCR on the sperm. If the PCR in the sperm was positive, then you put the trial on hold and you investigate it further. If you don't, then at least you stop putting the trial on hold every five minutes for negative sperm, positive semen samples.

DR. GORDON: My own view of that right now is that the frequency at which it's being discovered is low enough, so they're--probably looking at semen alone is more cost effective than going forward with fractionation. And down the road, it may appear to be needed, that you need to do fractionation from the get-go.

I do think one other idea should be introduced here though as proliferation of vectors, et cetera, goes on and different types of patients are treated, if you think the risk is much significantly higher, we can also tell men

to freeze sperm before they undergo gene therapy. This doesn't mean they won't have unscheduled sex with the sperm that are inside their bodies, but if they really want to conceive during the time of gene therapy safely, it's quite simple to freeze sperm and use them in artificial insemination.

CHAIRMAN SALOMON: Though of course if it--that's fine, right. But I think then I would be--you could modify what I said just modestly, and then say that you start off a trial by screening semen. When you get a positive semen sample, now you realize that you have an issue. From there on, you just recommend to go to sperm separation, that would be fine. And I'm trying to do that by way of helping the sponsors and the FDA, because I can just see them, you know, going back and forth every five minutes and some trial canceling their study, because I think there are a lot of leukocytes in semen.

DR. CHAMPLIN: What if you have a true positive?

CHAIRMAN SALOMON: A true positive sperm?

DR. CHAMPLIN: Yes.

CHAIRMAN SALOMON: Okay. Well, that was the second thing we said we would talk about.

DR. CHAMPLIN: What's the frequency of that that would be tolerable?

CHAIRMAN SALOMON: That's a really good question

as we sort of wrap up here. So let's say now we've dealt with the negatives. Though we realize that there's a gray here about how to do it, but I think the next question is, if you get a positive in the sperm in one patient in the trial--I mean, that's the start--what happens next? I mean, what do you guys think?

DR. SAUSVILLE: Revise the informed consent and do another one. And then if you do two and you get it two times, then that's a problem.

CHAIRMAN SALOMON: I'm okay with that.

DR. GORDON: I think the other males who have received the vector just need to be advised a positive sample was found, and it's under further study, and I think sperm fractionation should then proceed in a held trial.

CHAIRMAN SALOMON: So there's nothing you can do about--

DR. GORDON: That's what I just said, yeah.

CHAIRMAN SALOMON: So the question would be modify the informed consent, and you go on with the trial. So now after X number of samples are positive, what is it that we're finally saying here? I mean, maybe we can't say. Maybe we shouldn't be saying it. And maybe if it turns out that a particular protocol was making sperm positive again and again, maybe that's not for this advisory committee to deal with. That could be a societal or a philosophical

issue, what you want to do next.

DR. SAUSVILLE: It's societal, and it would also have to be couched in what you're trying to fix of cure and how much it's working, et cetera, et cetera, et cetera.

DR. CHAMPLIN: Again, we deal with teratogenic drugs routinely all the time with the provision that you don't have children while you're taking thalidomide.

DR. SAUSVILLE: That's why for the oncologists in the crowd, this discussion is sort of interesting.

DR. GORDON: Well, I think a proper thing to advise the FDA in the area of what about the future, is again, that they need to look at preemptively provocative testing systems that will give them some idea what risks they're really facing. We don't really have great animal test systems out there yet, and I think we should recommend to them that they try to develop them or RFAs try to develop them.

CHAIRMAN SALOMON: Well, I certainly think that, you know, I agree with what Ed and Dick just said. It certainly was the direction I was thinking as well, and that is, if sperm continues to be positive, then it's simply a matter of deciding for the specific patient group what the relative risks versus the benefits of the gene therapy are at that point and making a decision intelligently on that basis.

DR. WEISS: Also, that if it's positive in a large number of patients, you'd still want to know the duration of positivity and how would that then--I mean, if it's only through one cycle of spermatogenesis, then it still might--that needs to be factored in, obviously, to anybody's decision.

CHAIRMAN SALOMON: Yes. I think that that's a good point. So if the situation was that on day minus 8 or day plus 8, you've got an infusion of a replication competent vector or something, and then there was a transient 90-day period where you might have positive sperm. But after that, there was no further positive sperm and there was no further injection of the vector, one could relax and go forward with it, and the idea then would be the informed consent should be amended to say that, you know, during that whatever--you know, reasonable period of time, 180 days, around the time of the injection at day 8, that's when you don't have--we don't advise having unprotected sexual intercourse. Is that reasonable? I think that's--

DR. SIEGEL: I would just add to this discussion that, you know, in the hypothetical--one of the hypotheticals that was discussed--and I'm not sure how much discussion of various unlikely hypotheticals are necessary, but in the hypothetical that there was repeated positivity that was--could be localized to the sperm cell itself, I

suspect that we would make a determination that that's something that merited public discussion, notwithstanding the issues that we know there are teratogenic mutations in sperm that occur all the time. If a particular vector and approach were found to do that, I think that would be information we would want to have out in the public domain. We'd probably analyze it and discuss it. So I don't think we need to decide so much in advance what to do. We'd probably be at the RAC or here or somewhere, saying, "Well, here are the data. What should we do?" Rather than the--

CHAIRMAN SALOMON: No, I agree. And that's what I was saying, at a certain point here it's not really the purview or the point of this advisory committee that there--if there are societal issues, then those should be dealt with in whichever way that society feels comfortable working them out.

Though it does get interesting. It goes back to what French put on the table right at the beginning, and that is, even if you had a positivity of sperm, you know, he correctly pointed out that at least for the current generation of vectors that we have experience for, albeit we don't know what's going to change in the future, but for that current generation, we don't even know what the--you know, the risks may be much less than natural retroposition mutations are, and so that the significance of it is very

clear.

DR. SIEGEL: Right. No, and I wasn't suggesting that would be a cause for panic, just a suggestion that this is--the nature of this issue is such that we would want to make sure that there were public discussion of what's happening.

CHAIRMAN SALOMON: I think we've answered the questions. So, 5 minutes early. So anyway, I'd like to bring the session to a close. And thank, first of all, all the FDA staff, particularly Gail Dapolito and Rosanna, and Bill Fries and the others.

[Applause.]

CHAIRMAN SALOMON: And also all the speakers, and all the members of the committee and the audience. Thank you very much.

[Whereupon, at 1:25 p.m., the meeting was adjourned.]

CERTIFICATE

I, **THOMAS C. BITSKO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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