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P A R T I C I P A N T S

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Donald Gay
Deborah Hurst, M.D.
John Levy
Louis Zumstein, Ph.D.
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Amy Patterson, M.D., NIH Participant

FDA Participants:

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Philip D. Noguchi, M.D.
Steven Bauer, Ph.D.
Carolyn Wilson, Ph.D.
Jay P. Siegel, M.D.
Karen D. Weiss, M.D.
Philippe Bishop, M.D.
Anne Pilaro, Ph.D.
Estella Z. Jones, D.V.M.
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C O N T E N T S

P R O C E E D I N G S

CHAIRMAN SALOMON: Karen, is Jay here? We can't start if Jay's not sitting down, by the usual rules of order. If Phil is sitting down, we can do it. Phil's surrogate for Jay. Phil, I said the usual rules of order is I have to get Jay to sit down before we can start the meeting. No, I'm teasing.

Okay. Well, welcome to the second day of the BRMAC Advisory Committee. I think today is very interesting since some of these issues now of long-term follow-up that we're going to deal with I think have potentially very important implications for the design of trials and their conduct, and I think it's a potentially extremely interesting set of issues to deal with.

I have two things I want to do this morning. The first is our consumer representative, Abbey Meyers, who also has an organization called the National Organization for Rare Disorders, Inc., she was unable to attend the meeting today because of a previous commitment. But she feels very, very strongly about the issues of long-term follow-up, which is Session III's main topic.

So as there were no official public speakers that stepped forward, the first of two things I'd like to do is read just sort of an excerpt or two from the letter she sent as a way of showing respect for Abbey's position and at

least allowing her in some way to have contributed to the meeting today.

The second thing I'd like to do while I'm reading that is if there's anyone in the public who would like to step up and address the committee this morning before we get started, please, if you would come up and identify yourself when I'm done with the letter, you're more than welcome to contribute now before we get started. And as I said yesterday, let me reiterate you're more than welcome to participate at any stage along the way. Just come to the microphone, identify yourself, and help out.

So to do the first of the two things, in sum, Abbey writes: I want to explain that my involvement in the emergence of gene therapy has spanned more than a decade.

And she then goes on to point out that she's served on the NIH Human Gene Therapy Subcommittee from 1989 to 1992, and then the NIH Recombinant DNA Advisory Committee from '93 to '96 as a consumer representative. She has advocated from the beginning, her point is, that there should require--and she underlines the word "require"--long-term follow-up of research subjects. Unfortunately, neither the government nor sponsors have done this, so we still have many unanswered scientific questions.

NIH is not a regulatory agency and, therefore, could not and did not enforce the monitoring of patients.

NIH gene therapy rules in the points to consider required long-term follow-up. But investigators didn't submit data, and the NIH did nothing about it.

Therefore, my first recommendation is that the FDA and NIH formulate a joint task force to develop uniform rules and regulations that both agencies will abide by and monitor and enforce, and they should share data with each other and with the scientific community so that precious resources will not be wasted.

One of the greatest flaws of the current system is that once sponsor information reached the FDA, it automatically becomes a trade secret and cannot be shared with other scientists who need this information to formulate their own scientific decisions. In fact, in the case of the tragic OTC experiment in Philadelphia, the protocol was changed after it left the RAC and the RAC was never told. That at least is her writing.

I believe that gene therapy technology will not mature towards commercialization unless there's a determination to share information quickly, completely, et cetera.

Secondly, she's absolutely convinced that long-term follow-up of research subjects is critically important, that testing for gonadal dissemination, annual physical evaluations, and particularly autopsies are essential if

we're to avert possible future public health calamities. And she says this is why the patient community lobbied for gene therapy database which was supposed to track gene therapy research subjects throughout their lives.

Of course, she points out then in the following paragraphs that these were not instituted. There is no gene therapy database at the current time.

Finally, she's convinced that the most important element of long-term follow-up is the gene therapy database which Congress directed FDA to develop several years ago. It's my understanding that the FDA ceded responsibility for the database to the NIH and the Office of Biotechnology. She feels that one of the things that we ought to come up with today is some sort of recommendation that this whole issue be revisited in a practical way to see whether or not a database can't be instituted and brought forward efficiently.

I think I've given a general sense of where Abbey was coming from, and I'm going to stop reading from her letter.

But, again, you know, I promised her that I would represent her general sense that her feeling as consumer representative is that there is an assumption with the American public that, in going forward with these new technologies, we are saying, okay, fine, the public's giving

us some flexibility to go forward, but the quid pro quo, if you will, is that we are responsible about the potential long-term risks of this that might in the end affect the public, and that in the absence of really demonstrating honestly an acceptance of that responsibility, I think Abbey--and I'm raising the point now for the whole committee to consider this morning, you know, at what point are we actually not doing the right thing by the public. If we're really, you know, saying give us a break here, we're going forward with this new technology, but we really aren't doing the job that we've committed to following what the impact is on the public and on the long-term health of the patients. So I think that covers that.

The second thing, is there any public discussion? Is there anyone from the public who wanted to join in the discussion at the beginning that was not allowed to yesterday? No. Okay.

Yes, I'm sorry Please, Amy?

DR. PATTERSON: Yes, I thought it was important to respond to some of Ms. Meyers' very important concerns.

First of all, I think I'd like to note for the record that NIH feels that long-term follow-up is extremely important. We also feel, however, that it's important that long-term follow-up be done in a manner that generates data that is both scientifically and medically useful and valid.

And we also feel that long-term follow-up does impose a burden on patients to bring them back at regular intervals. And so the design of these studies, both from a patient's perspective, a caregiver's perspective, and the field's perspective, needs to be given a lot of thought. And we are planning a policy conference on this in the upcoming year about how to best design these studies.

At the upcoming safety conference on cardiovascular gene transfer research in December, on December 14th, we'll begin to explore long-term follow-up for both cardiovascular safety sequelae as well as non-cardiovascular safety sequelae in that particular context.

I'd also like to mention that we are also going forward with a database and we'll have a Web presence on--December 20th is the target date this year. This is purely a pilot. It's a beta type but we invite public comment on it.

We are going also toward working with FDA in these months to develop a more fully fleshed out Web presence with the database next year that will use the controlled medical vocabulary and allow comparisons across trials of clinical outcomes and adverse events.

I just wanted to go on the record that we endorse Ms. Meyers' concerns. We also recognize, however, that long-term follow-up can't be done randomly. It needs to be

done thoughtfully to generate useful data, and we also recognize that there may be some regulatory constraints for how long one can compel long-term follow-up and what is the authority at the hands of the Federal Government to compel long-term follow-up. These are very practical and real issues.

Thank you.

CHAIRMAN SALOMON: Yes, thank you, Amy. It's obvious that some of those issues we're going to kick around the table in a few minutes, but that was great.

French?

DR. ANDERSON: Yes, I just wanted to make a comment after Amy's. I guess it was Fred Lederle (ph) and I who were the first to push for a database back about 1990, I guess, and, in fact, I maintained a database in human gene therapy for a number of years, and then it got to be too big for one person to handle.

And one can be critical, as Abbey quite correctly is, about the fact it still doesn't exist. But let me say on behalf of both NIH RAC and the FDA that there has been a real effort to do this and to do it properly, both on the part of Amy Patterson at the RAC and Phil Noguchi at the FDA.

It hasn't been forgotten, but there are real logistic problems. There are real budget problems. Within

the constraints, I think they have done as superb a job as possible, and as sort of the originator of this idea, I appreciate the fact you two are still slugging away at this.

CHAIRMAN SALOMON: I guess if--I'm trying to think what Abbey would say right now.

DR. ANDERSON: She'd say, Why isn't it here?

CHAIRMAN SALOMON: I think what Abbey would--Abbey would start with that. Thank you. That was good. And I think what everyone should understand is that, you know, Abbey has served for many years as a conscience to all the medical and other expertise on this panel, and, therefore, I hope that no one's misinterpreting the seriousness with which I'm trying to represent Abbey's viewpoint here, because it's not just a personal thing of Abbey, who I have a lot of respect and personal care for, but it really is her role on this committee. And I feel like it's just not here today, and this is probably the one thing that she would really be the person to be passionate about.

So I think one of the things she would say is that it's not--it's rather--we talked about what was great about government working yesterday. This is actually what's bad about government working yesterday, where there are, you know, public concerns, congressional mandates, no funding, frustrated federal workers at the FDA and the NIH who--let's face it, you know, it's not rocket science to make a

database and, to be honest, there's really very little else to say about that.

Okay. So I'd like to introduce--is there further discussion? Please.

DR. GORDON: I just wanted to make a comment. I think, first of all, I understand her position as saying that she wants a database from the point of view of the well-being of those who participate in the study. But there are other good reasons as well for a usable database, not the least of which is identifying promising trends in the area of gene therapy. That's a scientific reason as well as a patient protection reason.

I disagree, respectfully, that it is not a rocket scientist's job, unless the rocket scientists have an easy job, because this is, in my view, a very challenging job to develop a database that can be accessed easily, where correlative data can be obtained with facility. And I've pushed as a member of the RAC, which I'm not here as at the moment, for very great care to be taken as this database is designed in terms of those issues.

There's another point and, that is, of course, I've never seen a research study involving human subjects where the human subject was not told you may withdraw from the study at any time. If a person is undergoing long-term follow-up, having received gene transfer at the age of

eight, they may choose at the time they get married at the age of 38, or whatever, to withdraw from the study. There's not much one can do about that. It would not surprise me if a significant number of people did that. And so there are these human issues, and I must say I have a lot of sympathy for those feelings, not that I necessarily would do the same myself, but I can certainly understand them.

CHAIRMAN SALOMON: I appreciate the comment. Part of what we'll do is return to all of this and those kind of discussions I think should probably be better saved for a few minutes. But I think the comments stand well, and there are a lot of different things that we need to talk about. For example, it will be a good debate about what's so hard about making a database.

DR. SIEGEL: It's easy to make a database. It's just extremely difficult to make a useful database.

[Laughter.]

CHAIRMAN SALOMON: Amy?

DR. PATTERSON: You have the Chairman's prerogative to tell me if this point needs to wait until later, but I just wanted to also note that in designing a database, as we are doing, it's important to keep in mind who the users are. And in the context of a gene transfer database, the users are quite a heterogeneous group. They're patients, patients' families, groups like Abbey's

National Organization for Rare Diseases. There's certainly the media and the press. But there are also investigators, there are federal advisory committees, there are colleagues at FDA, and there are NIH investigators and the RAC.

And all of those groups have very different informational needs, and one of the things that we're going to be doing over the next several months is setting up user groups with representatives from those various communities to tell us what is it--when you sit in front of your computer, what is the type of query you would like to be able to do with this data. That's an important issue to keep in mind. Unlike many databases, this is a database with a very heterogeneous user group.

The second and last point that I'll raise, it's also very important to consider whether the data that is put up is validated or not. And I think that NIH is very sensitive about putting up data from investigators and how does one express amply the caveat if this has not been peer-reviewed data and outcomes.

These are very sensitive and important issues.

CHAIRMAN SALOMON: Well, as I've pushed the Chairman's prerogative this morning quite beyond the usual pale, I'm not going to interrupt anyone else who wants to comment now. But I think we will get back to some of these things.

Okay. Well, it's my pleasure to ask Carolyn Wilson to give us an FDA introduction to vector classes with potential long-term risks. Carolyn?

DR. WILSON: As has already been introduced quite well, there is concern in the community that at least certain types, if not many types, of clinical trials in the gene transfer field carry with them the potential for long-term risks to patients participating in those trials.

What I'd like to do this morning is outline in part some of the scientific rationale for why we believe that there are long-term risks in gene transfer clinical trials. I'd like to distinguish a little bit between patient follow-up in that some of these long-term risks may require long-term patient follow-up; others may be able to be determined through short-term patient follow-up, and I'll explain that a little bit more later.

I'll be discussing what properties of gene transfer vectors are most likely to carry long-term risks and determine which of those vectors and methods that are currently in use share these properties.

I've focused on three main areas that are likely to cause concern about long-term risks, and the first is integration into host genomic DNA and somatic cells. I'll be discussing that in more detail in the next few minutes. Then I'll do in the second half of my talk integration into

host genomic DNA in germ cells, and actually, Dr. Philippe Bishop of our Division of Clinical Trial Design and Analysis will be discussing in a talk to follow mine the third risk, which is if a gene transfer vector is contaminated with a replication-competent virus that is capable also of integrating, that this would add an additional long-term risk.

When we talk about integration into host genomic DNA and somatic cells, the biological effects that could result from that are a spectrum. The hoped-for effect, of course, is expression of the transgene product with no other genetic alterations. And this in and of itself hopefully would not have a long-term effect, but as we heard about, for example, yesterday in hemophilia, you could develop antibodies and have, you know, with other diseases, autoimmune responses and so on. So even that in and of itself isn't trivial.

In addition, upon integration, depending upon the site and how it's done, a gene transfer vector may cause chromosomal rearrangement, such as translocations. If it carries strong viral promoters or enhancer elements, there's the possibility to activate gene expression at quite distal sites, up to 100 kilobases. And, again, depending on the site of integration, you could also disrupt the transcriptional or translational control agents of cellular

genes. And so these last three, in particular, the outcome could be just regulated gene expression.

Now, this in and of itself may have no clinical consequence, and as I'm sure many of you know, we have a diploid genome, there are two copies. So, in particular, if you're silencing a gene, hopefully the other allele could kick in and compensate for that.

Alternatively, you could also have a phenotypic effect in the individual cell that has the dysregulated gene expression without necessarily having a pathogenic effect on the organism.

However, in the case where you're activating a gene that may be controlled in regulation of cell cycle, this is an area that would cause--has the potential to cause tumor formation. And to try to give you some sense of what is the likelihood of that event, it's now considered that there are approximately 80,000 genes in the human genome. Of those, at least as of last week, on the Cancer Genome Anatomy Project website, approximately 130 loci have been identified as oncogenes or proto-oncogenes, those genes that would cause dysregulation of cell cycle.

But even should a gene transfer vector integrate into one of these types of loci, the risk of tumor formation still is not absolute in that tumorigenesis is still going to be a multi-step process with insertional mutagenesis only

being the first. And we can make that statement based on data that has come out of really two to three decades' worth of study on murine retroviruses, a particular type of murine retrovirus that is actually very closely related to those retroviruses that are used in clinical trials today, where it's known from those studies that in mice tumorigenesis is associated with high levels of virus replication, and that even past the provirus insertion event, additional steps, such as recombination with endogenous retroviral sequences in the genome, are also involved, and that because of these two points, tumor formation really only occurs after relatively long latencies. So we feel that this data allows us to suggest that in gene transfer vector integration that the risk of tumorigenesis is most likely low and that the effect wouldn't manifest itself until sometime after the treatment period.

This is the same graph that was shown yesterday by Dr. Bauer, just a breakdown of what gene transfer INDs we currently have, again, most of them being retrovirus, adenovirus, and plasmid, but we also have poxvirus, adeno-associated virus, and herpes.

One point I want to make on this slide is you can see there's a breakdown also of ex vivo versus in vivo, and I think it's important to realize this risk of somatic cell integration and potential long-term risks of tumorigenesis

would be the same, regardless of whether it's ex vivo or in vivo.

In terms of the potential for integration, retroviral vectors, of course, have high rates of integration. This is one of the reasons that they're so attractive for gene transfer clinical trials, is that they do allow for long-term expression because they do integrate into the genome.

With the other vector classes, it's not so clear-cut. Adeno-associated virus vector, while the wild-type virus from which that vector is derived certainly is known to integrate and, in fact, does so in a very site-specific fashion on chromosome 19, the properties of the vectors seem to be a little different in that it may depend upon the tissue type that you inject it in and so on. It doesn't seem to reliably integrate the way the parent virus does.

Plasmid DNA, at least in vitro, is known to integrate at much lower rates, certainly, than something like a retroviral vector, and also from in vitro data, we know that you can manipulate the method of introduction. For example, a report using an inhibitor of topoisomerase has shown that you can get about a 30-fold increase in integration frequency.

Adenovirus vector is traditionally considered a non-integrating vector, but, again, in vitro it's been

measured that these vectors can integrate themselves about 1 in 1,000, 1 in 100,000 is the rate, so it's very low. A recent report in Nature Biotechnology demonstrated that genetic modification, introduction of actually retroviral sequences, increased this integration, so that now 10 to 15 percent of the cells exposed to that vector had integrated sequences.

Herpes and poxvirus vectors don't carry--or at least data to date doesn't suggest that these integrate. But they may have other long-term effects, for example, concerns about latency with herpesvirus could not--may not manifest itself for decades.

So based on data that we have about the vector classes that are currently in use and thinking forward about modifications that are certainly going to happen in the future, we can recognize that there's a range of integration frequencies and that depending on what modifications or methods of introduction are used, even for one particular vector class, integration frequency may vary.

And so that really sets up the questions that we're asking the committee to focus on today, which are we don't really want to have an answer of, well, can you tell us what class a vector needs long-term follow-up; but, rather, we'd like to think about what properties of vectors need long-term follow-up. What would be the characteristics

of the particular gene transfer method and what are, for example, some minimum frequency of integration events that would give you greater concern?

Now I'd like to spend the last few minutes on the other long-term risk, which is integration into host genomic DNA and germ cells, and this is the one where I wanted to distinguish between where the effect of germ line integration would certainly be long term, the patient follow-up to assess the risk of this event could be achieved in the short term.

The risk of integration in terms of biological effects, again, would be a spectrum, depending on where a gene transfer vector were to integrate. Again, the hope would be that there would be no biological effect, but you could have genetic disorders, birth defects, lethality to a developing fetus depending on the site of integration. And, of course, there's the larger societal issues where it's been deemed unacceptable to do deliberate germ line alterations with unknown public acceptance of inadvertent germ line alterations.

Now, again, trying to make this a little bit of a data-driven discussion, we can go back to studies with murine retroviruses in model organisms like zebrafish and mice where these have actually been used as insertional mutagens to study key genes in the developmental program.

And what we've learned from those studies is that in order to see a phenotypic effect from provirus insertion, you really needed to breed these animals to homozygosity. So, again, our diploid genome can protect us from provirus insertion.

However, on the other hand, studies from H. Kazazian on line elements, which are transposable elements in the human genome, have identified that certain retro-transpositions or novel insertions into the human genome can result in human disease. But even this information should be taken in the background rate of retrotransposition, which is about 1 in every 50 to 100 germ cells. So, clearly, our genome can tolerate a fair amount of novel insertions, but, again, depending on the site of integration, disease may result.

When we talk about the potential for integration into germ cell DNA, now we need to think about not only the characteristics of the particular vector system that's being used, but also equally important is the route of administration. In this case, unlike somatic cells, ex vivo gene transfer would carry little to no risk. Localized injections, such as intra-tumoral, sub-cu, IM, again would likely carry low risk of germ cell integration. However, if you're doing localized injections into the gonadal regions or system injections, the risk may be higher. And we feel

these last two are more than just theoretical postulates because there have been two recent reports in the literature from preclinical studies suggesting that these types of routes of administration could cause germ line alteration.

The report by Sato et al. demonstrated that liposome-encapsulated plasmid DNA, when injected directly into the testes of mice, these animals were then bred within a two- to five-day period, and their progeny were shown to carry the transgene.

The second report where a retroviral vector was used to inject into rats by the intra-cardiac route, they were able to demonstrate that the hypertensive phenotype in these rats could be corrected not only in the recipient animals but in their progeny as well. So there are at least some data suggesting that germ line alteration can result from these types of injections.

Then, to summarize, the factors that influence long-term risks in our opinion would be, foremost, the ability of a gene transfer vector to integrate, and really as correlates of that are the dose of the gene transfer vector or presence of replicating integrating virus, as these would increase the likelihood of integration into a potentially oncogenic locus. The route of administration is going to be key for germ cell integration and really interplayed in all of these are other issues such as immune

status of the recipient.

The long-term adverse events data that's available that predict could occur in these patients are things like malignancies in the case of somatic cell integration, in the case of germ cell integration, genetic disorders, birth defects, embryonic lethalities.

And so really the broad question before the committee today is to ask whether we can achieve through long-term follow-up of patients whether or not--really, as Dr. Patterson was saying, whether we can use this to provide scientific data to assess the long-term risks of gene transfer research, and if so, how can this best be achieved.

I'd like to now turn the podium over to Dr. Philippe Bishop. We're going to take questions after both of our talks. He'll be discussing our experience and guidance on this issue in the case of retroviral vectors.

DR. BISHOP: Good morning. On March 6th of this year, we issued from the FDA a letter to sponsors of gene therapy trials asking them to describe for us their clinical monitoring programs. We wanted to know what it is that they had established for their protocols and the INDs.

In reviewing the responses, it became apparent that some of the sponsors had difficulty following the published recommendations, and we were especially interested in the feasibility and practical issues that pertained to

lifelong monitoring. Later in the latter portion of my talk, I will discuss some of those comments, and I hope that you will find what we have learned to be useful in your discussion later this morning. But before doing so, I would like to revisit the event that led the FDA to initially ask for lifelong monitoring, and then also review the current guidance documents.

Rooted in the initial request for lifelong monitoring was an event that occurred in 1992, a report by Donahue that described three of ten monkeys that had developed rapidly progressive T-cell lymphomas following autologous bone marrow transplantation using progenitor cells that were transduced ex vivo. These cells were exposed to replication-competent retroviruses. The monkeys were severely immunosuppressed following total body irradiation.

The pathologic analysis of these lymphoma cells was significant and demonstrated that numerous copies of replication-competent retroviruses were present. A direct correlation to the lymphoma cannot be overlooked, and at that time we had limited clinical experience with retroviral vectors, and a letter to sponsors was issued in 1993. For the first time, clinical monitoring programs were required for all clinical trials using retroviral vectors.

A key principle rooted in the--and prevailing over

time relates to a major clinical concern, and that is that clinical exposure to integrating vectors may pose risks to subjects that may not become apparent until years later. De novo cancers can occur following the activation or suppression of cellular genes. Autoimmune diseases may result from unwanted immune responses, and hematologic and neurologic disorders could occur subsequent to unanticipated replication events.

These long-term risks to patients serve as a basis for the current requirement in the newly updated guidance document. This document was originally posted in draft form in November 1999 and was just recently finalized and posted on our website in October of this year. It is available at the website that I have listed below there.

So what is in the current guidance document? What is it that the FDA is currently seeking?

Well, there are two assay that are mentioned for monitoring patients for evidence of replication-competent retroviruses. The first is an antibody assay. The second, which is more commonly used, I think, by sponsors, is a PCR assay looking for RCR-specific sequences in peripheral blood mononuclear cells. Sponsors only need to perform one of these assays, not both.

We recognize at the FDA that there are limitations to these assays, and as an alternative, if a sponsor feels

that a different testing method is more appropriate for their study, this should be actually discussed with the FDA, and we would be willing to consider alternative methods to implement for the monitoring of replication-competent retroviral vectors in patients.

There are five time points that are suggested for RCR testing: pre-treatment, at three months, at six months, one year after treatment, and yearly thereafter.

However, testing is no longer required beyond the first year if all samples are negative for RCR at three months, six months, and 12 months. In these cases, yearly blood samples should still be gathered, but archival would be sufficient.

If there are clinical concerns or if there are at any point positive results for RCR, additional testing and more extensive patient follow-up may be required. In these cases CBER should be contacted.

Upon completion of the intensive monitoring period, which is usually up to a year following the initiation of treatment, yearly clinical follow-up is required. A clinical history that includes questioning for the interval appearance of symptoms or diagnosis of de novo cancers, neurologic and hematologic disorders should be obtained. Any suspected clinical outcomes that could remotely be associated to the integrating--or to an

integrating or replicating event should trigger a phone call to CBER, and it is likely that this will result in additional testing or archived samples, in addition to obtaining new samples.

If a study participant develops a new cancer, it is recommended that a biopsy be performed and that the tumor be tested for RCR. When a study participant expires, an autopsy and tissue sampling for RCR testing is recommended.

Positive results that are neither positive--I mean, positive results, either positive laboratory or clinical findings, should be reported to us in an expedited fashion. All other outcomes should be reported in an annual report. These reports should be as complete as possible and should include a summary of all the laboratory results, including the negative findings, clinical updates, and autopsy findings.

If the goal of lifelong monitoring is for us to be able to acquire actual data to assess the true risk to study participants, then I think it is very important that we get good information with these annual reports.

Now, as I mentioned at the beginning of this presentation, when we began reviewing responses to the March 6th letter, it became apparent that many of our sponsors had difficulty following the lifelong monitoring guidelines. Consequently, we contacted sponsors and we asked them to

comment on their experience implementing the lifelong monitoring protocols that they had established for their INDs. Sixty-six percent of our sponsors that are currently involved in retroviral vector studies were contacted. This represented the majority of INDs and approximately three-quarters of all clinical trials under evaluation.

We confirmed that 89 percent of INDs, of all the retroviral vector INDs had an established lifelong monitoring of protocol for their studies. Almost all of the sponsors, however, noted difficulty meeting all of the requirements in the guidance document.

In an open-ended fashion, sponsors were asked to identify the barriers that were most problematic in conducting and evaluating patients for long-term follow-up. What I would like to do now is to review and to present a brief summary of this survey, and I would like to bring to this committee the concerns that were most frequently, at times universally articulated by the sponsors.

First, issues pertaining to cost. This was a nearly universal concern by sponsor investigators at academic institutions and also of commercial sponsors with limited resources. This was especially true for sponsors of trials in which the participants' life expectancy was measured in years, sometimes in decades, rather than months. Some sponsors volunteered their cost estimates for ongoing

trials, and these estimates range from $1,500 to $5,000 per patient per year.

Included in these estimates were costs relating to the yearly clinic visits, including the physician's billing, laboratory testing, sample collection, shipping, preparation, and testing for RCR in the first year, simple archival and storage, the equipment supplies and maintenance, the personnel required for data management, the clinical quality assurance, and adverse event reporting. It also included provisions for periodic auditing and monitoring costs.

Some of the sponsor investigators at academic centers were very concerned with the lack of resources, citing that most grants will only fund a study for up to five years and that alternative sources for lifelong monitoring are rarely identified a priori. In addition, many of our sponsors noted that third-party reimbursement is usually sub-optimal. It is unlikely to get an insurance company to pay for RCR testing for these patients.

Another almost universal barrier to lifelong monitoring is that yearly clinical follow-up is not always feasible for all patients. Some patients may move or may be lost to follow-up. There may be geographic barriers with some patients having to travel across the country to return to the research centers. Others may be from other

continents, such as Europe, Africa, and South America.

The patients or the referring physicians may lose interest in the clinical trial. This was commonly observed by sponsors of clinical trials that involve children. Now, these kids usually grow up to adulthood and typically would prefer not to come back to the research center. Their priorities just have changed.

Another issue that was raised by some of our sponsors and by sponsor investigators is the inability to consistently obtain adequately reports either from a referring physician to a principal investigator or a principal investigator to a sponsor.

Another almost universal concern relates to the unusual level of commitment that lifelong monitoring requires. Many ask: Who is responsible for monitoring if a sponsor--or if a principal investigator moves to another institution? What happens if that principal investigator leaves academia to the private sector or goes to industry? What happens if a business goes bankrupt and no one assumes responsibility for the long-term monitoring?

Commercial sponsors and academic institutions are reluctant to devote indefinite resources. In one estimate, in a large trial that was going to involve participants whose live expectancy is measured in decades, budgeting for lifelong monitoring requirements required a half a million

dollars per year per 100 patients.

I think it is fair to say that for most studies autopsies are just not being obtained, even if our sponsors are well intended and motivated. Most patients die away from the research centers at home or under the care of a hospice service or under the care of a treating physician. When the patient dies or is near death, it is unusual that the sponsor will be notified in time, and usually an opportunity to request an autopsy has been lost.

The hospice nurses or the local physicians are unlikely to ask the next of kin for autopsies, and if they do ask, families can decline that request, even in instances in which the participant had previously consented to an autopsy in a living directive.

When autopsies are obtained, unless this occurred at the research center, it is unlikely that the tissue sampling for RCR testing will be performed. If it is performed at those remote sites, it is unlikely that the specimen collection will be adequate or optimal for RCR testing.

Another commonly raised concern by the sponsors is that the assays that are used for RCR testing lack standardization. Some sponsors had asked for a central laboratory and archival center, essentially the equivalent of a core facility for which autopsies--for which the

samples are to be sent and tested and archived.

Sponsors are concerned about the sensitivity and the validity of these assays. Are these assays providing reliable information that pertains to the integration or replication events? Are the negative results reliable? How is this information going to be used to guide us in the future?

Some of the sponsors questioned the utility of RCR testing and the lifelong monitoring in studies in which retroviral vectors were used to transduce cells ex vivo, for example, the cellular vaccine administered intradermally after the cell had been irradiated. Some investigators view these studies as different from in vivo gene therapy studies and may not feel as committed to the lifelong requirements that are in the guidance document, and they may not work as hard at getting that information for us.

Since the March 6th letter, the FDA has received several requests to inactivate or withdraw retroviral gene transfer INDs, representing approximately about 15 percent of these INDs. In instances in which surviving patients were documented, the sponsors were asked--and I have to say have agreed--to continue following these patients annually. The FDA will continue to accept expedited and annual reports for all inactivated or withdrawn retroviral INDs until we have been informed that there are no surviving participants

remaining.

Now, to ensure monitoring will go on, the agency has limited enforcement options, and if it is the goal of lifelong monitoring to obtain quality information pertaining to the risks associated with the use of integrating and potentially replicating gene transfer vectors, it is unlikely that any of our enforcement options will get us better data. It is unlikely that our enforcement options will solve the problems that are associated with long-term monitoring of patients.

So, in summary, I have reviewed the current guidance documents and presented an overview of common barriers that are associated with lifelong monitoring of patients as articulated by the sponsors of retroviral gene vector studies. Significant issues that were raised pertain to the logistics of long-term follow-up, the costs, and sponsors' commitment to doing lifelong monitoring of patients. If it is our goal to obtain quality information that pertains to lifetime risk to participants, our strategy for monitoring must take into consideration the limitations that were presented here. Finally, it is unlikely that the problems associated with lifelong monitoring could be solved by the FDA's enforcement options.

Before I entertain questions, I want to thank everyone at the FDA who helped me with this survey, and I

also wanted to thank all of the sponsors who have actually volunteered this information.

Thank you.

[Applause.]

CHAIRMAN SALOMON: I'd like to thank both the speakers this morning for a really excellent and pragmatic review of the situation. And I think it clearly is a task for the committee to deal with, to maybe outline a series of reasonable principles upon which to do long-term follow-up that's more pragmatic than the current guidelines for all the reasons that were just outlined, which is going to be an interesting process.

Ed?

DR. SAUSVILLE: But a pragmatic question is: Where's the money going to come from for that? I mean, because we can make recommendations, but should it be required of sponsors to fund this ultimately? Should it be required of funding agencies?

CHAIRMAN SALOMON: I guess I have mixed feelings about whether that's something we ought to be discussing, or, you know, maybe I'll look to Jay and Phil and Amy to comment on it. Do you think that we should be discussing where the funding options should be, or should we not get caught up in that right now and stick with the main topic?

DR. SIEGEL: I'm not a--we don't fund clinical

trials, and perhaps Amy can comment more cogently. I would say this, though: If we're recommending that the protocol call for something, then it's somewhat duplicitous to have the protocol call for something to commit--in a protocol to commit to follow that protocol and to have that protocol call for something that costs millions of dollars that you don't have. So, I mean, it's hard to avoid that question. Should people be submitting protocols committing to do something that they can't afford to do? I just don't know.

DR. SAUSVILLE: Yes, but to follow on what we heard from Dr. Anderson yesterday--and perhaps you could go where I think you would go with this--if you're worried about sequencing a few kilobases of DNA in terms of what physician investigators would react to this requirement, I think that pales by comparison to the potential implications of a sweeping generalization in this mode.

DR. SIEGEL: Oh, absolutely. And that's why it's on the agenda. I mean, the current status, as you've heard, is that we've asked for this commitment. There is potentially some perception in the public domain, until an hour ago, that maybe even this data were in some sense being reliably collected.

So I think we move to move forward from here with an honest--either saying we don't need the data, we need the data but we're not going to get it, or come up with a

solution to ensure that we get.

DR. SAUSVILLE: But the biology is obvious. I mean, from any of these vectors we clearly need it if this is going to be widespread. I mean, you know, everything ranging from the particular patient to the larger societal concerns of people who might be treated at an early point in life, as you pointed out or someone pointed out, with a vector and then these people have long-term reproductive potential. So, I mean, it would seem to me that from a biological standpoint the answer is pretty clear.

But, you know, there's a discordance between biology and practicality that is really, you know, coming up now.

CHAIRMAN SALOMON: Well, I mean, a couple other people want to make comments, but so far what I'm thinking as a strategy here is I think that we should start by going through sort of what we consider based on solid biology, science, and some consideration of what is reasonably practical, what should be a monitoring scheme, and then come back to this sort of funding issue. Because the real problem I have with the funding issue is that my NIH grant is for five years and then I'm done. So if that's really true, then there's no long-term monitoring or I can't do any gene therapy trials, period, end of story.

So, I mean, can't--if we make it that simple, we

might as well all go home. The sponsors then can worry about it, you know, because they're the only ones who've got any kind of money that goes longer than five years.

DR. SIEGEL: Let me respond to that to say I think that's correct, because I think that both the practicality and the costs associated with long-term follow-up depend greatly on what is long-term follow-up. If you want to simply determine if somebody's alive or not, you know, you can do that through serial postcards, phone calls, and maybe get a pretty high reliability. If you want them to answer a question or two, you know, you're going to get less data and more expense. If they need to come in to draw specimens or to do physical examinations and have that reported into a center, that's going to require a lot more resources and have a lot more missing data.

Whatever we do, I think if we focus it on what's most important, we're more likely to see it done better. So I think you're right in suggesting first we need to figure out what it is we want and then how to get it.

CHAIRMAN SALOMON: I know French had a comment and Dick Champlin wanted to, and then Dr. O'Fallon and Amy.

DR. ANDERSON: The first time FDA brought this up was about four years ago, and I was sitting about where Xandra is and, Jay, you were sitting about where Phil is, and I violently disagreed for lifelong follow-up--not long-

term follow-up. I agree with long-term follow-up. Lifelong follow-up for many of these reasons. And at the end of that session, it was sort of left vague as to whether it would be lifelong or not.

Afterwards, I contacted a number of people who run programs and their bosses, the deans, vice presidents of medical affairs and so on, and I posed them the question: If the FDA requires lifelong follow-up, what would your reaction be? And I basically had to first ask the question, well, what's the value of lifelong follow-up? And in trying to answer that in terms of this sort of, well, what if this happened, what if that happened, the usual response I got was: Well, if people start having cancer based on their gene therapy, then everybody would look for it, so why do you have to spend a lot of money to do a really long, detailed follow-up for something that might never happen. But when we got past that, they said, well, what if it's required, the response was we will not commit to that. If we have to commit to a lifelong follow-up, we will not allow gene therapy trials at this institution. That's what I got across the board from a number of major institutions.

Therefore--I mean, this is deja-vu. We're now bringing up the issue again, and I don't have to say what I said yesterday because people know what I would say, and that is, you have to balance, and to budget a half million

dollars a year to follow up patients for life on the grounds that you might find something, it doesn't make sense.

CHAIRMAN SALOMON: I think what we have to be careful now is that we don't take--I mean, I appreciate your comments, but what we've done now is gone to the end of the discussion and we haven't had the beginning of it. I mean, I think what we owe the FDA--and really, if we are taking this one, we owe the field--is an intelligent discussion of what follow-up should be and why you should do follow-up. And the politics of that follow-up and the funding of that follow-up and sponsors versus academic institutions, albeit all extremely important issues, shouldn't be the first thing we talk about, I think.

You know, you could take a different view, but that's the view I'd like to take in the committee.

DR. PATTERSON: I'd like to say something, not about cost, actually, but I think an even more fundamental question or equally fundamental, what the biology is, what is the regulatory authority that FDA has to compel follow-up. We can talk about a grant being over, but it's also important to consider if an IND is withdrawn by a sponsor. What is--I think the committee, before we go down talking about the biology and giving recommendations, I think you need to understand what the FDA can and cannot do in this arena. So that's the comment that I--I think if FDA--

CHAIRMAN SALOMON: I guess that's what I don't want to do right now. In other words--

[Laughter.]

CHAIRMAN SALOMON: Now, you can override me, Jay and Phil. But, I mean, we have a choice here that I think has a lot to do with what we do this morning.

If you want to talk about--before you decide what follow-up should be, you want to jump ahead--this is the way I'm putting it: that we're jumping ahead to talking about what the FDA can then insist based on no recommendations yet on what it is they're supposed to be insisting on or regulating, then I think that's premature. But if you guys disagree, then override me and we'll put this--

DR. SIEGEL: Yeah, I'll override you. I think you can't--thank you for empowering me to do that. I would simply say it's hard to tease apart the two issues, that you can't discuss--what we don't want is a discussion of what should be done in the ideal. That's what we've had in the past. And then to go on doing what we're doing, which is fooling somebody, ourselves, industry, the public, into thinking that we're getting what we all said we should get knowing that we can't get it. So that said, it's hard to tease them apart. I think when you discuss what we should get, you need to discuss it pragmatically both because of costs but also because I think it's very much a fact that

the more things we try to get, the less good a job we'll be able to do at getting any of them. I think that's a practical issue in terms of how you follow up patients.

I think it would be worthwhile to give a little bit of clarification on that issue. Our lawyers believe that a withdrawn IND, if the protocol calls for continued patient follow-up, the sponsor and investigator retain all their obligations for that follow-up and for reporting of adverse events. To date, when we've received requests to withdraw, in that case we've asked just to avoid any confusion that instead they be inactivated, which means they can't enroll, but with clarification that they would still follow up. And every sponsor has agreed to do that. If they were to insist on withdrawing, it would not make too much difference from a legal point of view, but I think Philippe made a point at the end, which is that they're still required to do so but it's very hard to tell how much commitment and effort is going on. You know, if we don't see data, we don't know what to make of that. There's not a lot we can do. We put trials on clinical hold, but if they're finished, that's not going to matter.

We can send an inspectional team out and try to determine whether they're making good enough efforts to follow up patients, and if they're not making good enough efforts to follow up patients, you know, we could--there's

not a heck of a lot we could do. We could try to disqualify that investigator from doing FDA-sponsored clinical trials. Then we'd get into an argument as to whether, in fact, their failure to follow up was because of lack of diligence or because, in fact, as we all know, it's very hard to follow up. And I'm not sure--you know, none of those avenues look particularly promising as a way of making it happen. But, yes, you are--you do need to continue to do that.

CHAIRMAN SALOMON: I promised Dr. Champlin and then I know Dr. O'Fallon would like to talk.

DR. CHAMPLIN: In other fields, of course, we try to do long-term follow-up for late events in hematopoietic transplants. We've been trying to do this for many years. And my observation is that as time passes, it becomes exponentially more difficult to get the patients back and to get good follow-up information. And so as a practical matter, beyond five years, it's really--it's just a major problem getting even compliant patients to return, and all the problems that were raised--investigators leaving, companies closing down, et cetera--come into play.

The other issue is that, particularly in blood tests, it's hard to envision that something that you haven't seen in the first few years is going to pop up 20 years later. So even though there is a risk of cancer perhaps 25 years down the road, as it is with radiation exposure--you

see solid tumors peaking at 25 years after exposure--so you do need long-term follow-up, at least in terms of the history of those events. I'm not sure getting blood samples for that long is going to help you. And so one might have a strategy of sort of intense initial follow-up with sampling of blood and tissue samples as appropriate and then some longer-term postcards and/or registry function that might contact people for the core information about birth defects, unusual diseases and/or malignancies. And you're going to be looking for increases above the expected levels, of course, and so you're going to see birth defects and you're going to see cancer in patients as they live long enough, and the important thing is it's not going to be above what you'd expect in the background.

The other issue is that you may not need to follow every patient. If you would construct a study, you know, to look at a sample of patients for a given outcome over a period of time, you might avoid the need of 100 percent sampling of every patient for the duration of their life.

DR. O'FALLON: I might be expected to know more about this process than most of the others in the room, but I certainly don't know anything about it in the context of this particular category of patients. Jay just said it perfectly. The more you ask to collect, the more you try to collect on these patients, the less likely your study will

be successful and the whole thing will die because of the weight of the process.

Earlier, you used the term this isn't rocket science. They're making it into rocket science because they're trying to shoot a rocket at a very precise target. And if you have to do that, you have to treat it as rocket science. If, on the other hand, you're perfectly willing to lob a rock in the general direction of the moon and are happy if it encounters some of the moon's gravitational pull, you might be able to pull that off.

We have a horrible history in this country of doing things to patients and having no knowledge of what it is that's going on because we're not even keeping track of where the patients are because we don't even have a way of finding out who has had these materials inserted or this whatever we're talking about. And the legal profession is stepping in and taking all sorts of actions and making all sorts of determinations that somebody is or isn't responsible for all of this. And, of course, it's never possible for us to do a study to find out what's going on because we can't even identify the people who have had these insertions, or whatever.

I have been involved heavily in the breast implant controversy, and we could not find women who had had their breasts implanted because nobody was following them up,

nobody was keeping a record.

If we didn't do anything other than try to keep an annual postcard follow-up on where these people were so that when people began to observe adverse events we can mount a scientific study, that I think is possible. But if we insist that every protocol carry with it the extra burden that we've just been talking about of samples and follow-up and whether the samples are archived for 20 years or 30 years or studied immediately, that will ultimately spell the death of any program that you try to put in place for all the reasons that we've just heard, because of the financial aspects, the financial weight.

But I think we owe it to the patients and we owe it to ourselves and we owe it to society to try to find some way to just keep track of where they are and who they are.

CHAIRMAN SALOMON: Okay. I know Carole wanted to...

DR. MILLER: Again, from the bone marrow transplant standpoint, we know that it is important to follow these patients long term, and we've had major publications in the last couple years out of the International Bone Marrow Transplant--the Autologous Bone Marrow Transplant Registry, on 10- or 20-year follow-up of patients looking at the risk of secondary malignancies, et cetera, which really move--which really help us when we talk

to the patients, you know, who are starting out now. So I think as a scientific community, much less a legalistic community, we should be doing everything we can, I think, to collect as much long-term information on these patients as possible. And it's possible through, you know, the national registries that are scientific in nature to follow up, you know, transplant patients, which are a volunteer organization, but are funded through a group of committed researchers who know that this is a life-threatening complication and there's long term--they've got together 20 years, 25 years ago now for the IBMTR and says we're going to follow these patients long term. I think that that should be--that that type of rigor is really benefiting us, and so from a scientific standpoint, I think that that's what should be strived for.

From a practical standpoint, I'm understanding of the risks and the difficulty, but this is--you know, I think that the minimum amount that we should be able to--that we should do is at least very aggressive follow-up for the first five years. It works very well in bone marrow--I think reasonably well in bone marrow transplant, that you tell the person when they come to begin with that you need to be followed up for five years. All these people getting gene therapy studies have a disease that, you know, unless gene therapy cures it, is going to need follow-up anyway,

just like bone marrow transplant, you know, you need to follow up their leukemia, you need to follow up--I mean, and we have experience with genetic diseases where we transplanted people 20 years ago and we follow them out. This can be done and most bone marrow transplant programs don't have a sponsor, except for the Federal Government and their academic institutions.

So I really strongly think--support that we need to obligate people who are doing very exciting protocols to commit to long-term follow-up.

On the other hand, I agree with Dr. O'Fallon that the easier you make it--and the archiving samples for 20 years is probably not necessary, if you put a finite in, you need to archive samples for five years, because that's the expectation that they're going to come back, and for the next 20 years you follow them up, year after that, and after 20 years, you know, we hope that by that time we'll all know what the answer is and not worry about that, and then you'll commit to lifetime, which scares people, but you commit to 20 years, which is four granting cycles, and we've had our BMT program project for 25 years, it can happen. So that's from the transplant standpoint.

CHAIRMAN SALOMON: I wanted to amplify from the organ transplant standpoint, there's already very well established precedents, and in the U.S., our renal disease

database has tracked patients through HRSA, through dialysis, all the way through to transplantation, and there's follow-up now available that's over 20 years. It's accessible through the Web. It's accessible to the press. It's accessible to investigators. There's United Network of Organ Sharing, which follows all kidney transplant, liver transplant, heart transplant, pancreas transplant patients. There's another--a series--there's North American Pediatric Transplant Registry. There's the ESOT Registry for transplantation, and I can list two or three others, Tarisoki's (ph) Registry, some of which have 20-year follow-up. We all voluntarily--they're Web-based access. I mean, there's a lot of things that can be done. This is plenty of precedents for very functional, long-term databases in other disease states and therapies, and we just, you know, heard about the International Bone Marrow Transplant--

DR. CHAMPLIN: I think the common feature of all this is that you need an infrastructure. You need an organization whose job it is to collect these data, and there needs to be a funding mechanism, and you have to have a nurse, a research nurse or a data manager that calls the people. And it's going to become an increasing burden when you've got thousands of patients that you're following and not just a handful. And so gene therapy programs over time, assuming the growth--expected growth of the field, this is

going to become an enormous burden. So there has to really be an organization whose job it is to do this function, and it's a big cost.

And so it always comes down to, you know, on the grand priority scale, should we be putting millions of dollars into this function or should we be putting millions of dollars into fundamental research in cancer therapy or gene therapy or whatever? And it's a big cost for possibly a small return, but we all agree it's an important question.

DR. SIEGEL: One other point that adds to the complexity here is that for most of those registries that you've mentioned, most of the patients are getting essentially the same treatment by essentially the same route for more or less the same disease, although the etiology--well, you're shaking your head, and I know there are lots of reasons your kidney can fail. But let me assure you that when you start collecting--if you start doing something like that for gene therapy, are you going to start--you know, in determining cancer incidence against background, are you going to, you know, compare a topical therapy, a local injection of an adenovirus with an intracerebral injection of a retrovirus, or that with a three order of magnitude higher dose of a totally different retrovirus that's been engineered to avoid some of the problems of the first one? It's like there's so much variability that it's hard to know

even how or where to group the data when you think about that, which is--

CHAIRMAN SALOMON: The reason--

DR. SIEGEL: --exactly on point for long-term follow-up but is on point as to the ease with which simply creating a registry is a solution.

CHAIRMAN SALOMON: Well, the reason I was shaking my head is that if you go to the website right now at UNOS, you can follow kidney, heart, lung, liver, pancreas, small bowel. In other words, they're all different. They're all--over the last ten years there have been at least ten different immunosuppressive regimens. So, I mean, all I'm saying is that you can collect data. That's all I was shaking my head at. If you want to talk about how to evaluate the significance of data in gene therapy, all your points are well taken. I have no quick answers for any of that.

DR. PAPADOPOULOUS: I just wanted to make the point that, you know, this whole concept of collecting data is really the same--this is the clinical version of the sequencing issue that we had yesterday. In the ideal world, we would want to collect data forever, clinical data forever, and that's just not feasible.

There is also the other issue that there's the public perception of what we're doing and what we need to

do, and perhaps what would be an intermediate step is to demand, request information be collected and samples be collected for a certain period of time, and then make the public comfortable that beyond that period of time, through extensive patient education--and that's not cheap, either--that the patients are fully aware that--and as Carole said, these patients usually have an illness which requires ongoing medical follow-up. It's not as if the majority of these patients are going to be lost from any medical follow-up. But to have patient education of the importance of follow-up and through just yearly postcards and surveys and things like that, that information be collected. The key thing is that there has to be, as Dan mentioned before, an infrastructure, there has to be some organization to receive that information, like the IBMTR, ASBMT, et cetera, et cetera. But perhaps putting some of the burden on the patient that they have to be educated early on in the process, those that are going to be long-term survivors, obviously, may leave an out for the public awareness that we're doing something for the patients who are alive 10, 15, 20 years down the line.

DR. SAUSVILLE: I was going to pursue a point that may be a corollary of an issue that Jay raised and actually does want to point to a potential difference in comparison to what we'll say, the organ registries. I mean, you know,

you don't have pancreas version 1.1, 1.2, pancreas with a different promoter. I mean, you know, there are numerous technological issues that come into differences between different trials, and in a sense, you're making a requirement of sponsors that is going to be perceived as treating them differently, for example, than other drugs. These things are sort of on the interface between an organism or an organ and a drug.

So I think that we should consider, again, with an eye toward promoting the many possibilities of this field, to consider how sponsors would react to requiring them to put in some sort of quasi-public database what ultimately are, shall we say, strategies in formation. And I think that's an additional difference in comparison to the transplant-related issues.

CHAIRMAN SALOMON: Well, I think, you know, I mean, there's an obvious danger here I'm going to try and step aside from, and that is, you know, get into this ridiculous, well, no, but pancreas transplant, you know, you could do with steroids and without steroids and with cyclosporin and with FK506 and with micro-fanolay (ph) mofitil and with rapamycin and in all different combinations--

DR. SAUSVILLE: That actually illustrates the fact because all of those immunosuppressive regimens after the

fact become legally defined treatments that we can all talk about. But in the anterior case, when you're developing the agents, I mean, I'm sure we don't have the detailed, shall we say, dossiers, the registration dossiers, for those agents in anything that approaches the public domain. So there is a difference.

CHAIRMAN SALOMON: So Ed makes a couple of interesting points here that I actually have a note to bring up, and so this is a good time to bring it up. That is, who is the target for a database? And who are we designing a database for? Are we designing it for scientists? Are we designing it for a regulatory agency, specifically the FDA, or for government agencies like the NIH and the CDC, et cetera? Is it for sponsors? Is it for the press? For the public? And for the patients? Who is it for?

DR. SIEGEL: Well, I think Amy spoke very well to the fact that there are many potential consumers of a database, and they're all quite valid. But I would like to focus today's discussion not so much on who to build a database for but on what information FDA should be requesting and requiring, because that's a question that we need an immediate answer to, independently of how the database is structured or whatever. Hopefully there will be a database that will be populated with information, but it's likely to be populated only with that information that

protocols call to be collected and that we--and that is feasible for people to collect in an efficient way. And those decisions are the decisions that we really need to be making now as we're reviewing the protocols. What information will be collected, how, and by whom?

CHAIRMAN SALOMON: Well, you could narrow this conversation to a database for the FDA, which, of course, is a big narrowing of the conversation of this morning--

DR. SIEGEL: Fair enough. Which isn't to say that we're by any means the only or not necessarily even the primary consumer. But it is our current interest, what information we're going to ask for people to collect and ultimately submit to us and presumably--

CHAIRMAN SALOMON: So I guess my response to that, in a question form, is: In one way, of course, it satisfies Ed's issue because if it's to the FDA, it's all confidential and we don't have to worry about all this stuff being in the public domain. I don't know if that's a good answer, but that would certainly satisfy that problem.

But the other question really is: Is that the best advice that this committee can give the field at this point? I mean, I think we've not succeeded because every time we get at these issues, we become divisive. So we're talking about a database that the public wants, but now we're talking about only the database that the FDA wants,

but not the database that the RAC wants or the database that the Congress wants or the database the sponsors want. And then, of course, nobody has any money to do any of it.

DR. SIEGEL: First you have to collect the data or you can build all the databases you want and you won't have data to put into it. It is our hope--it is our intent, as we've publicly stated in the past, in the last year in the FDA, that a significant amount of gene therapy information that's submitted to the FDA will be releasable into the public domain, but the rules--you know, there's a limited amount that one can discuss rules that are under development. Suffice to say we have stated publicly and committed publicly to promulgate rules that would allow substantial additional release of information into the public domain. So it would be our hope that if more information were submitted, whether to the FDA or elsewhere, that could be used to populate a database whether it's at the NIH or elsewhere, or that would be--or directly from the FDA that would be publicly accessible.

But, again, the issue is what information to collect, and I might--you know, as we've moved along and talked about the types of information and the pragmatic implications, I think, you know, the wisdom of your earlier remark is growing in my mind, not surprisingly, and I'm thinking that maybe--

CHAIRMAN SALOMON: I was going to point it out in a second.

DR. SIEGEL: Right. But I didn't want to divorce the science from the pragmatism, and I think we need to address the pragmatism, but we need to address the science, and the first question goes to that, because we're talking about gene therapy as a group, for one thing, and as we all know there's a great deal of diversity in gene therapy, and to date, as highlighted in the talks, our policies have focused on retroviral gene therapy because of--largely because of concerns about insertion, but then, again, there are--there's a variation among retroviruses and how much insertion there is. There are other vectors that insert and there are long-term risks besides insertion, and we would like to focus on where--how to determine when and how much long-term data is necessary.

DR. CHAMPLIN: One other side of that is, you know, who's going to look at the data, how is it going to be presented. It would, of course, in the public interest to know what the cumulative risk of malignancies related to retroviral systemic treatment would be, just as it's been published what the risk of secondary malignancies is after an autologous bone marrow transplant. So you're pooling thousands of cases, you know, from different centers here. One would be potentially looking across many companies for

protocols, but someone would need to access that data, analyze it, and then present it publicly, and with all of the, you know, considerations for proprietary information. But, still, this is what Amy and others are calling for. Somebody wants to look at the public safety of the overall strategy of gene therapy.

CHAIRMAN SALOMON: Dr. Noguchi, and then Dr. Torbett.

DR. NOGUCHI: Yeah, I'd like to try to just address Dr. Sausville's very cogent point, and this is a very unusual field. Actually, in terms of the proprietary nature or what we would term commercial confidential typical FDA submission, that's much less of an issue in this particular field because of the presence of the RAC and the public review process. Whether or not a protocol is discussed publicly, information that is sufficient to really distinguish between promoters and retroviral--within retroviral vectors as an example is available. And I think that we should not try to distinguish this as an FDA requirement or public requirement, but the fact of the matter is that FDA is charged with the regulation of this field, and as such, information is submitted to us. But we certainly do feel that the scientific information has pretty much a public domain aspect to it by its history and the continued public exposure through the RAC.

We too often get into that if it goes to FDA it's all private. That's not totally true, and especially in gene therapy it is not true. Much of it is public. Some of it is not.

DR. CHAMBERLAIN: I guess some of us at this end of the table are a little confused, because when you set up a database, you know what you're going to use that database for, and you have to have inclusion of that, what particular--who you're going to--what audience you're going to address, how that information is going to be assessed. And I guess I haven't heard--at least, I think all of us have an idea of what database internally means, but I think it's clear from each individual here that we all have a different idea what that database should be and who the database is for. And I don't think that's clear to some of us down here at this end of the table.

DR. GORDON: Yeah, I think I'm quite impressed by the differences drawn between procedures such as bone marrow transplantation and organ transplantation as global field and gene therapy. I really think one thing that could help the FDA would be to advise them that a blanket protocol for follow-up is not suitable here, that what we need to do is look at what the protocol is, make some assessment of what kind of information would be important in long-term follow-up, and gear the follow-up protocol to what's actually been

done to the patient.

I mean, on RAC, we've seen normal people get subcutaneous replication-defective adenoviruses to see what kind of antibodies they develop. Well, it's still going to be very difficult to give that person a lifelong follow-up or do Southern blots on all their children if they're not going to cooperate with that. So, you know, in the cases where people are seriously ill, the follow-up won't be as difficult. They're going to have to be followed for their illness. So I think one thing at least we might be able to do is advise FDA that follow-up needs to be tailored and the data collected would then be tailored.

DR. SIEGEL: But wouldn't that lead to only seeking long-term follow-up on people who aren't going to live for a long time?

DR. GORDON: No, no. Not at all. You could easily have a person born with an enzyme deficiency who receives a retrovirus, and they could live a very long time, but that could be tailored as a long-term follow-up protocol.

Now, again, I'm not typically thought of by people other than patients as a patient advocate, but here I have to say that to tell a person--I mean, sure, it's a burden on the sponsors to follow people up. But what about the burden on the patient to be followed up? It's a big burden, and

they may not cooperate. But I think FDA can't control that. They can just say, look, if you're seven years old and you're getting an enzyme deficiency correction by gene therapy, we recommend the following follow-up protocol, and that would be different from a person with a melanoma getting an intratumoral injection.

DR. BREAKEFIELD: Yeah, I mean, I think the more scientific information we can gain and the more hands it is in to be analyzed is going to be beneficial. But I guess the thing I worry about most is just kind of a real epidemiologic disaster. You know, some of these replicating vectors that could have altered tropism and could be shed into the population or trials where, you know, they're putting BEGF in to cause angiogenesis in the heart, but actually it could cause tumor formation even in a relatively--you know, five-year period. I think we have to target our questions as much as we can. What are our concerns, our wildest concerns? And we have to make sure that we get that information. We don't want--you know, these are amplifying drugs, as somebody once phrased it, and we have to at least make sure that we capture anything that is going to be a real public--you know, major public problem, whether it's that you do induce cancer in somebody within five years based on a certain type of therapy or that you generate a novel vector, a novel virus that's going to

cause--whether it causes warts or whatever else it does, people are not going to be happy.

DR. ANDERSON: Well, in the first place, let me say that this discussion is infinitely superior to what we did four years ago, and it's getting me thinking, particularly some things Carole said in terms of we already follow up many of these patients because they have a long-term illness. And so I was just thinking about my own personal compliance if this were a requirement. Some protocols, like our ADA protocol, Ashi DaSilva (ph) doesn't have an illness that I'm not on the phone with either the family or the doctor. It's been ten years. That will go on--well, she'll live longer than I do, but certainly my lifetime. A lot of the protocols that have been associated with it didn't work. I don't know. There's no way we'll get a follow-up on these for 20 years.

So I guess what I'm trying to think of is what is something practical. I mean, that's what we're here for. What's the practical--and so I'm going to make a proposal simply as a start, and it's going to be exactly what Dr. O'Fallon said, because I think that is right on, and that is, clearly for five years, every one of us agree five years is perfectly appropriate, intense follow-up, exactly as the FDA says.

But after that point, there are going to be

specific protocols like replicating adenovirus where one can have a feeling that one would like to know where those patients are. And my feeling is, having listened to everybody, thinking about it, that what is enforceable, what investigators and sponsors will do--and, you know, in the last analysis, if investigators don't think it makes sense, you know, it's going to die. I mean, you can pound and you can shout and so on, and you can say we'll send an inspection team. You don't have the resources to send an inspection team. Even when there are--not big problems, you certainly do when there are big problems, but even when you know there's a little problem.

So I guess if it's five-year follow-up and then there is a clear agreement to maintain contact with the patient, whether it's a yearly postcard--you can give your list to a secretary to simply call once a year to get a follow-up, get a current phone number and who the physician is, and that's doable. But as soon as you talk about bringing the patient back, come back from Cleveland to get a blood study and the patient or the family says, Why are you doing this? Well, because the FDA demands it. That's--

DR. SIEGEL: Are there--you know, Question 1, which asks: FDA currently asks that gene transfer trials using vectors with demonstrated potential for genome integration would include plans for long-term follow-up.

What characteristics of gene transfer methods should trigger the need for long-term follow-up? Well, you've suggested that there might be certain types of vectors where you want more. Are there not somewhere, in addition to knowing where they are, you'd want to seek information about, say, malignancies, congenital anomalies, maybe neurologic, hematologic disorders in the case of retrovirus?

CHAIRMAN SALOMON: Jay, before French answers that specifically, what I wanted to do is do exactly what you started to do.

DR. SIEGEL: I'm sorry.

CHAIRMAN SALOMON: No, no, no. That was perfect. So you just did what I was going to do, is read Question 1, because I think we need to get on with specific questions, because I think that the conversation has devolved back around to it, is let's be practical, but what it is that--you know, what protocols, what principles for long-term follow-up can we come up with that are reasonable now, and then we can vet it against the discussion we already had about practicality. And I'm not giving up so easy on the idea of--I can't advise the committee at this point to restrict it to just what we think the FDA wants. I'd like to just see it in general and then we can maybe ferret out--if there's something unique that the FDA wants that the RAC doesn't want or the public doesn't want.

DR. SIEGEL: I don't think that's a real or a significant distinction in any case. I think we're all interested in learning what we need to learn about the safety and efficacy and long-term effects of this environment. It's hard to imagine--you know, different people have different opinions, but it's hard to imagine information that's of interest to the RAC or the NIH and not the FDA or vice-versa.

CHAIRMAN SALOMON: I'm more comfortable with that then the idea that this is just about the FDA.

So let's pick up these things that we've sort of come to logically, and that is, we've got--like we spoke yesterday, there's a universe of different sorts of vectors, retroviral vectors, adenoviral vectors. Actually, we've discussed these. Let's have some discussion about by vector--I mean, there's a whole bunch of different issues, but let's just say by vector type first. I'm just trying to start somewhere, with the different kinds of follow-up. So integration, does everyone agree that an integrating vector is a dividing line for, you know, a follow-up issue?

DR. BREAKEFIELD: Well, I would say integrating vector and certainly any vector that has potential replication competence needs to be tracked.

CHAIRMAN SALOMON: That's two things: an integrating vector and a replication-competent vector. Does

anyone want to add--is that a dividing line? So if you approach a gene therapy--any gene therapy trial at any point, would a general principle be is it integrating or replicating, and that would be an important thing to consider. I'm not saying there aren't five other things, but does everyone agree those would be two important things?

DR. GORDON: Yeah, I think that overlaid on that is the issue of whether they're put into a cell with the potential of replication. In other words, I would make a distinction between irradiated cells that receive integrating vectors ex vivo and are put back from integrating vectors injected directly into meiotically competent cells in the person. So I think if you generalize to say replicate--vectors with the potential of replication, whether it because they're integrated and the cell's replicating its DNA, or whether they're replication-competent is a class of vectors that requires special attention.

CHAIRMAN SALOMON: Okay. So if a gene therapy protocol would involve a cell that's irradiated, so that there's no reasonable expectation that any of those cells would survive, that wouldn't fall--that wouldn't cross the line, let's say, into this group of--but if it otherwise would be some--there'd be long-term survival or at least a reasonable expectation, we should say, because we don't

really know what the efficacy of a given trial is before it's done, but if there's reasonable expectation if the trial is successful that the cell line carrying an integrated vector will survive, so that now covers an ex vivo treatment and transplantation of some sort or in vivo treatment with the design to get integration. Or if we have replication-competent virus--

DR. SIEGEL: That's an important issue. I think Philippe noted that a number of investigators have proposed that ex vivo transduction not be followed the same way. I just want to make sure we've explored that because you potentially can create 10^{12} insertional events, right, ex vivo in non-replicating cells and put them into the body to exist long term. Are we, in fact, saying that because that's limited, those cells aren't going to reproduce, there's not going to be more virus, and it's not going to get any more exposure than just 10^{12} cells that we don't need the same sort of follow-up?

CHAIRMAN SALOMON: I guess the purpose of trying to articulate these principles is to deal with that; in other words, to--if a principle is fulfilled by ex vivo therapy, then it's fulfilled. And if it's not, then it's not. But the idea is that there are any living cells that are not replicating is just not biologically very valid any longer. I mean, any cell that's living can replicate. We

even know that neuronal cells, which for many years the paradigm was couldn't replicate, we even know they're replicating.

So, you know, certainly any cell that there is a reasonable anticipate is going to survive function in a dynamic tissue environment, to me fulfills the principle of a cell that--you know, of a therapy that should be followed in a different way than, let's say, an irradiated cell or a cell that doesn't survive.

DR. BREAKEFIELD: Even a cell that isn't going to--even if it wasn't going to propagate and is infected with, let's say, a retrovirus vector that was contaminated with RCR, so we have to decide whether our level of contamination could go on to produce those on-site. So--

CHAIRMAN SALOMON: Right. So that would fulfill the principle of replicating vector.

DR. BREAKEFIELD: But I think it's less of a chance than if you flood the body systemically with a retrovirus vector, for sure.

CHAIRMAN SALOMON: I was saying that that's a good example of the principle working. So there the principle was that there was a replicating viral vector that was put in, even if the cell itself was irradiated, we know that an irradiated cell can replicate--you know, can do gene transcription and replicate viral vectors. In fact, we all

know that radiation actually can enhance retroviral gene transcription, for example. So I don't think the irradiation has anything to do with anything if you've got a replicating vector being transplanted.

DR. NOGUCHI: But isn't it also--if you're talking about a replicating cell or living or not living, I think for many of us at FDA when we review something, irradiation is not killing the cell. It's inactivating the component of it, but it's still metabolically active and may be secreting cytokines. So I think we need a little clarification, Jon, really, on what you meant.

CHAIRMAN SALOMON: Well, let's--I mean, the question here is, if you irradiate cell, so Phil is saying if I irradiate a cell and transplant it, would that cross a line into a long-term follow-up by the principle? Now, my argument would be that that cell wouldn't survive, that it would last a couple weeks, at least in vitro, I've never had any irradiated cell survive in any of my cultures for more than a week or two, though some stable epithelial cell lines maybe longer, but, I mean, essentially no. So I think you could still argue that those wouldn't cross the line by the principle to long-term follow-up. But, you know, other comments from others, including Phil? You don't agree?

DR. SIEGEL: So is the issue cell survival or cell replication? Because I'm confused about the scientific

importance of cell replication. If a virus replicates, well, as we saw in Neenhouse's (ph) animals, you have the opportunity for many new insertional events at different loci. What particularly is the relevant risk factor of whether the cell replicates, or is it really whether the cell survives? That's the concern.

CHAIRMAN SALOMON: I wasn't making a distinction. If the cell survives--I was just pointing out to you that any transplanted cell that's not irradiated and survives replicates.

DR. NOGUCHI: I guess we're still a little confused here because what happens in vitro is by no means the same as in vivo. We really don't have a whole lot of information of how long irradiated cells would last implanted in any given site. So what we're looking for is, I guess, a brighter line. Are we talking about cells that we expect to survive beyond a certain time when implanted? That would be very useful to know.

CHAIRMAN SALOMON: Well, that's excellent. So we could say, then, as a--you know, to the list of the principles, if you don't have confidence that an irradiated--that irradiation per se doesn't necessarily guarantee that the cell will only live transiently or survive transiently--and I'm not going to argue with you because I don't have any in vivo data--then the response to you would be that a

protocol involving an irradiated cell with gene therapy, with integration, right, that was transplanted, that either the sponsor or the investigator would have to show very clearly evidence that convinced the FDA review that it wasn't surviving, or that it would cross the line into a category that would require long-term follow-up. Does everyone agree with that? I have no problem with that. Carole?

DR. MILLER: There's two reasons--I mean, there's many different reasons, but, I mean, you can separate cells that are used to be--are gene altered in order to provoke an immune response--we're talking about vaccines--versus alterations that are either ex vivo or in vivo intended to survive and replace something that is missing, correct? Isn't that the two major--if you're doing it simplistic--

CHAIRMAN SALOMON: Well, if you get a vaccine and the--I would just--following the--again, I'm trying to test the principle with these different examples, but if you did a vaccine that irreversibly modified a cell and that cell survived, even if your strategy was rather a short-term interaction with the immune system, if the integrated cell survived and/or propagated, it still would fulfill the principle and require long-term follow-up. Just because you decided that it only had its impact for the first three weeks, if the cell survives and has an integrant, it would

still fall under the principle for long-term follow-up.

DR. ANDERSON: Well, using your principle of hypothesis-driven science here, a non-replicating cell is not going to pick up the additional hits to end up with a cancer--I mean, all we're really concerned here is are you going to get cancer, are you going to get in the germ line, are you going to affect some other gene so that it messes up the immune system or the neurologic system or something else.

So what are the chances? Well, yes, you could argue, well, there might be one chance in 10^8 that a non-replicating cell might turn on a gene that might turn on a fact that might be next to something in the--but, you know, now you're going way out.

If you've got an integrated gene into a blood stem cell, I'd say that this is long term. But just because you're in a cell that survives but seldom divides, you're not going to pick up the multiple hits to really have an effect. So I think we're pushing people--what you--what you're trying to get at, and I agree with, is where's the percentages of seeing a problem, because what this field cannot survive is another unexplained death--much less an explained death, which is something worse. And what we want to avoid is that suddenly there's a rash of hundreds or thousands of patients that develop a lymphoma or leukemia

because of a gene transfer ten years before.

But, of course, if that happens, it won't be stopped or detected because of a database. It'll happen because hematologists look at this and say, great, you know, this person got gene transfer, let's look and see what we find here.

So I guess--I was trying not to say anything, but it sounded like we were starting to push too much and including too many things, and I'd rather stick with Occam's razor and just say what are the most likely things where you need a special long-term follow-up, and a replicating virus or integrated virus in a dividing cell fits that, and I'm not sure if anything else does.

DR. NOGUCHI: Just to argue a little bit on that, French, the fact that if a cell survives that has an integrated virus, that you can guarantee would never replicate is one thing, but this is biology, you can never guarantee that. Certainly there are multiple cases of things coming from a non-dividing cell can cross to another cell, thereby lending it--and I would say that the experience with cold culture as a more sensitive method of detecting replicating-competent retroviruses would just suggest that the chance of something happening with a long-living but not dividing cell with an integrated virus would not be terribly different than with a growing cell. I mean,

you could still get those things.

The question, I guess, we're just trying to articulate is, based on the science that we know right at the moment, is the distinction between dividing cell and non-dividing cell sufficient for us to make that distinction at this point or not. And I think we're getting very good discussion on trying to hone in on that, so I wouldn't--

DR. CHAMPLIN: What do you consider a non-dividing cell?

DR. NOGUCHI: Non-dividing living cell is what we're talking about here, specifically because irradiation may or may not render that cell capable of long-term survival.

DR. CHAMPLIN: If it's irradiated--and so I guess I would just think of three sort of simple categories. You have that example, say the example of a transduced endritic cell or immunotherapy protocol where you've irradiated the cell, it's expected to survive only a short time, and it's a non-replicating integrating virus, you would not expect, logically, at least, in that situation, late events to occur, assuming you don't--you can't demonstrate replication. So that would be perhaps one setting that you wouldn't need long-term follow-up.

On the other hand, if you are having a non-replicating virus in a long-term surviving cell, say, for

example, a lymphocyte, is transduced with PK or another vector, those cells might become lymphomatous presumably over a long period of time and you would need long-term follow-up for such a trial. Or if you transduced liver cells, you know, that could develop hepatoma over a period of time.

And then any time that you had a replicating virus, of course, then you'd need long-term follow-up. So the one situation where I would envision you might not need long-term follow-up is an irradiated short-term cell with a non-replicating virus.

CHAIRMAN SALOMON: Xandra?

DR. BREAKEFIELD: Yeah, I just wanted to add, I think I actually agree with everything that French and Richard have said. I think it depends on how you put the gene in though. You know, if you just use DNA transvection to put a gene in and the cell can't divide, I mean, I don't think there's much of a risk. But, you know, if you put it in with a retrovirus vector, then you do have to worry about the recombinant replication-competent vectors. So in a way, it's how you alter the genome that determines if it succumbs to the potential risk to generate a virus in the future.

CHAIRMAN SALOMON: But can I just make one point as a cell biologist? There is no such thing as a non-replicating living cell.

Okay. Now you're playing rate, but I'm just telling you that it's replicating.

DR. SIEGEL: Next somebody will probably say that there's no such thing as a non-integrating virus, it's just a matter of frequency, right?

CHAIRMAN SALOMON: Now, one thing that--so I think you've got a set of principles out of us that we, you know, touched on a couple examples and they, you know, created a little controversy, but nothing that we couldn't handle. So maybe that's, you know, a step in the right direction.

The question I now have is: Retroviruses definitely integrate. Now, but we can't--that's the easy one. Let's talk about viruses that create these episomal DNA, such as the herpesviruses, EB virus, poxvirus, and then I'd like to go to the really hard one, which is the adenoviruses, which apparently can catamarize and that they can detect DNA later and there's a possibility of recombination in the genome. So let's deal first with, you know, these different forms of episomal DNAs. Are those--they're not integrated, so what do we think of that?

DR. SIEGEL: Let's also put on that list plasmid-vectored gene therapy because we're--it's a significant class that we need--

CHAIRMAN SALOMON: Okay, okay. Fine. Let's start with just the herpesviruses because I brought that up first.

Then we'll do plasmid and then we'll do the adeno, because I find the adeno is not my area of expertise. I'll look to others for that.

DR. BREAKEFIELD: So if we just take EBV and herpes as examples of episomal states, EBV is in a replicating episomal state. It replicates along with the cells. So I would say that although normally it doesn't integrate, its chances of integration are probably higher than certainly something like an adenovirus, I would think, a non-replicating adenovirus. So it's--I think you have to--people haven't actually, you know, quantitated that in great detail. I think you need to know that. But it's there. It's replicating along with--it's associated with the chromosomes. Its chance of integration is relatively high.

With herpesvirus, when it's in the episomal state, it's a very condensed nucleosomal configuration. It doesn't even express genes very well. And so I don't think it's a problem of integration when it's in that state. The problem, of course, with herpes is reactivation. You know, that you can't--is it going to at some point reactivate and especially if it's replication-competent, cause, you know, additional problems. So it has its own problems about integration, but it's a different type.

But the other issue is that, you know, the new

trend in vectors is hybrid vectors. So people take mixed and--many people in gene therapy want to integrate, so they take elements from retroviruses and put them in the context, so they're trying to get integration. So I would say discuss the common viruses now that people use is just very early stages now, we're going to--

CHAIRMAN SALOMON: Just so that we kind of go back into these principles, again, if we put in a replication-competent vector, then that fulfills the principle that we go on and follow it, right? So in the sense that a herpesvirus, let's say, can be reactivated, we should say that that's interpreted as therapy involved being transplantation of a cell with a replication-competent vector, it fulfills the principle and needs long-term follow-up. Right?

DR. BREAKEFIELD: Right, and I would say any genome, even if it's non-replicating herpes, that's in there, that's in there for a long time, and when it--when it reactivates, it doesn't have to make new virus. It could reactivate and then make itself available integration. So there is always a chance that that DNA is staying in the cell long term that's integrated. It's just what is the relative frequency of that and at what point should we be concerned. We need to know the relative frequency, and then we can say this level of frequency we're going to live with,

you know, and what those levels would be, I'm not sure, actually, right offhand, but I would say there's probably some--the relative rates will be so low we won't be concerned about it.

CHAIRMAN SALOMON: Okay. So I would say by the principles of caution, given what we know now, it would be reasonable not to exclude the herpesvirus vectors from any of this, in other words, it's not just retroviral.

Dr. Gordon?

DR. GORDON: I just wanted to say the same, that I think if vectors are replication-competent, even if it's only a potential competence, then I personally have the intuition that the risk of integration is commensurately increased and, therefore, I think that's the major categorical division in my own mind, is if they're replication-competent, a different level of attention needs to be paid to them.

DR. ANDERSON: I think Xandra has made a superb point. I suddenly feel like the old thing about generals are always planning how to win the next war based on the previous war, and it never works that way. And I was thinking about the main things that we're doing, we're developing hybrid vectors, adeno-retroviral, adeno-linthy(?) virus, replicating this, adenovirus with a replicating retrovirus inside of it. And I've been thinking, looking at

the tables in here, as we have adenovirus--that's not where we're going. So we've got to do it based on function and what happens, not is it a herpes or is it an adeno or is it a something, because that's not where we're going.

DR. SIEGEL: You'll note our question, in fact, for that very reason doesn't ask which classes of virus. It says what characteristics of gene transfer methods should trigger.

CHAIRMAN SALOMON: I think that--I'm hoping that's what we're doing here. So how about plasmids?

DR. NOGUCHI: Before we go there, Jon, could I ask a little more detail there? You said replication-competent or potentially replication-competent.

DR. GORDON: Well, if you have a latent virus, it may not be regarded at the moment as being replication-competent, but it could make itself available for integration, which would make it replication-competent, because the cell can replicate. All non-replicating vectors that we know about will have some possibility of replication-competent contaminant. So how does that--does that make any difference to you?

CHAIRMAN SALOMON: Phil, I think the principle here that we're saying is it's not that there might be a small contamination of replication-competent retroviruses. That you have to figure out up front, and if we can't

satisfy--I think if a sponsor or an investigator doesn't satisfy you that they've--that that's enough, then it--you could use the same principle and say I'm not satisfied, there may be contamination by RCR, and that would be--that would fulfill the principle.

I think what we're talking about here is the distinction of latent virus, that a lot of these vector types are latent, and so they may--they're not really correctly replication-competent, so we were amending the principle to say replication-competent virus or latent virus that could become replication-competent given stress or immunosuppression or something else. Is that fair?

DR. GORDON: Yeah. I just wanted also to make a brief comment about the tenor of the discussion. I remember when the guys went to the moon and they came back, and they were sitting there on the runway or whatever, and there was some question as to about when they should be let out because they could have picked up some infectious organism on the moon, for which we have no resistance. So should they still be quarantined today? I mean, I don't know. But I'd say that an appropriately defensive person might have done that, then I think at some point we have to figure out what is our best guess about what is the greatest risk. We can't do everything in every situation.

DR. ANDERSON: But, Jon, you remember what

happened when that happened. Lyndon Johnson just broke the quarantine, walked over and shook their hand in front of television.

DR. GORDON: Well, whatever happened there--

DR. ANDERSON: And nobody died and so they forgot the quarantine.

DR. GORDON: What I'm trying to say--

CHAIRMAN SALOMON: That's great TV, French, but I don't know if that's public health. But my point is--

DR. SAUSVILLE: Actually, I think Lyndon is dead, but--

[Laughter.]

DR. GORDON: Well, what I'm trying to say is I think if you have criteria for a level of contamination, I don't think you should then get paralyzed because you're never going to eliminate all of it. And I--

CHAIRMAN SALOMON: My strategy would be--no, I think that's fine, and my strategy here is enunciate a series of principles that would require some type of long-term follow-up without any implications yet from the committee on what that long-term follow-up is, and then deal with that issue directly. So you're just one step ahead of where I was trying to go.

Carole?

DR. MILLER: Since French got to make a little

statement yesterday and I'm the other retiring person, I just wanted to comment on this. I was a little concerned about what French said about whether the field can withstand another death or unexpected death. And as an oncologist, somebody who in general understands in a bone marrow transplant that unless you--5 to 10 percent of the patients die, you're not giving enough chemotherapy, and attempt to cure a disease which cannot be otherwise cured. So I just wanted to bring it to the public domain that in general gene therapy--in general, the risk has to be worth the benefit. And, therefore, in an attempt to cure diseases which cannot otherwise be cured, we're likely to get deaths. And what the public wants us to do is to make sure that patients are adequately informed of the risks and benefits so they can make an informed decision, and that's our role to advise you how to do that. And, secondly, that rules are made that can be reasonably followed and, therefore, with some expectation in that.

So, I mean, I heartily expect that at some point more people will die related to gene therapy, but I even better expect that there will be more people potentially cured or long-term disease. And so you have to expect some potential deaths. And what I'm hoping, that 20 years down the road that we'll understand what the risk of lymphoma will be after this, expecting that there will be some

lymphomas, and as hard as it is as an oncologist to see a patient die of a secondary lymphoma after treatment of Hodgkin's disease, you have to understand that this patient is alive 20 years later from MOP(?), which at a time 20 years ago was fatal.

So that's less than three minutes, but I just wanted to put that into the demand, and so when we're talking about this, we have to think about what it isn't.

CHAIRMAN SALOMON: Can we go back to plasmids?

DR. ANDERSON: I just want to say, Rick Weiss is sitting in the second row. Did you hear that, Rick? Did you get all that written down, get that in your notes? Thanks a lot.

DR. GORDON: I think plasmids deserve attention as long-term follow-up potential because of their potential for integration.

CHAIRMAN SALOMON: So plasmids can integrate even though they're classically a transient, everybody agree with that? Okay. So, again, as we go vector by vector, it seems that no one's convinced, based on what we know today in the field, which is fine--that's what we're here to tell you--that any of these vector classes are particularly devoid of the potential of integration in some way. Ed?

DR. SAUSVILLE: Yeah, I mean, well, DNA, I mean, it's well-known DNA (?) is a mutagen, basically. And so

with that I think all this has to be on the table.

CHAIRMAN SALOMON: So somewhere here, my sympathy with one of French's earlier comments comes back, and that is, at some point here, though, maybe we're getting a little too gray. In other words, plasmid might integrate and now we're getting into the principle of any time there's DNA in a cell, it might integrate; but we're not now putting--and so that would by our principle trigger a long-term follow-up. I'm wondering at some point whether we ought to put a brake on it. In other words--based on what we know now. Are there--would you accept that there are some things that could be done before a trial got initiated that might satisfy the FDA that you were below the level of concern, you know--

DR. BREAKEFIELD: Yeah, I don't know what that should be set at, but I think if investigators, whatever they use, plasmid or whatever vector, there was some kind of assay they did to look at just integration. You know, it's harder to look sometimes at low levels of replication-competent virus. But--and gave a number of what that relative frequency was in, you know, a couple of standard cell type, and then--like we said, because I agree, I think the chance of plasmid DNA integrating is very low. And, you know--

CHAIRMAN SALOMON: Ed, go ahead. Do you have a

follow-up?

DR. SAUSVILLE: Well, that--I mean, building on that way of starting to think about it, I mean, one thing that's been sort of missing from our conversation this morning is something that has come up in other meetings of this group, and that is the reliance on the preclinical model that you're trying to emulate in the clinical trial to help guide one's sense of risk. And in thinking about the way we've been discussing this, I really think that many gene therapy trials are actually going to come to the fore based on somebody doing something in a model. In fact, we've actually taken the position in other fields of requiring such a thing or strongly advising that such a thing be required.

So I guess--so to frame the question, is there any way that we can delimit the nature of the follow-up based on how things behave in a model and have that make it more tailored, actually, to address the point that was just raised.

CHAIRMAN SALOMON: Okay. So that's a really interesting point. So up until now, we've come up with a set of principles that really are triggered by the nature of what we know about the vector and are independent basically of depending on any preclinical model to modify it. So, in other words, if I had a retroviral vector that integrated

and I had a non-human primate model for it and showed that I didn't get cancer in a three-year follow-up or whatever--I'm just trying to put a concrete example to the discussion--then I could say I don't need long-term follow-up because there's no cancer risk. I don't think that there's any model design that would satisfy that, and that's why I don't think that in developing these sort of principles that the--for long-term follow-up I'm talking about now, not for efficacy.

DR. SAUSVILLE: Right. It wouldn't--

CHAIRMAN SALOMON: If this is reasonable.

DR. SAUSVILLE: It wouldn't satisfy it, but, again, applying the principle of what proportion, again, it can certainly give some pretty good hints, right? I mean--

CHAIRMAN SALOMON: I guess that's what I was getting at, that at a certain point here, if we can argue that it's getting gray enough, like plasmid, then maybe it's reasonable to go and argue--for example, if you're going to do a cell transplant, modification with plasmid, if I take a percentage of the cells that I was going to transplant and demonstrated that there was no integration at the time, you know, would that be useful?

DR. SAUSVILLE: To pursue the point, if we took a cystic fibrosis-related plasmid vector that gets inhaled into a bronchial tree, and then you follow the animals along

and you show that within a certain finite period of time you can detect the DNA in some sort, but they never pass into the genome, they never develop any tumors within the lifetime that you would project the animal, I would feel pretty comfortable with having a relatively low threshold for mandating an onerous follow-up procedure to follow up all of those possibilities with that.

Now, that's very different than the retrovirus situation where, you know, 10^{12} events and to something that's pumped back into the bone marrow and you get lymphoma later or leukemia, that to me is a far more, shall we say, pressing potential risk.

DR. CHAMPLIN: The sample size considerations here come into play. You're talking about, you know, an unacceptable cancer risk, say, of 5 percent, you know, you need a huge n to be able to detect--

DR. SAUSVILLE: But as Carole pointed out, I mean, this gets into what you're trying to fix, and I think that, you know, given the magnitude of a disease that is frequently treated that patients can be given some sort of boundary conditions, and then they can make their choice.

DR. CHAMPLIN: But to even know if cystic fibrosis treatment is going to cause cancer in X percent of people, you need to study it. And, you know, it's important information to have, either positive or negative.

DR. SAUSVILLE: Again, to make the distinction between--yes, I take the point. But a person who--or a patient who receives a gene therapy within the lifetime of the model does not seem to indicate that you'd need to follow for neoplasms. If 25 years from now they then all come down with this, I mean, that would form a very epidemiologically distinctive cohort that you could just say that wasn't well predicted by the model. But you still would have been able to make that inference. The issue is between 0 years--0 and 25, are you going to tell the originating company or sponsor or academic investigator, they're going to have to have in place a plan to collect samples for all that period of time?

DR. CHAMPLIN: I don't think you need samples, but I think you need a postcard: How are you doing? Do you have lung cancer?

CHAIRMAN SALOMON: That's a pleasant conversation with the government. So, I mean, I want everyone to go on, but so one principle I see sort of being articulated here, which I think is very interesting and appropriate to add, is that in a situation in which you have, let's say, a retroviral vector or a latent viral vector, it's really clear that right now that you're going to either get integration or have a latent virus, et cetera, at least within the bounds of the science right now. Then you've

triggered by the principle that you'd have some form of long-term follow-up.

When it gets grayer, like a plasmid, let's say, then it's reasonable to bring in a number of modifying factors into the decision, which we've heard could be excellent animal data, albeit issues that Dr. Champlin raises, that one would have to demonstrate what you'd expect in that population and what you'd predict and whether your animal model modeled that properly, like a 1 percent--0.1 percent or 5 percent; also would be the different patient populations, right? Obviously a dying cancer patient, you know, in extremis might have a different risk profile than a young patient with a genetic defect that you were trying to ameliorate.

DR. ANDERSON: It's the second time that a number got tossed out that's an incorrect number, and I just want to correct it for the record. Twice now a statement has been made about 10^{12} hits in blood from retrovirus. That doesn't happen. Adenovirus certainly you get 10^{12} hits because you can get a titer that's up high and there's--it's highly efficient. Retrovirus, if you have a titer of 10^{8}, that's really good and you had to play a lot of games, and if you do 100 mils that's really extraordinary, which would be 10^{10}, and that's 100 percent efficiency. You don't get 100 percent efficiency. So you're probably three orders of

magnitude less than 10^{12}. The 10^{12} number I think came from, in those monkeys that had lymphoma and the report that I wrote, and I went back two lab notebooks--I mean, there was a lot of lab notebooks, so it was easy to get to them--lab notebooks, and there's a lot of information that report that it's not in any other published paper. I calculated the total hits that it took in those animals, with 100 days, 120 days of retroviremia, and the total hits in the animal was in the 10^{12} range. But that took months of chronic retroviremia.

CHAIRMAN SALOMON: Well, I think one of the things, though, that we--that I've learned as a transplanter over the last 20 years is 100 days may seem a long time to a fellow in the lab anxious to get his next paper out, but it's really meaningless, because I blink my eyes and it's, oh, my patient's back for their six-month visit. So I think that, you know, one-year, two-year, five-year follow-ups is--you know, if there's really a risk, it's...Phil?

DR. NOGUCHI: I'd like a little bit of discussion on the question of animal models because, actually, earlier it was suggested that if you could demonstrate, let's say, in an animal--in a reasonable animal model that an irradiated cell that's transduced disappears after a certain amount of time, that that would--that we could potentially exempt that from long-term follow-up. That seems to be

something that could be reasonably done in an animal and would reasonably give you data.

I think the question is really open about inputting something into an animal and really expecting that you're going to get a tumor at all. I've spent many years with tumor models, and unless you put in a tumor cell, it's really hard to do the opposite with, say, DNA or chemicals or anything like that. So we have two things with animal models. One is where you can reasonably be sure it will give you data to make a decision, and the other could be just simply a stochastic determination that, well, at least we didn't see a tumor. And is that sufficient?

CHAIRMAN SALOMON: I think that--Ed, you should comment, too, but I think that none of us are suggesting that there's any good animal model, because I think Ed and I sort of had that to and fro when he made--I mean, I don't think Ed's suggesting and I'm not suggesting that there's any animal model that's going to predict tumorigenesis very well. I mean, if it does immediately and positively, no one's going to argue about it. But I'm saying, you know, these sort of low risks, how many hits and how many animals, et cetera, I don't think anyone's suggesting that.

I think where an animal model could be relevant is if I was a sponsor and I wanted to do a trial with plasmid, and you said, well, does it integrate, I think what Ed was

saying is that you could potentially design an animal model that would allow us to sufficiently argue with you that it was gray enough that I would be asking for exemption from long-term follow-up based on that.

DR. SAUSVILLE: I would comment simply that, you know, the nice thing about DNA is you can follow the vector. I mean, you can put boundary limits around what you would consider likely and unlikely events. And with the issue of tumorigenesis, I certainly agree with you that if tumors are your endpoint, you're going to get a real spectrum because depending on the strain and the background and what you're inciting stimulus is, you can have 100 percent tumors or you can have 0.1 percent tumors as your readout.

But I do think, though, that if you closely model the intended use that this would allow more or less certainty as to what expected behaviors might be. And the "might be" is there whether you're dealing with genes or drugs or any of these substances. The animal models only go so far. But I do think that instead of just making blanket statements that if you're DNA, you've got to do X, Y, Z, A, B, C, that's where I think there could be a lot of useful input.

DR. MILLER: A point about exemption, and I guess that we could--you could do standards that say that these are the routine follow-ups that need to be done, but you can

have sort of a proviso in there that if adequate studies are done and if the company wants to, instead of--or the sponsor instead wants to make a system for long-term follow-up, wants to spend enough money to develop reasonable model systems or collect the data that will be able to present it, and the FDA with their prerogative, similar to the secretary of state in Florida's prerogative to grant exemptions, would be able to say, you know, yes, this is--this we'll exempt. But I think you should--if you set a minimum and then make it the burden to say why you don't need to meet those minimum, clearly if they got, you know, the case where the normal volunteers are getting sort of a--something that's not expected to have any integration attempt, and, you know, you just say that--you know, say that, but just, like, leave some latitude and there may be a very reasonable way of doing it, but set a minimum.

DR. SIEGEL: I guess what I'm envisioning, based on integrating this discussion, which has really, I think, touched well, if not yet completely, on all three of our questions, would be moving from a system which I would oversimplify by characterizing as saying we're requiring rather intensive annual in-person follow-up on all patients who receive retroviral vectors and we're treating other gene therapy pretty much as any other therapy that might have some long-acting effects, you know, and which you do your

year or two study and wrap it up, to a system where we employ a much broader range of tools over a much--phased in based on the risk factors discussed, there might be a lot--a much broader range of therapies than just retrovirus where we should be collecting information long term, but at one end of the spectrum where the information is--where the risks are low, theoretical, but not negligible, that might be limited to just ability to track the patients so that somebody can come back and do an epidemiological study. As the risks get higher, it might be intensive two- or five- or whatever-year follow-up as appropriate, followed by postcards that not only--and phone calls that not only support tracking but may ask the three or four critical questions about the complications of concern and potentially graduate from that in some particularly high-risk protocols to a more intensive follow-up requirement.

That seems to be at least what I'm envisioning coming from this. My guess is that--and I don't mean to wrap up this discussion because I'd like to hear more discussion--

CHAIRMAN SALOMON: But what you're doing now is exactly where I was going to go next, and that is, let's talk--we've sort of articulated principles that have stood the test of at least today's discussion, and, you know, they've given you--we've taken you all the way to the gray

area and then added, you know, that whereby--we've given you, told you where animal models and other kind of studies could then be used by sponsors and investigators to argue one way or the other, and we've given you principles in which if you get integration, if you get survival of the cells, if you have replication-competent or latent virus, you have--you now fulfill the long-term follow-up, right? I mean, so--and it's not just retroviral vectors, which I think is probably the most--one of the key things you should be hearing this morning.

Then the next step would be what is long-term follow-up. Right? I mean, I think that's where we need to go next.

So with that in mind, what--I mean, what kind of thinking do you have on this? I mean, I think that it's really clear from the discussions that preceded all this that if we now get off on this indulgent, you know, sort of self-righteous thing of long-term follow-up means daily blood tests and, you know, archiving the right arm every week, you know, then I don't think that's going to work. So, I mean, let's--what is long-term follow-up?

DR. SAUSVILLE: I like postcards. Okay? I mean, I think that is, shall we say, the most minimal position for everybody. I'm open to the idea that for particular indications--and, again, this would be where the animal

models and the nature of the therapy would be informative--it might be prudent to consider more invasive or more sample-driven things. But to me, I think as long as you're able to construct a numerator and a denominator of who gets a problem and who has a basis for getting a problem, that's going to be setting the stage to be doing future science, should the need arise in a way that's going to cost fairly little. And I would even go so far as to say, given the policy and confidentiality and proprietary natures of things, maybe even something that could be requested by the FDA as their special response to this concern and could be something that could be a right of the FDA, or--I mean, I just put that on the table.

CHAIRMAN SALOMON: I think that's important. I mean, let's make sure that we all agree that what we're talking about right now isn't the first year. Can we all agree that we're not discussing the first year? We're going--we're not going to touch that area, right? You're going to archive. You're going to do the biopsies. You know, if it's lung, you're going to get lung. If it's blood, it's going to--okay? So we're only talking about what goes on after the first year, not that those aren't important issues, but we're not--we're taking them off the table. Okay.

So getting back to this idea of is it postcards, I

actually would go another step further, and I would think that what you need is a database like UNOS that's publicly supported. And it's--but, remember, UNOS interactions are basically a postcard kind of interaction, so I'm not talking about any more intensive interaction with the patients, but I am talking about a little more organized than asking the sponsors to send postcards. I don't buy that.

DR. SAUSVILLE: I mean, I agree. I certainly think publicly supported--the issue of whether publicly available and such is clearly another separate issue.

CHAIRMAN SALOMON: I wasn't talking about publicly--I'm talking about publicly supported. I think there's no way out of it that the recommendation--now, this is for discussion, but my position is there's no way out of the fact that someone's going to have to put a dollar down. I'm not saying it's the FDA, but someone's going to have to support it, and then you have a competition, and like we do for the UNOS and for these other databases. And whoever wins the competition, you know, basically gets the contract the next five years.

DR. NOGUCHI: Just remember, though, the UNOS public portion of the contract is relatively small. Most of it is now done through user fees by UNOS. So I would not want to imply that this is easily supported by simple public funding through grant mechanisms.

CHAIRMAN SALOMON: I guess I'm not talking about easy. I'm just saying if you want a database, somebody's got to have to put a buck out. But I think the committee has the right to disagree with what I'm saying, and they should now if they do. But the question is where is going--where's the onus for this kind of follow-up? And what I think is very important is that the onus shouldn't be on individual sponsors, because then what you have to do is you have to supervise 150 different sponsors who are in and out of academic positions and companies closing, et cetera.

If you have a central group that says if a patient is--gets gene therapy just like a patient got a kidney transplant or a patient got a heart transplant, then you follow from a single spot. Then you just have to follow the patients.

DR. SIEGEL: Let me follow up on this idea, because I'm not sure where it's going. The group you propose--I mean, this is an interesting--an important policy proposal and one that needs discussion and consideration. It has received a great deal of discussion and consideration, and input is appreciated. There is no group sending out that postcard. You're saying it shouldn't be the sponsor. So if I get a protocol tomorrow, I shouldn't require that the sponsor follow up the patient because that's an unfair onus and I should just wait until some