DR. SIEGEL: Right. The tiers came out in the November discussion to try to incorporate those principles. What you are saying is you endorse the principles but it is hard to be too highly prospective and specific about exactly how to use them. I understand that. I made the case for why there is a lot of advantage to trying to be prospective and give guidance on how they are used. But I hear what you are saying.

DR. MULLING: But the other message, certainly my message is that I think there ought to be a very deliberate incorporation of some of these principles into the actual product review. That is the other part of this, a kind of a different way of thinking, that those things that are most of most concern to people that are bringing up issues, taking samples for the first five years -- you know, we maybe ought to be thinking a little differently about those.

DR. SIEGEL: Just to clarify further in terms of the way you set the goals for the end of today, surely, basically it is feasible but I question setting them too low, and there is some consensus there needs to be longer follow-up because where are we in the process? That is, I

said before we are all in agreement that we need -- I agree, by the way, with everything Amy said -- further consultation about the best information and about who to collect it and how to collect it, and funding, and whatever, and yet there appears to be, unless I am wrong, a strong consensus on this panel that the right thing to do with the protocols that we receive next week at the FDA is not what we have been doing, which is if it is a retrovirus, there is five-year specimen collection and long-term follow-up, and if it is not a retrovirus, one year and then you are done.

So, while I don't disagree that other areas need to be put forward, I am suggesting that we come to a point in time where it would appear, based on this advice of this committee and assessment of the situation, that one of the steps of the process, and one that we are moving toward, is to request that sponsors commit to more extensive long-term follow-up for a broader class of vectors. And, I think you already said it is kind of the sense of the committee that there is be general support for that. But we also need whatever we can get in terms of practical input in terms of what the nature of that would be.

While recognizing that it is not final, it is also the case that the easiest time to work these things out often is as the research is beginning, as people are funding the research and planning the research and thinking through the research. It is much harder, if not impossible, to go back to a study that was started ten years ago and say, huh, you know, you really needed a twenty-year follow-up, so even though you haven't done anything for the last five years it is time to reopen the study and find those patients and ask them all these questions. So, we don't want to be twenty years from now not having gotten started.

DR. SALOMON: And, I think what we are trying to say is what is it in this phase one that this committee would agree with you doing next week when you get such-and-such and I want to try and get there. Then we can stop and discuss in general principles of long-term follow-up that would be advice but not, you know, a specific guidance to you in the sense of how the committee thinks you should do things next week, and that might be setting up a framework for consultations with other groups that I think all of us accept as a principle.

DR. MULLIGAN: You know, there is a sensitivity about your existing retrovirus long-term follow-up requirement. I mean, I hate to take on another thing for us, but it seems like you raised that in that there is an inconsistency. In a way we are tacitly rescinding -- you could interpret that we are rescinding the need to do this stuff that is now in force. Is that something you want us to address?

DR. SIEGEL: Well, one of the reasons we came here in November was the growing awareness that we had advice that it was important to collect certain types of information. We were asking for that information and it wasn't being collected. Okay? So, I personally, and I think many others of us, didn't just want to sit on that, you know, that the whole world thinks that we are getting archiving specimens. And, one of the questions I asked the committee was, well, given that we are not collecting this information in the current infrastructure of a higher incidence, does that mean that we are asking (a), for the wrong thing, (b), we should collect the best we can or, (c) should we put all the research on hold because the fact that we can't collect it makes it too unsafe

to conduct the research?

The answer I got, at least as I understood it, was that while there has continued to be some level of confusion -- not confusion, I don't mean that, some level of lack of consensus about exactly what is the best thing to do, there was no strongly held belief that the appropriate approach is to stop the research until we can work up the mechanisms to gather the data right.

Now, we have had some discussion about those mechanisms here and the relative value of having simple postcards and whatever, and focusing and whatever, and those were useful. We have had other discussions. I think as Amy points out, CDC, other groups that have expertise to bear on that. And, also some of the issues that we got into discussing are infrastructural issues. You know, there should be an organization that does this or something like that. And, I think that sort of advice is useful but I think we are feeling also a need -- you know, was it Amy who said short-term solutions and long-term follow-up -- those are the sorts of things that you are going to build organizations, structures, governmental or not, cohorts, whatever, that need to be under discussion

and, indeed, are under discussion. But, at the same time, we need to know what are we doing tomorrow? Should we stop all the research until it exists, or should we ask them to commit knowing that they will do their best but that their best may have some significant holes in it?

DR. SALOMON: We are going to try and do that. So, what I think we should talk about now is what do we, today, phase one, agree should be done for gene therapy long-term follow-up -- some of the details now. What do we feel is the phase one, the first cut? Then we will go on to talk about what we could see being done as part of the consultation with others interested in this area in phase two and three. What do you, guys, think? Phase one? What is the bottom line?

DR. CHAMPLIN: What I have sort of been wrestling with is I think we all agree with sort of detailed follow-up for the first year is non-controversial. We have sort of signed off on that. Then a survey for some extended period of time of late, unexpected consequences. I guess what I am sort of wrestling with is the middle ground, what is now listed as the five years of annual physical examinations and review. And, that

is sort of protocol specific I think in terms of the vector involved and what data is needed to analyze that vector. If you are expecting long-term expression, of course, you want to measure is it being expressed, etc.

But in terms of toxicity assessment, I would probably try to simplify that to not necessarily requiring a person to come back to the treatment center and the sponsor assessing the toxicities in those patients during that five-year period by interactions with the patient directly and with their local physician, and then getting whatever samples are necessary for the study protocol itself. But it becomes increasingly hard to get people to truly come back to the treatment center, if it is a long distance patient, beyond the first year, and it is asking for missing data and problems in executing the protocol if you require that.

DR. SALOMON: One principle that maybe we could agree on is that there should be a database in which all patients who have been in a gene transfer protocol are identified, that details of the protocol are identified, that the vector, the promoter, etc., etc., the purpose, the initial

patient data, the response -- all these different things, that this should be in the database; that the integrity of that database should be assured, should be easily searchable so that if ten years from now or twenty years from now any question is raised in public or in the halls of the CDC, or whatever, all this information is immediately available and you can instantly say how many people got this and this vector, for what disease, etc., and why, and what were the details of the protocol. Can we start with that one principle?

DR. SIEGEL: Right, and I think we are pretty comfortable that that is well on its way to happening. NIH and FDA have put substantial efforts into that.

DR. SALOMON: Now, the second principle -- does everyone on the committee agree? We all agree with that? I mean, we have covered that before.

The second principle would be what is the sponsor? Would that be an individual investigator on an NIH grant, or a biotechnology company, or some mix thereof? What is the responsibility of the sponsor to this first principle, the database, the integrity of the database? My feeling would be it is the sponsor's job to make sure that all this

detail is in this database. It is not the sponsor's job to be the database but it is to submit the data requested by the database holder, and whether you, guys, do that within the FDA, the NIH, I know the RAC has done some work on that. It is fantastic. Or, whether in the end you contract -- I don't think that is this committee's issue right now. But it is the sponsor's. Do we agree that it is the sponsor's duty to obtain and provide the integrity of that data?

MS. LAWTON: One comment I would add to that is if this is for the purpose of tracking patients, you also have to look at how frequently do you want the sponsors to keep that information up to date.

DR. SALOMON: Right. That is good.

DR. CHAMPLIN: So, there are precedents for these kinds of organizations. For example, there is the international bone marrow transplant registry that collects transplant outcome data on patients. Basically it is operated under contract from the NIH. Similar to what you envision, they then develop case report forms; they have annual reports on all the patients that are submitted. This would seem to be a sort of parallel function

that we are describing here.

DR. SALOMON: Yes, there is also UNOS. There is the end-stage renal disease database. There is the AIDS vaccine trial. So, I think a principle here would be that these should be web-based from the sponsor's point of view. They should all be available at web-based data entry sites so that would facilitate data entry.

MS. LAWTON: I guess I wouldn't get into that level of detail here. I think we should be saying there should be a registry. Sponsors are responsible and there should be a way of updating it. But we shouldn't start recommending whether it should be web-based, whether it is held at NIH, FDA, whatever.

DR. SALOMON: I agree. We are not telling where it is going to be. I am okay with stopping there. I was just trying to get a sense that it didn't get ridiculous, you know, that we had to have carrier pigeons. I mean, there has to be some limit. I think a principle here is that it has to be technologically made in such a way that it is not an onerous burden on the sponsor. I shouldn't give any more detail now. I agree.

DR. SIEGEL: I would like to say that I

would like to really focus in that regard on what information to collect. For example, there are issues that we are trying to address right now that relate to securing the privacy of the information.

DR. SALOMON: I agree. Mahendra, you had a comment?

DR. RAO: You already addressed it. I was going to say the two points we should only make about the database is that all the information from the sponsor should be in the same format because it is all going to be kept in one place. The other thing is, from what we have discussed before, there will be levels of information depending on the category of trials that you have. So, it is not that all information is going to be identical on all the samples that you have. Right? You are going to have patients on a trial where you might have just a simple questionnaire. Right? Or, others where you might have additional data.

DR. SIEGEL: Yes, just so that you all can feel somewhat comforted by this, there have been ongoing efforts that have included broad consultations with groups such as UNOS, and bone marrow transplantation, and other people who work in this area that have also had input from our

efforts, people at NIH, FDA and CDC working on gene therapy or working on xenotransplantation where some of these issues arise. And, a lot of efforts to date have gone into defining what are the data fields and the databases, which would determine, of course, partly what information you collect; how should that be defined; how we classify vectors; how do we classify events; how do we track sites, patients, physicians or whatever in the database. And, how do we build systems that will allow analysis for that. Where we are trying to get at this point though in a sense, at least from the perspective at least of long-term data, is what efforts need to be made to get the data to populate those systems so that we can analyze. That is right, Dr. Rao, we anticipate that it wouldn't necessarily be the same.

DR. SALOMON: So, picking up on where Dr. Rao left off, I guess where I was going -- I got a little bit off detail when we were talking about the web base -- I guess the principle I would like to see if we agree on -- and this was an issue that we got into some discussion with the leadership of the American Society of Gene Therapy at the meeting in Seattle a few months ago, and that is, we really

think that efforts have to be made by the federal agencies to harmonize this information. I know you, guys, have heard this message and are doing your best to do that, but I think as a principle from this committee, unless again my colleagues want to disagree, it is very important that there not be twenty different data reporting requests from twenty different federal agency groups. I think one of the things you should hear from us is that we would hold you responsible for harmonizing some of this information the very, very best that you can. Is there any discussion on that?

DR. PATTERSON: I would just like to request time at a future meeting to go over with you some changes, some significant changes to the NIH guidelines and reporting requirements that I think they will speak directly to the issues. We heard very clearly the call from investigators and industry that you wanted wherever feasible or possible one set of federal requirements, and we are harmonizing our definitions, time lines and scope of reporting to parallel those that the FDA has set forth in 21 CFR.

In addition, we have a number of initiatives under way that I think this committee

could make important contributions to, a series of ongoing safety symposia on the database for setting up a gene transfer data safety assessment, and we will be working closely with colleagues at FDA to help prepare reports for that. Just whenever you have time on your agenda, I would like to maybe give you a more detailed update on those efforts that we have heard and paid attention to.

DR. SALOMON: That is excellent. We are on a roll here. I don't know how long it is going to last. So, the next step would be getting a little bit closer to what would be the generic detail then. What do we advise now needs to be done for this first phase?

DR. SIEGEL: Maybe to help focus more, I will ask a more specific question although, again, all comments and all aspects are welcome, and that is how long? I think you pointed out at some point in time we thought we should be following people for the rest of their lives. At this point, to summarize what we have proposed in analyzing risks, at least on the basis -- and we don't know for gene therapy of course, but on the basis of other treatment, the nature of the disease, the nature of virus-induced disease, and the nature of genetic

mutation-induced disease, I think our summary, looking at malignancy and neurologic disorders and perhaps those that might take the longest time, we would still see much of what we were looking for in ten years, and most of what we were looking for in fifteen years, and a very large proportion of what we were looking for over twenty years of follow-up, and I don't know that we have a good feeling for the additional costs or even additional yields as you go to ten, fifteen, twenty or longer periods of follow-up. But we put on the table time ranges between fifteen to twenty year range as a standard amount to do this sort of follow-up, and it would be interesting and useful to get feedback on that.

DR. SALOMON: Okay. So, we can look at time frames. I think that is a great place to start. Five years? Ten years? Fifteen and twenty? I think what I would like to return to when we are done is a second principle that is connected, and that would be do we think it would be more intense in the first year, five years versus ten years? But let's get to that in a minute.

How about comments from the group about phase one, all patients on a gene transfer vector

clinical protocol, what time frame are we going to look at data for?

DR. MULLIGAN: I think one issue has to do with trying to not dissociate that question from what it is. What is the data collection? It is sort of ridiculous to talk about that and then have to spend another hour or two rationalizing it. So, I mean, I would almost do it in reverse. You know, if you are talking about ten years, fifteen years, twenty years is there a significant difference in the amount of information you will add based on the kind of system that you put in place? If it is an automatic e-mail that goes to people, you know, something like that. I think that is going to end up dictating where we are going to cut down because I still look at this as a pretty raw database that we will have, and I do look at it as changing over time. Ten years, you know, from now another group here may have to rehash this whole thing.

But at this point, I would be interested to hear what people think about ten years or twenty years in terms of getting info, and if you have an attrition rate between ten and twenty years, do you care? That is, are you still getting the info? Then, you know, almost base a decision on that. I

would be most interested to hear what people think would be the manner of data collection. You know, what would be the actual kinds of questions, questionnaire, how would you get it to people? I think if you don't understand how you get it to people, then we can't really give a sense of how long to keep it.

DR. SALOMON: Fair enough. Comments?

DR. HIGH: I would just say that looking at the field in general, to me, it is more useful to collect a minimal amount of data between five and twenty years than to collect a great deal of data between one and five years. I think that for what we need the amount of information is really minimal. I think we could just have, as you said, a one-page questionnaire or even a postcard. You want to know causes of death, development of new medical conditions, that sort of very minimal information, and it could go first as a questionnaire to the patient and if it fails to elicit something, you know, the sponsor could follow-up with the treating physician.

DR. CHAMPLIN: I would think after about five years you are going to be dealing with very rare events and you are really concerned about

malignancy as the number one thing, possibly neurologic disorders. So, you could have three questions on the card, basically, did you develop cancer? Then, some more general, did you develop a major medical problem? And, pretty much leave it at that. Whereas, during the first five years you are going to try to screen more comprehensively for the acute and the intermediate toxicity.

DR. SALOMON: The only thing I would add is we actually have a little bit of a framework here that I think is useful, and that is, you know, did you develop any kind of cancer? If so, what kind? Did you develop any sort of autoimmune disease? If so, what kind? Did you develop any neurologic disease? Just basically following the patterns that we have come to because I think there is a lot of very reasonable, scientifically based work there that I think was very nicely reviewed for us this morning by Philippe and Steven.

DR. MULLIGAN: From a database point of view, going back to that tier system, not to throw that away, you could, indeed, organize a database somewhat along the lines of the tiers so that you would at least know that you may be most interested in getting to the database that deals with that

class of patients.

DR. SALOMON: Sure. I mean, I personally don't see that as being a big advantage but that is a detail. To me, what is going to be most interesting I think down the line would be vector classes, promoter types and the nature of the gene construct that has been delivered and, of course, its interaction with the disease. That is going to be the most interesting thing.

I think the weakest part of the long-term data is going to be this whole issue that was, again, nicely described this morning, and that is you are going to give it to a disease population and the population that has that disease and that didn't get the gene vectors is really the only one that is going to make any sort of sense. Then, the reality of defining disease groups is going to be extremely fallible, and that is going to reduce the quality of the data and make the interpretations much, much more limited, I am afraid. Even when you do something, as we will discuss on Friday I guess, but even something as simple as defining heart failure in an AIDS patient, or define a specific type of leukemia -- it is going to be very difficult.

So, I think if we can go with reasonable kind of data so that we could say twenty years from now that we saw 200 cases of thyroid cancer and we can trace it back to this group of patients, and that all relates to a certain class of vector or it relates to any class of vector in anyone you use the CMV promoter, or something like that, I think that would be incredible kind of data. It is probably the strongest data that will come out from long-term follow-up.

DR. GAYLOR: Obviously, follow-up is not new. There are a lot of studies on a number of drugs particularly with follow-up on chemotherapy trials, for example. These people will tell you the worst thing to do is to mail out a questionnaire. It is much better to have a nurse conduct a telephone interview. A well-conducted follow-up on a hundred people may tell you a lot more than mailing out questionnaires and getting ten, twenty, thirty percent response, especially years down the road.

So, I would encourage FDA, CBER in this case, to really look into what has been done in other long-term follow-up and consider sampling rather than just trying to follow up a hundred

percent of the people. I can't sit here today and tell you what you need to do, but one advantage is, if you are looking for rare events, you don't need a large sample. You don't need tens of thousands of people. Three rare events can be statistically significant. A hundred people can tell you if you are getting an incidence of five to ten percent.

Epidemiologists tend to look at relative risk but if you look at just the absolute risk, what is the chance that your population has a five percent or ten percent incidence of some adverse effect, that is not that difficult to pick up from a relatively small sample. It wouldn't be a terribly big burden, I don't think, for a sponsor to follow a hundred people carefully, and two or three years down the line maybe you can go to fifty people, or maybe decide you have to go to two hundred people. But, of course, you sort of want to tell the sponsor up front what is expected, and you sort of hate to say, well three years from now we may decide to go to a thousand people for follow-up and you have been doing a hundred. So, that would be a little tough to deal with, but I would certainly recommend sampling rather than trying to do a hundred percent follow-up.

DR. SALOMON: The problem I see with sampling is that you are treating this gene therapy as this population and then you are going to sample within it, which makes sense until you realize that that is really not the population. The population is all these little groups, each one getting different vectors, and different genes, and different diseases. So, I think that sampling is not likely to be as powerful as it is conceptually when you have a unifying disease process and a unifying treatment.

DR. GAYLOR: Sampling would work for following up in a clinical trial group --

DR. SALOMON: If it was big enough.

DR. GAYLOR: If it was big enough and if it is only fifty people, you would probably follow all fifty of them.

DR. HIGH: I would just second that. I mean, there are 4000 patients on 400 trials approximately. So, to try to sample in that setting is not meaningful.

DR. SIEGEL: Maybe within the next few years we are going to be seeing large, multi-center Phase III trials.

DR. SALOMON: Right, and I think then Dr.

Gaylor's point would be that perhaps at that time, in negotiation with the sponsor, detailed follow-up might be done on a sample and that would be great to reduce the onus of a twenty-year follow-up.

DR. SIEGEL: One thing I have reflected on relates also to the concept about long-term follow-up and a comment or two in areas outside of gene therapy is that one of the issues here -- if somebody starts a trial of a new experimental product, often a few years later it is either approved or it is dead -- the product is dead, and the long-term follow-up of the patients, depending on the nature of the product, may be important to the patient's safety. But if the product is not going anywhere it is not critically important to the understanding of the product. So, often we face these issues at the time of product approval when it is going to much larger numbers and it is going to be around for a while, and we can work out with a company about what is necessary to find out even longer term than three or four years they have already been studying it about long-term effects.

But the premise we are working from in gene therapy is that if we are dealing with 400 and 4000, whatever those numbers are, the information

on one product, as long as we are talking about, you know, vector specific rather than highly protocol specific risks, the information on one product is relevant to all products and we have kind of an obligation to look at it all together, and that is why we are talking about databases or studies. Even if you do a study today, even if that product doesn't work or you find a somewhat better vector, the long-term follow-up of those patients is important not only for their welfare but for understanding the study risks of gene therapy. That is one of the reasons we are specifically focused on this issue in this field.

DR. SALOMON: Yes, I think another scientific argument is just to look at the Donahue report where the rhesus monkeys got the lymphoma. Now, nobody would do a retroviral vector trial designed like that where they have homologous sequences and a packaging vector that allowed for the RCR. Obviously, we have learned our lesson. Obviously, we don't design vectors like that. We are way past that. So, you could argue that that is a dead issue but it is so important because it explains why, like on Friday when we look at vector issues that were brought up with the RAC about

possible recombination, about how many plasmids they had divided there, packaging sequences, and so on. So, I think that it is valuable even if we discover a complication in a retroviral vector or another kind of vector product that we all realize, God, we would never do that again. It still defines the field.

DR. SIEGEL: I don't want to go too far down the lane of being philosophical, but one of the things that we noted that was particularly difficult in this field as it got started with preclinical studies, and it is still the case to some extent, is we would ask, say, French Anderson who was doing some of the first experiments, we would ask for a two-year animal study to look at some of the longer term concerns. Invariably, at least for the first few years of therapy, and it may still be the case, by the time you got a two-year animal study on the safety of a vector there were other generations of vector that on paper just look like they would be safer. They had been engineered to have less risks. So, now you start that one in a two-year study, at the end of which you have something better to go with.

So, it is a reasonably good guess and it

is something to bear in the back of the mind because I think it is relevant that when we get this twenty-year safety data it is going to be on products that we are not interested in using because even if it is an effective approach to a given disease, we are going to believe that we have developed testing and manufacturing and genetic and molecular mechanisms to make a better product. So, we are working on the presumption that there are certain general principles that we may elicit about what the risks are. It may not be quantitatively true that the risk is exactly the same, but if it turns out, as you say, that a CMV promoter is associated with a certain disease, that that general principle will not apply quantitatively to any given specific product would be extremely important to elucidate.

MS. LAWTON: Jay, can I just comment on that because I assume we are not just going to collect this and look at it in twenty years --

DR. SIEGEL: Oh, of course.

MS. LAWTON: -- we are going to look at it on a routine basis. So, hopefully, you would gather other information along the way that may lead to making decisions about not wanting to use a

particular vector anymore, or maybe even, you know, that is recognized and at that point you say you don't need to continue with long-term follow-up for twenty years because nobody is going to use this vector anymore. I mean, those are the types of decisions you can make along the way; it is not just at the twenty-year time point.

DR. SIEGEL: No, that is right. I guess I hadn't specifically thought through that if a type of vector isn't used it doesn't need to be followed. But, as I alluded to earlier, there might well be a case where even a single patient report, whether at year two, five, eight or twenty, if it is associated with appropriate biological data may raise enough of a concern that, as long as we get that report in, it will be enough of a signal to tell us that we have a problem. Absolutely. We would anticipate, based on our analyses, that even for malignancies most of the signals are going to come in the first five or ten years.

DR. MULLIGAN: On the philosophical part, one of the things that I always used to tease French about is when he would get up and talk about his eight monkey years of safety testing was that

that only proved that if you didn't have gene transfer it is perfectly safe. I think it is very relevant here because over the time period, you know, you will be getting data, safety data, where there is a learning curve on the gene transfer efficiency. So, the same clinical trials using the same vectors, as you get more efficient, undoubtedly bad things or more bad things will happen. I predict that that will be the most significant aspect of the long-term follow-up, that as the learning curve, not so much technically on the actual vectors but, you know, how you manipulate the cells to get them infected, and that is something that somehow we are going to have to work into all this. I think there is going to be an amazing difference when people begin to get fifty percent stem cells infected in bone marrow transplants, as opposed to 0.001 percent.

DR. SIEGEL: So, while we have heard some advice that once we know something is safe we may have less oversight in that area, as often happens, you are suggesting that as technology evolves, more efficient and effective technologies may also raise new safety concerns that aren't addressed.

DR. SALOMON: Right, which is a good

argument why we need to get something going now, and we owe that to everyone. We owe that to history, if nothing else, to document what is going on, and to realize the cyclical nature of science. You know, a lot of things come back around. I mean, the vector that we throw our or the promoter that we throw out today could be the key thing tomorrow when some new disease comes along that we didn't anticipate.

So, how about the referring physicians? I mean, we have talked about postcards to the patients. Maybe on a yearly basis, once a year, at the same time should we match it to the referring physicians and also, of course, try and keep track of not only where the patient is but whom the patient is seeing as the doctor at the time, realizing that has definitely, you know, holes in it?

DR. CHAMPLIN: Particularly during the first five years of follow-up, I would say that the sponsor working with the patient and the referring physician would be mainly collecting information. As you get further and further away, again, patients move, they get new doctors and that is, again, much more chaotic.

DR. SALOMON: I was just thinking that getting a postcard back from a patient saying they developed, you know, an autoimmune disease and then getting a postcard back on the same patient from the doctor saying, yes, the patient has scleroderma would mean a lot to me, as opposed to this patient is whacked -- you know, has no idea what is going on and has decided they have some unknown autoimmune disease.

DR. SIEGEL: I am trying to think this through from a pragmatic point of view. I think Dr. Champlin pointed out very well that the reality is that people will have moved out of town and after a year, not withstanding Dr. Bishop's comments, that perhaps the investigator knows what best to ask and the likelihood is much better, or even samples if it is done by a referring physician.

In terms of what a sponsor can and should commit to in a protocol, I would think that that would require making the referring physician a co-investigator on the protocol and getting appropriate paperwork. I am not sure how else -- do you want to comment about that? Can a sponsor just call up a referring physician, if not an

investigator, and say we need you; please contact your patient and get this information?

MS. LAWTON: It is a good point. I was shaking my head when you said trying to make the patient, physician a co-investigator. That would just be a nightmare and, obviously, there is no way that you can go that route to track that. I don't know whether you could do something along the lines of the patient and the informed consent, that they have a responsibility to inform their physicians, whether that goes on their medical record, or something, when they change physicians so that you are able to contact a physician. I don't know.

Is there no experience out there of these types of long-term follow-ups? For the most part, we have only ever only contacted patients and then you could maybe ask for informed consent from the patient to contact their physician to get more information. That would seem the obvious route to go, to be honest.

DR. SIEGEL: Right, I wasn't sure you were shaking your head because you disagreed or because you were concerned. Because I am concerned and that is why I threw it out there. Just from a practical point of view, usually we deal with

contact through the sponsors, investigators and patients. There may be precedents for other approaches. To the extent I am aware of them, if significant amount of the follow-up involve follow-up by the local physician, that is in some cases written into the protocol and they are made co-investigators. But I certainly recognize that that is not something that is easily or lightly done from an organizational point of view. That is why I just rolled that out there. Whether there are other legal ethical ways, you know, consistent with principles of informed consent, and all of that, are things that we can explore but I am not sure I am in a position that I want to comment on what the possibilities are at this point of time.

DR. SALOMON: I brought it up for that kind of a point. In practice, at least in southern California where I work, you can't get referring physician data without a signed permission from the patient. I think the conservative view of that is that that shouldn't be a blanket either so that every year one would probably have to update that because I think to say, "sign here and, if for the next twenty years, you are okay, you need to get data from your referring physician." I don't think

that would be legal. Assuming consent and they are going ahead and trying to reassure referring physicians that for the next ten years I am going to send you a postcard, and the patients have consented -- just assume that unless you hear otherwise from the patient or me. I don't think that is going to work.

So, I think we have to agree that the referring physician, despite the important corroborative data that a physician could provide, would probably have to be brought in, in a second loop. In other words, the subset of patients who have autoimmune disease, if it suddenly rises above some trigger point in the review of the database, you would now contact that subset of patients and request confirmation of the results of the skin biopsies, the autoimmune antibodies or whatever the specifics were. Is everyone kind of comfortable with that?

DR. CHAMPLIN: So, in reality this is going to be the rule and not the exception. Long-term follow-up, meaning that the patients got home; they go to their local doctor and don't come back, you know, a thousand miles to the treatment center.

DR. SALOMON: If that is true, do we agree that this should be done once a year? We still haven't quite said ten years, fifteen years or twenty years yet, but we are going along this line.

DR. CHAMPLIN: I would hope that once the registry is formed that they can get into the nitty-gritty of what data needs to be collected once a year, and I also agree with Dr. High that the data that you collect on year two should be very different than the data you collect on year nineteen or even ten, and that you want more comprehensive, broad-based data early and as you get further out, you know, far more generally focused information that we are going to discuss. And, I would probably argue for more detail maybe for the five-year period and a very limited data set after that time. But I think this really is going to be a job of organization and we hope that we will get people involved and excited as a sort of an intellectual pursuit to try and identify problems that are going to exist in these patients.

MS. TICE: You were asking for an example, and Schering-Plough [not at microphone; inaudible]... the protocol usually has data that is detailed over three months and analysis [not at

microphone; inaudible] ... but this is all protocol based now, and the first year is very detailed, every three months CT and [not at microphone; inaudible] ... then every six months unless it is triggered [not at microphone; inaudible]. Now, for long term we are doing a yearly fax back to the referring physician, and the referring physicians [not at microphone; inaudible] ... then there is a communication to that referring physician [not at microphone; inaudible] ... and we ask them four basic questions, autoimmune disease, cancers, hematologic and neurologic, and that is where the doctor can put in the right diagnosis. A patient cannot tell you if they have had the appropriate diagnosis. They can't do that. So, we have been doing a fax back and if there is a "yes" then we treat it as an expedited report and tell the FDA that something is going on there. Then the FDA can follow-up with the site if they want to get more detail. [Not at microphone; inaudible].

DR. SALOMON: So, what you are saying is that your strategy built in your protocol has been dealing with the referring physicians, not with the patients. None of these go to the patients.

MS. TICE: None of these go to the

patient. They get faxed back to the site.

DR. SALOMON: So, how did you deal with the question that just circled here regarding the legality of a referring physician providing privileged medical information on the patient?

MS. TICE: When you sign on, I mean the protocol is signed by your investigator; the investigator has agreed to follow what you stated in the protocol.

DR. SALOMON: But that is the investigator; it is not the referring physician.

MS. TICE: Okay, that is a good point. There may be some type of setup between how that person got referred to a site. I don't know the relationship between that referring to the site. Typically, our patients are local. They don't travel thousands of miles.

DR. SALOMON: Right. Just so that we are clear on what you are doing, you are sending your CFR clinical --

MS. TICE: We are sending the clinical form.

DR. SALOMON: But you are sending it to your investigators, not to what we are calling referring physicians.

MS. TICE: Right, but typically our investigator is the treating physician.

DR. SALOMON: And, you are not really concerned with how that investigator gets the information as long as you get your response form back.

MS. TICE: Yes, after they are finished all their routine CT scans and what is required in the protocol, then maybe it is a phone call, maybe they come in for their yearly checkup but we ask the investigator to answer these forms.

DR. SALOMON: Right. That is very useful. Thank you. I think the critical point here in trying to come up with some practical suggestions is going back to your principal investigators is relatively straightforward. Thinking about twenty years of going routinely to referring physicians out in the community to which your patients have dispersed and maybe changed three times as they change their health plans -- I don't know what is going on in the rest of the country but in southern California it is like changing your tie to change your health plan. You know, that is the part that I don't think is going to work, at least not under the current situation we have with information

rights, etc.

MS. TICE: You are saying that they are changing four or five different times, moving from Nebraska to New York. We cannot, as a sponsor, track patients down like that. I mean, we give up.

DR. SALOMON: But as a sponsor you are not even trying to track the patients. Right? What you are doing is you have an investigator at institution XYZ -- it is easy for you, you send it to that guy and he either comes back with it or tells you, "I'm sorry, I lost contact with the patient," and you are done.

MS. TICE: [Not at microphone; inaudible].

DR. SALOMON: Make sure you identify yourself.

MR. REYNOLDS: Tom Reynolds, Targeted Genetics. I want to echo the sentiment. We typically, for confidentiality reasons, don't know who our patients are. We have heard numbers assigned by our investigators, and typically every year we provide them with a list of all the patients that they have had who have responded in the prior year. Then they try to contact the patient, usually by phone or by clinic visit, and do the long-term follow-up and report back to us.

One thing that I think is going to be a big issue for this over the long haul with that kind of approach is that we know a lot of investigators move from site to site to site. The institutions to which they belong are not really funded to do that kind of work. Once that investigator-patient contact is broken it is not clear how that can be reinstituted, whether we need to sign on a new investigational from that site, or now that the guy has hopped from site A to B to C, we have to contact there and trail them back. Usually there has been a fair amount of attrition.

DR. SALOMON: Okay. So far yearly questionnaires to patients. Referring physicians are left out of the loop in the first go around but in targeted patient groups referring physicians would be fair game, but it would have to be under appropriate, at that time legal allowance for disclosure of privileged information between a patient and a physician. That is probably about as far as I can see us going, except that we have to give you a time frame now. But I don't think you have heard us say that they need physical exams. I don't think you have heard us say that you need to be archiving materials.

DR. SIEGEL: I guess I am not sure what I heard in that regard, but if that is correct I would like to hear some further discussion of that point, if we are asking for too much in the retroviral area in general in terms of archiving. I think we have laid forward a philosophy for why we thought it might be useful to have those specimens.

DR. SALOMON: Yes, that is why I brought it up, Jay, so we could have some discussion. I guess the principle I am trying to hone to is that this is what the committee is comfortable telling you for all gene transfer vector protocols, not trying to exclude you in individual cases, individual protocols, from demanding anything else on top of it. It is just that this committee is sending this message --

DR. SIEGEL: No, I understand. I am simply saying that at the present time for all retroviral protocols we are asking, although not necessarily receiving, and maybe we should stop asking for it or maybe we have pointed out reasons that we might want, in retrospect, when we have safety concerns and be able to look back at some serologies, viremia, other issues. On the other

hand, one might make the case that if you have samples out to one year on that, that is going to cover most of what you want to know, and five years is not going to happen anyhow and we should stop asking for it. But I would like to hear a little more before assuming that there is a consensus of the committee, a little more discussion about that situation.

DR. SALOMON: Fair enough. Go ahead.

DR. MULLIGAN: I would say that I would rescind the blanket archiving of samples. I think you can definitely think of different applications where there would be different reasons for having or not having them. So, coming back to the tier system, you know, if you are doing transduction of tumor cells, irradiated tumor cells with a retroviral vector, I think the need for archiving is completely different than doing bone marrow infections with a retroviral vector during bone marrow transplantation. So, simply put, I would say that having archived samples for retrovirus probably, at this point, doesn't make sense. It probably did make sense but I think we are much more sophisticated in classifying different applications.

Then, I would say you do it on a case by case, and I would argue that there would definitely be, in the case of retrovirus vectors, certain cases where you would want to ask them to do that.

DR. CHAMPLIN: In terms of the physical exam, it is very rare that an asymptomatic patient has a striking finding that just pops up in a physical examination. So, again I would call for toxicities based on a global assessment, however you make it, working with the referring physician or directly with the patient. But the actual physical exam part is usually not informative.

DR. SALOMON: With respect to the physical exam, if I could get my head around the idea that it is easy to do, I would argue that in the context of getting an expert to sit down with a patient at some point or points post closure of the protocol would be one of the most ideal ways of saying, "oh my gosh, you do have glomerular nephritis."

DR. CHAMPLIN: So, it is the history that you take from a patient is much more information than anything else, and the actual examination part is not or it just complements your analysis of their symptoms. So, much of this can be done on the telephone or working with referring physicians,

again, to make life more realistic for the people in the treatment center.

DR. GAYLOR: Something more than an annual postcard has to be done. You get two major biases with postcards. You get the people with the disease or perceived disease -- "yeah, I've got something because maybe I can sue somebody." So, you get that bias. The worse bias is those people that died due to gene therapy perhaps, you don't hear from. So, there has to be some kind of quality control beyond an annual postcard. I will go back to my sample again. If you have half a dozen on the important vectors, maybe half a dozen categories of vectors and you make sure that somehow you sample at least thirty people in each vector category and do some more extensive follow-up on one or two hundred people perhaps.

DR. SALOMON: I think that is an excellent point. And that probably deserves a minute of consideration by the committee, and that is what do we feel comfortable with as a guideline to sponsors for how they should pursue the quality of this sampling protocol? I mean, the lightest obligation is every year you will send out a postcard or a form to every patient that you put on this

protocol, and that is it, to going as far as saying not only will you do that, but you will follow through with the ones you didn't get back, and even those that have a problem you will contact or make a good faith attempt to contact their referring physician. So, maybe can we get some discussion of that from the committee? Again, there is a lot at stake here because what we demand out ten, fifteen years of sponsors is going to reverberate through this whole system.

DR. SIEGEL: I would like to say in that regard that in the setting of clinical trials where people try, whether a cancer or an MI trial, to get half year, one year, two year, five year follow-up, there is a broad spectrum from simply sending a questionnaire to sending a questionnaire and multiple reminder cards, followed up by phone calls, and also by having patients give, at the start of a trial, the name and number of a reliable contact who will know where they are if you are not at this address and phone number. And, we see a huge spectrum from people being able to follow over 99 percent of patients out to at least half a year, a year or two years, and also incentives, you know, send in the card and you get a free dinner or

something.

[Laughter]

I am not sure we are necessarily in a position to require that but I do think it is an issue. We are all facing the fact that it is one thing to say, you know, attempt to get information; it is another thing to actually get the information, and there are efforts and there are real efforts.

DR. GAYLOR: As far as death is concerned, the FDA can check the death registry.

DR. SIEGEL: We don't have patient lists.

DR. GAYLOR: Oh, that is right, you don't have that. So, it has to go back to the investigator.

DR. MULLIGAN: I propose that we may not be the right people to figure out how many postcards and so forth. So, the message that is key is there needs to be thinking about how to make sure that the word gets out to the people. I think our message is that it has to be simple.

DR. SIEGEL: Can I follow-up with that question of simplicity because I have heard both the comment that we should focus efforts in the areas we have been talking about, but also the

comment that we should not lose track of other areas. So, the general issues of collecting information -- have you had any medical problems or perhaps any hospitalizations or causes of death -- certainly, one can see that getting more information that could be useful. On the other hand, it has implications regarding the simplicity, as pointed out, if somebody says, "yeah, I'm having kidney problems" and what is the next step? And, the other issue, of course, is even if it is more specific and you start with a low index of suspicion about it, what do you do with it in an uncontrolled case report? So, now it is, you know, twenty years later and you say ten percent of the people developed heart attacks. Where do you go with that? Whereas, if ten percent of the people develop a chromocytoma, you know you have something. So, I guess I am a little uncertain as to whether we want to be only focused or whether we think there is a value to creating broad data tracking for all major health events or lethal events, or the like.

DR. HIGH: Well, one relatively simple way to get that is to just put on the postcard something like "what medications are you on?" I

mean, it may give you an indication about diagnoses that the patient may not know otherwise.

DR. SALOMON: Yes, I agree with that. You could also certainly put in a question of "have you been hospitalized in the last year? If so, why?"

MS. LAWTON: Maybe an easier way of doing this is to actually have the sponsors make sure they regularly contact the patients and ask who their current treating physician is, and then have the sponsors follow-up directly with the physicians because then you can ask some of those questions and actually get reasonable information back.

DR. SALOMON: I think that kind of follows what PhARMA does. You know, I am trying to walk the fine line here is NIH, principle investigator sponsored research where you get a five-year grant, and we are talking suddenly about -- we haven't define the time yet but, you know, ten- and twenty-year follow-up, and anything that comes out of this committee, I am hoping, is consonant with not putting the onus or knocking all these guys out of the field, including myself.

It is 12:50. I was thinking a minute or two ago, well, if we just push on we will be done and then go to lunch, but I don't think that is

going to quite happen. I don't think we are going to satisfy some of the broader final phase two to three kind of questions that I think, very properly, Dr. Siegel and the staff wants to address. So, unless there is something we really have to say right this second, I thought maybe we would break for lunch and come back at 1:30, a little less than 45 minutes for lunch. Is that enough? It is not exactly gourmet dining here, and we will try and finish it up. Is that okay?

[Whereupon, at 12:40 p.m., the committee was recessed for lunch, to reconvene at 1:45 p.m.]

AFTERNOON PROCEEDINGS

DR. SALOMON: Welcome back, everybody, to the afternoon session here. Where we were at was kind of working step by step through what it was we could specifically request of a sponsor, and the premise was that when we kind of got as far as we could in defining that we would go back and revisit the very specific question of five-, ten-, fifteen-year follow-up in that context.

Just so that we are all on the same page, so to speak, what we have agreed so far is that there should be a database that has all patients that have been involved in a gene transfer clinical protocol, that that database should be maintained by one of the regulatory agencies, presumably the FDA or the NIH but really that is not the committee's concern today, but that we do agree, all of us, that there should be such a database and it should be monitored. We are not trying to tell you whether it should be monitored weekly, monthly or yearly. That is, again, a detail that we expect the agencies to work out and we don't feel that is the purview of the committee.

We agree that the sponsors should be, however, absolutely responsible for providing that

data set agreed upon to the registry, wherever that registry is, and for whatever period of time we end up deciding.

We agreed that at the moment the most comfortable position we have is that all gene vector protocol patients should be followed long term within the guidelines of what we are going to spend the rest of the time talking about.

As far as long-term follow-up went, we intellectually accepted the discipline that there were more risky vectors, more risky inserts, more risky diseases and less risky vectors, diseases and inserts but that as a principle for long-term follow-up, if we accepted the fact that everyone would get long-term follow-up and we could be comfortable defining sort of the generic baseline long-term follow-up, that additional, more intense follow-ups that would be specified by appropriate scientific reasoning for specific vectors, specific diseases, specific construct or any combination thereof would be between the sponsor and the FDA staff.

So, pursuing that, we talked about the fact that long-term follow-up would focus on the patient and instrument of contact, whether that be

a postcard or a phone call -- I don't think we really specified that at this point, not to the referring physician as a routine -- we are getting pretty close to where we were just before lunch.

Oh, and that questions would include, but not be absolutely limited to, the four major categories, neurologic disease, malignancy, autoimmune disease and hematologic disease. And, additionally, that we would request information of hospitalizations and medications as, again, a clue to potentially other complications that might have occurred during the interim, and the general concept we all agreed on was if there was a new medical problem, unexpected medical problem that should be reported regardless of whether it fit into any rigid criteria we set. For hematologic disease and a whole bunch of patients with heart attacks, we definitely weren't excluding the importance of reporting that.

So, I think that brings us up to when we went to lunch. Does everyone agree?

MS. LAWTON: Sorry, I just wanted to try something as far as the comment about direct contact with patients. One thing I should say for most of the corporate-sponsored clinical trials is

that that would have to be through the investigator, obviously, because we wouldn't necessary have direct access to patient information. So, that is just for the record.

DR. SALOMON: So, somewhere here we had better decide we have gone as far as we are going to go in specifying it, and then we can get back to the years. Right? So, let's pursue that. Does anyone on the committee want to go any further in terms of yearly contact at this point? Do we need to go further than that today?

DR. CHAMPLIN: So, you are talking about after the first year?

DR. SALOMON: Right.

DR. CHAMPLIN: There would be sort of a minimum of yearly contact. It sounds good.

DR. SALOMON: Again, the premise is that we are not excluding the FDA staff and the sponsor from agreeing to any additional follow-up. It is just that this is what we considered the baseline for everybody at this time. Dr. Siegel specifically wanted us to be real clear about the fact that we were drawing a line there and not at physical exams. So, we need to make a specific comment on that, and archiving of specimens.

DR. SIEGEL: First I want to say that I think you summarized well much of what was said. Most of the points you made seemed to be consensus. There are one or two things that were put in the category of advice of individuals but haven't really been discussed from the point of consensus -- medication records, hospitalization and so forth.

DR. SALOMON: Let's go through that. Hospitalizations, does everyone agree or disagree that we should capture hospitalizations? I think we should, and I think medications is easy. It is certainly something I have done many times in the past. I do agree with Dr. High that that very useful. You know, all of a sudden they are on hypertensive medication or gout medication, or an anti-inflammatory shows up or Imuran or Celcep those are very valuable.

DR. SIEGEL: So, as clues to specific diagnoses, you are not necessarily suggesting we create a database of all the medications that everybody is on, but asking about medications is a way -- because if somebody is taking some chemotherapy or immunosuppressive that could trigger --

DR. SALOMON: Right. I mean, in the example of a patient who might have chronic fatigue syndrome it would be hard to diagnose that. So, you have to be really, really cautious about it. But if suddenly a patient shows up on any kind of steroids and azathioprine and they tell you they have an autoimmune disease, I would be willing to believe them.

DR. CHAMPLIN: Part of this is sort of a method as opposed to the form that you send in at the end. I am not sure I would want to list all the patient's medications but, certainly, as you would be talking to the patient and asking him what has been going on in the last year since your last survey, you would ask them about important illnesses and drugs that they are on, etc. But, actually, the information that would be submitted, I would actually try to make it in a more abbreviated, focused kind of fashion.

DR. SIEGEL: Well, I heard a number of comments that sending in postcards may not be either efficient enough accurate enough as opposed to contacts. Also, Alison Lawton's comment pointed out that it is not just the sponsor and the treating physician and the patient, there is also

the investigator and if there is probably some practical way this is going to be carried out, carried out meaningfully, as your comment would reflect, you would want somebody with some technical background getting some specific information.

DR. SALOMON: We are getting close to where my concerns start to rise, and that is, if we go down the path of we have to have absolutely one hundred percent data on a hundred patients, there are ways to do that but I don't feel that is a appropriate. That is my position. I don't feel that is appropriate at this time in the field. I think it would have a chilling effect on the field that wouldn't be justified to date by any of the complications so far found. You know, the idea that we need to report is fine, but are we talking -- I am okay with a survey instrument approach. If Dr. Champlin is saying he doesn't agree with the survey instrument approach and that there has to be a nurse practitioner or a physician, then that has to be discussed.

DR. CHAMPLIN: I guess my concern is that the survey is likely to provide such fuzzy information that it won't really be useful. But

the more practical thing is to have somebody calling and interviewing patients in a very abbreviated format. One of the real problems with all these kinds of things is that an organization forms and now they want data, and then next year they want more data and they want even more data, and you get new questions and you get excited about collecting the data and before you know it you have a book that you have to submit each year on every patient. So, the postcard idea is something that appeals to all of us but realistically it needs to be like a one-page kind of form and beyond that it really does become onerous.

DR. SALOMON: I certainly agree that a postcard may not be quite the right image I wanted, but a single page format.

DR. CHAMPLIN: I also made a comment earlier that, needless to say, you know, dead patients don't return the postcard and so there has to be some other mechanism to contact people to try to really ferret out if there is anything serious going on.

DR. SALOMON: So, would you go on with saying that there should be certainly a good faith effort on the part of the sponsor to account for a

hundred percent of patients enrolled?

DR. CHAMPLIN: Yes. The other issue is we are sort of looking at a couple of different issues. There is the sort of generic long-term side effects issue that can be handled to some extent with a sampling where you wouldn't necessarily need to have hundred percent compliance in terms of data reporting to at least have meaningful information. On the other hand, you do want to have early data on an individual product. So, to try and look is there an issue of CMV promoters, you know, it wouldn't be necessary to have a hundred percent in all gene therapy trials and twenty-year follow-up to address that issue. So, a good faith effort wouldn't necessary need to include a hundred percent of patients in terms of the ultimate delivery of the data.

DR. SALOMON: I think what I have heard from a number of people, not just today but also today, from sponsors, the comments from Schering-Plough and from Doug Jolly and his experience at Chiron, is that if we do this and we do a good faith effort, we are not going to get a hundred percent compliance. It is definitely not a true sampling strategy because it is not random,

but it is probably what we have to be realistic about getting, and it will be valuable but it might not be invaluable.

So, we are at the point here where I think we have defined about as much as I think we can define and be responsible at this point, with no commitment from the NIH or Congress or FDA to fund this sort of thing.

DR. SIEGEL: You said you were going to get back to the issue of whether it is twenty years.

DR. SALOMON: Yes, I thought the premise we went through this was define what it is and we will talk about time. So, I just want to make sure that the committee feels like we are done with that process, and also that you and staff feel that we have addressed it in detail.

DR. SIEGEL: Then the other issue that I am not sure is still on the table or whether we have heard all the comments we are going to from this group, is whether there is general guidance about if and when, and how often or whether archiving of specimens -- we have heard about the difficulty after a year. We have heard about people in general coming back to the study site

after a year, for example, and, indeed, we know the difficulties we would have in archiving stuff. But from a scientific perspective, if the thinking is that this is not one of the more critical pieces, and I think I heard just a general comment from Dr. High that she would be more worried about getting general information or focused information after twenty years than a lot of detailed information over that three to five year period, or one to five year period.

So, we are now faced I think with one of the questions we are going to need to decide in the future for retroviruses, where current guidance asks for this sort of information and other areas where it doesn't is, is this not only unrealistic but not all that critical or not worth trying for, and we need to look for other ways to do that?

DR. SALOMON: The way I am thinking right, and again the group can modify this, but the way I was thinking about it is finishing this cycle of what we think is a phase one where all gene transfer vector patients should give you this data. Then, when we are done with that, signed off, we are clear and done, then we could stop and say, now let's go to the general advice, and relax and not

feel like we are burdening the field with everything we say, and talk to you about sampling issues and retroviral vectors. Are we okay with that?

I think right now all of us on the committee feel a heavy pressure to be very clear and specific about what we feel is practical and responsible for a developing field to address, you know, all the constituencies -- regulatory agencies, the public, the patients and our ability to do investigator-sponsored research. That is what we are trying to do now. All right, fifteen, five, ten years, twenty years, life? What? A resounding silence here! Dr. Rao?

DR. RAO: Since nobody was willing to give a number, I thought I would start the discussion at least by saying it seems that fifteen years maybe a reasonable number to consider.

DR. SALOMON: I personally would second that. I think twenty years is just an additional five years with an extremely small yield but really expensive; and ten years, I think there would be enough examples of people saying, gee, a lot of stuff happens at twelve and fifteen. Why did you stop? Fifteen kind of crosses those both off.

DR. MULLIGAN: I think so too, for no good reasons.

[Laughter]

DR. CHAMPLIN: The signal to noise ratio becomes untenable as you get further and further out. So, I think a happy medium is fifteen years.

MS. KNOWLES: That is a long period of time, I think it is probably appropriate.

MS. LAWTON: Yes, I think fifteen years is a reasonable period as well.

DR. SALOMON: So, I think you have consensus on that issue as well. I think we are done with this portion. We could try, if you want to do more for five years or for one year, and all that, but I think that this is good enough. Fifteen years of follow-up. Everybody can be followed up. It is all going to go into the database. It will give you big things like cancers and autoimmune diseases and unexpected hospitalizations or unusual drug occurrences. I think for a first phase, again without really any reassurance from anyone that they are going to fund this, I think that is pretty good.

DR. BISHOP: Certainly, I think fifteen years will capture all the examples that we put

into the briefing document for all the four clinical areas that we have. So, it certainly would be encompassing from this perspective at least in the discussions that we have had.

DR. CHAMPLIN: I don't want to burst the bubble but, you know, there is an example of the later malignancies but I still think it is going to be a small frequency and it is going to be a lot more work than it is worth to ferret out these very late cases. So, this becomes sort of a reasonable compromise of resources for the return that you will get on those resources.

DR. SIEGEL: Are there examples of later malignancies that don't occur earlier than fifteen years?

DR. CHAMPLIN: I was thinking of the radiation-induced solid tumors that peak around twenty or twenty-five years after the exposure. They probably begin at some earlier point but their peak incidence is quite late. Leukemias and lymphomas are much earlier. That is the only example I can think of now.

DR. BISHOP: Testicular also, we came up with references at twenty-five years.

DR. SALOMON: I think I would speak for

the rest of us, just again from the gestalt of talking today and at previous times, that in a case where the NIH or Congress stepped up and said we are going to create a registry; we are going to really take responsibility for this sort of follow-up, I am not sure that this committee would object to indefinite follow-up under those circumstances but that is given a different practical set than we are faced with today.

DR. CHAMPLIN: The mechanisms, as we talked about outside of the meeting over lunch, often in these registries is payment for case report forms to cover the cost of actually doing the follow-ups and providing the information. So, that is the unfunded mandate that is sort of implicit in our recommendation. Right now there isn't a mechanism to really fund long-term follow-up. So, such an organization needs to be created with a mechanism to pay the people doing the work to collect the data.

MS. LAWTON: I am going to state the obvious again, and I know it was said earlier but I still want to say obviously we are saying fifteen years now. Fifteen years is a long time in the life of gene therapy and what we are going to

learn, and I think we do need to make sure that we have that regular review of the data that is in that database, what it means, what we have learned about the field, and we adjust our expectations of what is needed.

DR. SALOMON: I also think that we have a consensus that the message should be very clear to FDA that a big concern for this committee is the fact that investigator-sponsored research with the NIH is three or five years, and we realize that in agreeing to a fifteen-year follow-up we are doing so as responsible physicians, scientists, employers, members of the community but that it is implicit in our recommendation that the FDA stand ready to work with all the involved bodies, including NIH, general Congress, to obtain a better a solution in which funding is specifically put aside for these sort of mandates of long-term follow-up. It is the public that wants this; it is the Congress that wants this; and it is very appropriate for us to be very clear about saying that we have done our job today, and we are putting the onus back on government and regulation and Congress to come through with that sort of a funding process for us.

DR. SIEGEL: Let me reiterate what I have said before to reassure you in that regard, we recognize that that is just one of several practical questions that need to be addressed. Impediments for getting this done, from a pragmatic point of view of where the resources come from, and also some of the points that we have discussed of how you could do it, how to pose questions by the investigator, the sponsor, whatever, that needs to be addressed. And, those issues are under discussion and I hope will continue to be addressed.

There is a chicken and the egg situation here, where it is somewhat difficult to decide on mechanisms, funding and infrastructure to address a problem, to collect data without deciding what data you need. It is somewhat difficult to decide what data to get without knowing what the mechanisms are and what is possible.

So, we are going to come back from this committee with a recommendation to collect data for fifteen years, fully aware that NIH investigators are on a five-year cycle and we do not see as a solution to a problem to simply ask everyone to say, well, we are going to make a good faith effort

knowing full well those efforts are going to fail. So, we see this as a step to a complex problem whose solution is multifactorial and involves many parties, but I think is an important step that needs to be taken.

DR. SALOMON: I think, again, for the committee, we have agreed that to take this step forward was necessary, and we have gone as far as we feel comfortable doing in the absence of this sort of funding assurance. I hope that even though it will get out, well, they demanded fifteen years follow-up, I hope that it will always be with an intelligent look at what we are demanding for fifteen years.

So, that is settled, guys. Now can we relax and answer some of these larger questions as a discussion and not making the whole field responsible for our decisions? What Dr. Siegel wanted us to address would be specimen archiving, for example, and why don't we talk about retroviral and lentiviral vector systems specifically and more generically? How about comments on that?

DR. CHAMPLIN: I think even with retrovirus it is complicated. I don't want to dredge up another albatross from the past but the

PA317 issues are relevant to this I think because there is that question of the need to look for replication competent virus depending on what system you have, and I think we will actually get into that over the next couple of days too. So, putting that aside, I think that archiving retroviral or related products is important and will become more important when there is better gene transfer. Whether you are going to be looking for abnormal blood counts -- I don't know. Bone marrow transplantations would be a context where I think it is going to be important. Whether other in vivo applications of lentivirus vectors will be, I am not so sure. But I would just leave it that I would look at that as a very individualized case by case. So, the precise vector they have and we have some outline of the different issues with the retrovirus vector production systems; and the length of persistence anticipated of course. So, again, I think that having archival samples from a vaccine or something where you are just going to end up with dead cells, I don't think that is important.

But I do, I think this will be more and more important. I think that the risks of

retrovirus insertion and lentivirus insertion will probably raise their ugly heads at some point as we get more and more efficient, and it won't be replication competent virus but it may be integration, activating something or repressing something that will cause the cells to misbehave.

DR. SALOMON: I also agree. As a principle, I think it is very reasonable for two things. One would be appropriate specimen collection at several key points in the follow-up of the trial. I don't want to go to whether that is one year or two months, but at least several time points afterwards going out to at least the first, third, fourth or fifth year afterwards. I think in general, as you say, as we get more efficient gene delivery we should increase rather than decrease our concerns.

I think we should also be careful that for each trial we should specify -- we shouldn't be just random; we should be very specific. Peripheral blood collections are very appropriate in, let's say, ex vivo T-cell or hematopoietic stem cell involvement but I think it is absolutely useless in maybe something you are injecting into the liver or into the thyroid gland. I think at

times the simplicity of getting plasma and peripheral blood T-cells has overcome our good sense about their value. I think a good example of that has been xenotransplantations where, if you do an islet cell transplant and all they do is follow plasma, and are amazed that they put some cells in the brain and they didn't have any exposure in the peripheral blood and, therefore, the procedure was safe. I mean, how anyone can do that with a straight face is beyond me but that even gets published. So, I think we have to be very clear about what is appropriate here. In some cases it is very appropriate. So it shouldn't be just random.

The second thing, I think it should be mandated that if somebody develops an acute complication like a T-cell lymphoma or a tumor, that a really good effort be made -- it isn't always possible, but a really good effort be made to get tissue from that lesion, and that should be specified in the protocol approval, whether that be bone marrow or a leukopheresis unit, or whatever, in the appropriate disease.

Another question that came up would be seeking evidence for replication, retrovirus,

replication competent lentivirus in terms of long-term follow-up. How far should we go with that?

DR. MULLIGAN: I think there the issue is much more complicated because everyone has their best system and everyone thinks their system is safer than the next person's, and there are clearly differences. But the measurement of those differences is often tough or impossible. But I think certainly some of the things that are out there that are being talked about would be candidates for looking at it, continuing to look for replication competent virus. Alternatively, there are systems out there where I think it is probably not necessary at this point.

DR. CHAMPLIN: If you didn't see any RCR within the first five years, is there a reason to look as routinely beyond that point in a stable individual?

DR. SALOMON: I would think if you didn't see RCR in the first six months there would be no reason to look.

DR. MULLIGAN: Yes, I would say probably the best indicator of the need to look for it might be whether you have a certain level of gene

transfer, vector gene transfer too. That is, if you see nothing initially, probably nothing got transferred, helper or vector.

DR. RAO: It just really does seem to boil down to the fact that archiving seems to be specific for the protocol that you are going to be using, and the sample that you collect and the frequency at which you collect it will all depend on the protocol. I think the point that Dr. Salomon made is critical, that once you have indication of an adverse reaction, then you should have a clear-but set of samples that you need to collect or archive for that particular problem because that will give you a clue as to what might be happening. So, that should be clear-cut in the guideline. Even that would depend on the kind of problem you have because if it is a malignancy then, you know, you collect a certain set of sample; if it is another, you take a different sample.

DR. SALOMON: I think we certainly are not objecting or trying to suggest you go in a different direction with respect to your current thinking about approaching follow-up in a retroviral or lentiviral vector, that specimen

archiving is an appropriate request.

DR. CHAMPLIN: But for a limited period of time.

DR. SIEGEL: We will, of course, be discussing lentivirus in more detail.

DR. SALOMON: Just in terms of generically for the retrovirus. I think that we all agree -- I mean, whether it is a year or six months but I don't think you need a five-year specimen to look for replication competent retrovirus. That is all that we were trying to say, unless someone comes down with an acute lesion of some sort. Then you have to stop and start again.

How about things like bringing patients back for physical exams with the principal investigator? That was an issue that we left out of the details. Do we agree that there would be a need? I am just trying to address things that Dr. Siegel brought up earlier. Would everyone agree that there would be circumstances for a period of time, early to late, relatively late, that this would be appropriate, to demand that the sponsor to have hands-on contact with a patient?

DR. CHAMPLIN: During the first year I think is what I think we had talked about this

morning, it is appropriate, but beyond the first year you want to collect toxicity information, however you can get it, either directly from the patient or working with the referring physicians. But I don't think you necessarily need to have the person return physically to the center.

DR. SALOMON: Dr. High?

DR. HIGH: I was just going to say I agree with that, and I agree with the point that Dr. Champlin made earlier. It is really unusual for the sorts of complications that we are talking about to be picked up on a physical exam with an asymptomatic patient. The patient is going to be presenting in some other setting.

DR. SALOMON: One thing that came up was the concept that there should be sort of a national ID that, if you were in a gene therapy trial you should have a little card that says, "I was in this gene therapy trial" and maybe a number to contact. If you entered an emergency room for a complication you would sort of produce this, have it on your wrist, or something. Does anyone have any comment about that?

MS. LAWTON: I am not sure what that will do other than scare the patient so that nobody will

enter a gene therapy clinical trials.

DR. SALOMON: I think we are done unless there is anything else that you, guys, want to put on the table here.

DR. SIEGEL: Well, thank you very much. I think obviously as we anticipated, we don't have solutions to all the questions but I think we have a lot of very useful advice. We really appreciate the efforts.

DR. SALOMON: Any last comments from the committee? And from the audience?

MS. TICE: I just have a question. How are you going to determine relatedness fifteen years down the line and you only gave one dose? Fifteen years is an awfully long time and you are going to go back and try to determine relatedness. I think you have to think about this.

DR. SALOMON: I think, in Dr. Patterson's words, there are experts. We have one at the table, Dr. Gaylor, who is really trained to figure out what are statistically appropriate connections to be made with data from patient groups. I don't think that the committee's expertise is there. We encourage that as part of the consultation process with the different agencies and with the rest of

our community to establish that kind of detail, but we do agree that it is fair. I am sure there is an incidence of cancer, and autoimmune disease, and hematologic and neurologic diseases out there, and there are all kinds of sampling errors that we have already articulated, and we absolutely agree with that I think, and we will defer to other experts. Dr. Gaylor, do you agree?

DR. GAYLOR: Yes.

DR. SALOMON: I thank everybody for today for a good job and all your attention and input, and I will see you here tomorrow at 8:00.

[Whereupon, the proceedings were recessed at 2:30 p.m., to be reconvened Thursday, October 25, 2001 at 8:00 a.m.]

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CERTIFICATE

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

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