Food and Drug Administration
Center for Biologics Evaluation and Research

59th Meeting of the

Cellular, Tissue and Gene Therapies Advisory Committee

February 26, 2014

Hilton Hotel
Grand Ballroom
620 Perry Parkway
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PROCEEDINGS (8:04 a.m.)

Agenda Item: Opening Remarks, Conflict of Interest Statement

DR. SNYDER: Why don't we get started?

When last we left our heroes, they were poised, answering the following question -- before we can get started, we have to hear the conflict-of-interest again.

MS. DAPOLITO: Patience. Bear with me. Thank you.

This announcement is an addition to the conflict-of-interest statement read at the beginning of the meeting on February 25 and will be part of the public record for the Cellular, Tissue and Gene Therapies Advisory Committee meeting on February 26.

The committee will continue to discuss topic I, oocyte modification in assisted reproduction for the prevention of transmission of mitochondrial disease or treatment of infertility. This is a particular matter involving specific parties.

For topic II, the committee will hear updates on guidance documents issued from the Office of Cellular, Tissue and Gene Therapies, the Center for Biologics Evaluation and Research. This is a non-particular matter.

For topic III, the committee will discuss considerations for the design of early-phase clinical

trials of cellular and gene therapy products. This is a particular matter of general applicability.

Based on the agenda and all financial interests reported by members and consultants, no conflict-of-interest waivers were issued under 18 USC Subsection 208. Dr. Jane Lebkowski is serving as the industry representative, acting on behalf of all related industry, and is employed by Asterias Biotherapeutics in Menlo Park, California. Industry representatives are not special government employees and do not vote.

With regard to FDA's guest speakers, the agency has determined that the information provided is essential. The following information is being made public to the audience to objectively evaluate any presentation and/or comments. Our speakers from yesterday, Drs. Dieter Egli, Mary Herbert, and Shoukhrat Mitalipov, have associations with firms that could be affected by the committee discussions. There may be regulated-industry speakers and other outside-organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interests of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflict of

interest.

This conflict-of-interest statement will be made available for review at the registration table. We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships you have with any firms, its products, and, if known, its direct competitors.

Thank you.

Again, I would just like to say that the media contact is Ms. Jennifer Rodriguez, who is over there waving her hand. Thank you.

DR. SNYDER: That was just in case anybody started a business overnight.

What we're doing is winding up the discussion of topic II. Just to refresh your memory, that question was: Please discuss the potential risks of mitochondrial manipulation technologies to the women with either mitochondrial disease or infertility and to the resulting children.

At the time we were getting last bits of summary

comments from going around the table. I think we had left off with Dr. Cripe.

Agenda Item: Committee Discussion of Questions (cont'd)

DR. CRIPE: Despite having slept overnight on it, I did not come up with any other important points that haven't been already articulated well.

DR. SNYDER: Dr. Emens?

DR. EMENS: I agree with all the prior discussion as well.

DR. SNYDER: Dr. Bugbee?

DR. BUGBEE: First thing in the morning, I came up with one question. As far as the child that's part of this trial, after hearing the complexity of phenotypic expression of mitochondrial disease, I think there should be some safeguards to the child. Any symptom, illness, or anything the child presents with, would it have to be worked up for mitochondrial disease or do we have enough knowledge about that that we could tell this individual that every cold or every muscle cramp is not a manifestation of disease we didn't previously know?

So that would be one thing that the trial would have to address.

DR. SNYDER: Dr. Cedars?

DR. CEDARS: The only thing I had to add has to

do a bit with efficiency, and in terms of risk to the woman. Because this requires an IVF process, I think the efficiency of the IVF process itself is relevant, because it has to do with how many cycles of stimulation and retrieval the person might undergo. I think there's a lack of awareness that even in young, fertile women, each egg only has about a 10 percent chance of leading to a live birth. If the efficiency of the system diminishes that even more, I think there needs to be an awareness of what that might involve and the number of cycles that might be required to move forward and be successful.

DR. SNYDER: Great. Dr. Cohen.

DR. COHEN: All my comments will be made in the next session about clinical trials and the design.

DR. SNYDER: Great. Thank you. Renée?

DR. PERA: I didn't have any additional comments.

DR. SNYDER: Carmen?

MS. BUSTILLO: I didn't have many comments either. I agree with Marcelle. I think we have to be very clear about the efficiency because of the repetitive nature, perhaps, of the procedures the patients might have to undergo.

DR. SNYDER: Okay, great.

To help flesh out the discussion before I kind of summarize what the sense of the meeting was, Dr. Hursh

wanted to make a few comments concerning certain aspects of diagnosis.

DR. HURSH: There was one thread that I picked up on yesterday. People were saying, why would you do this procedure if you could actually determine that a woman had good oocytes by PGD? I think Dr. Herbert addressed that in her talk yesterday. There are women with a level of heteroplasmy in which PGD would be useful and predictive, and there are women whose level of heteroplasmy is so high that you cannot assume they will have any normal eggs.

So as we go forward to enrollment, I just wanted to make that distinction so that people understand that that might be a useful thing to think about. Maybe Dr. Herbert would address what level of heteroplasmy -- if that could be addressed -- you would think would be appropriate for enrollment.

DR. HERBERT: For a homoplasmic woman, she’s not going to have any normal oocytes. All of her oocytes would be affected. That’s a definite. For women with high levels of heteroplasmy, it may vary between mutations -- I think other people might be better qualified to talk about that than I am -- but you have a reduced chance of getting normal oocytes with high levels of heteroplasmy, we can say. We have had patients for PDG who had no embryos to replace because they were all affected.

DR. SNYDER: Go ahead.

DR. MITALIPOV: There have been a few cases of PDG done, especially with MELAS. The issue is what percentage of heteroplasmy is safe. I think at this point it's not clear. There has been a recommendation of maybe 30 percent and lower. But many patients now realize that even that's not safe, because the child, after even 30 percent detection at the PDG, may have higher after birth. So they are actually opting out by 5 percent lower. In most cases you're not going to have an embryo with that low heteroplasmy.

So that's a limitation of PDG. Even if you could select, you could never select low enough the heteroplasmy that would be safe for the child or the next generation.

DR. PERA: Can I just comment on that? I don't know how good that data is. I would actually really question that data. I think that if you look at a population, there should be some level of heteroplasmy that is safe. I have heard also that most people have some heteroplasmy. So that seems unreasonable.

But I would agree on the homoplasmy that if a person has complete penetrance, that would seem to be a reasonable thing.

But it would seem to me that there would be some need for some research on the levels that might be

acceptable.

DR. KEEFE: There are actually two papers in the last two years that directly address this. One is from Treff and Scott of RMA in New Jersey, where they had a single case, where it was a woman with MELAS who had 40 percent in her leukocytes. The heteroplasmy level in her eggs varied from 9 percent to 90 percent. They were able to find in trophectoderm a very low level and transfer a boy. So they used it for sex selection.

The other case is more of a review. It's a modeling paper from the group in Maastricht in the Netherlands. They looked at pedigrees of women that had a variety of different mitochondrial DNA diseases. They had a number of cutoffs. This was not using PDG data, but it was modeling what would be predicted based on what the kids were and what the mother was. They argued that a woman who has 18 percent or less heteroplasmy has a 90 percent chance of having a child that was unaffected. Of course, it's a sliding scale. It depends a lot on the specific encephalopathy.

It might be helpful to get those papers distributed. They are published. People can go online now and pull them up.

DR. SNYDER: Do any of the speakers have any comments they want to add? Go ahead, please.

DR. DIMAURO: Just a brief comment. I think we have to be clear when we talk about heteroplasmy about which tissue we are talking about. If you talk about blood leukocytes, that's extremely non-representative of other tissues. In fact, it has been shown repeatedly that if you compare the heteroplasmy in leukocytes and in urinary sediment, another very easily accessible tissue, the difference is huge sometimes. You are much more likely to detect a substantial level of mutations in urinary sediment than in blood.

So we have to be clear what tissue we are talking about.

DR. BUGBEE: Can you clarify, then? If someone presents with some clinical signs of encephalopathy, do you have to do a brain biopsy to determine the heteroplasmy in the brain tissue? How do you diagnose that?

DR. DIMAURO: Not quite. Fortunately, muscle is a very good representative, apparently, of the mutation level. I'm not saying the muscle represents brain necessarily, but muscle gives you a very good idea of risk of developing the disease.

DR. BUGBEE: So back to my original statement I made. If someone presents who has been in this trial who has some symptomatology that may be ascribed to mitochondrial disease, you can simply do a muscle biopsy

and get the information that you need to tell this individual whether or not they may be at risk or have mitochondrial disease. Is that correct?

DR. DIMAURO: That's in fact what we do. I am a great advocate of muscle biopsy. Yes, it is invasive, but minimally so, really, and it gives us a lot of information about diagnosis.

DR. BUGBEE: If I may ask one more question, back to this discussion topic II, this child that's in this study as a recipient could have a muscle biopsy at an early age -- one invasive procedure -- and you could have the information you need to understand the risk of that or the success of the treatment. Is that correct?

DR. DIMAURO: As I understand at least the preliminary data from the treatment, hopefully that would not be necessary. But, yes, that would be an extremely cautionary measure to reassure ourselves that the child has in fact almost no mutation road.

DR. SNYDER: Do any of the other speakers want to make any comments before we summarize?

(No response)

Okay, good. I'll restate the question, but what I will do is -- Dr. Gearhart did do his homework assignment and came up with a way that he and some of his colleagues would suggest we rephrase a lot of these questions. So

I'll just throw that out there. It doesn't necessarily need to be discussed. It talks about trying to capture more accurately what it is that these procedures do.

The question as written is: Please discuss the potential risks of mitochondrial manipulation technologies. What Dr. Gearhart would suggest is that, rather than simply calling them mitochondrial manipulation technologies, we describe them as "spindle and pronuclear transfer technology in assisted reproduction for prevention of transmission of mitochondrial disease" -- or a shorter way of phrasing it, "oocyte and embryo manipulation for the prevention of mitochondrial disease."

Regardless of how I read the question, if you prefer, hear this in your mind, as to the way it's being phrased.

The question for topic number II that we just completed discussion was: What are the risks of these procedures to the women with mitochondrial disease or infertility and to the resulting children?

Again, I'll try to summarize what I thought the sense of the meeting was and what the committee felt.

With regard to risks to the women -- and the reason why this will be important is relevant, obviously, to the next question, which is going to be dealing with how one would actually design a clinical trial that takes these

risks into consideration -- risks to the women here would be the standard risks of IVF technology, which include ovarian hyperstimulation and the recognition that there can be variability of efficiency of these procedures, even in young, fertile women who sometimes have to undergo many cycles. There may be some psychological issues, as well as medical issues, in the pressure to give informed consent to become pregnant, perhaps in situations where a woman with these diseases actually should not be. So there may be some psychological vulnerability to give consent -- everything ranging from feelings of guilt when they should actually not be doing this and a lack of appreciation of what the real risks are -- and then the actual risks of pregnancy, which may actually be even greater in a woman who carries a mitochondrial disease.

Then there are the standards risks of pregnancy, which can include preeclampsia, which may be greater in this population.

Then it was brought out that there are even risks of being enrolled in a clinical trial:

• Sometimes these women can become quite sick, particularly if they have a disease and are undergoing pregnancy.

• Subjecting a woman to procedures who is actually at low risk for giving birth to a child with these

mitochondrial diseases.

• Conversely, subjecting a woman who is already sick from these diseases to even greater risks.

• The risk of cryopreservation of the gametes, which is still a bit unknown.

In terms of risks to the fetus:

• It was brought out that there's the risk of aneuploidy.

• The risks of aberrant imprinting.

• The risks of decreasing the number of mitochondria or manipulation of the number of mitochondria. Right now it's unknown exactly what the proper number should be.

• The risks of actually undergoing PGD.

• The risk of some health issues that are actually unrelated to mitochondrial disease as being attributable to the mitochondrial disease or to the procedure -- that new diseases could actually emerge in the fetus as a result of the manipulation, everything from microtubule abnormalities to the influence of the Sendai virus extracts.

• Ultimately -- and this gets into the child -- whatever the psychological burden might be of a child with the knowledge of having been selected one way or the other or having been in a clinical trial or been part of an

experiment.

Once the child is born, it was brought out that, particularly if they do have some degree of the mitochondrial disease or as a result of the manipulation, there could be subtle problems noted in behavior, everything from developmental delay to subtle developmental problems, to autism, to exercise intolerance, ranging all the way to some fluoride(?) problems, like major cardiomyopathy.

It was thought that one strategy that could be used to try to minimize these risks would be careful screening of the donors, very sophisticated informed-consent procedures, and also very sophisticated and detailed genetic counseling, ensuring, since a lot of these problems may not manifest until much later on, that none of the study subjects -- particularly the kids, but also the women -- are not lost to follow-up, and this very long-term follow-up.

There was, finally, a debate over the degree to which PGD could be predictive and whether this was influenced by the degree of heteroplasmy. For example, it was cited that if PGD did determine that there was less than 18 percent heteroplasmy, there might be a greater than 90 percent chance that the offspring would not be affected. But this is a matter of debate and requires further

investigation.

The last point, in terms of strategy, is knowing which tissue to assay that would be most predictive of the impact of heteroplasmy, and muscle might be one of the most informative tissues.

Did I get anything wrong? Did I miss anything? Should we add something?

DR. KEEFE: Not exactly wrong, but just a refinement of the issue of PGD versus this procedure. The concern is that a woman could be led down the primrose path towards a procedure that's experimental, missing the opportunity to pursue an established procedure -- relatively established -- that may have fewer of the concerns. The specific data is that in a muscle biopsy showing 18 percent or less heteroplasmy, there's a 95 percent chance that, with nothing, her kids will be fine, that she will have a normal kid, through IVF and PGD. That's the data.

So the concern would be, if you willy-nilly established a protocol, many participants may pursue this and neglect a presumably safer and more established procedure. I think it's a slightly different point than what you made with the PGD issue.

DR. ROSE: I actually have a question about that. You said that was a model. Has it been shown with patient

and clinical samples -- i.e., really a validated diagnostic test that can be relied on in the way that you would normally rely on a validated diagnostic?

DR. KEEFE: Specifically -- and, again, I refer this to anybody who is interested; it's *Human Reproduction Update*, July 2012 -- the model is using pedigree. So if anything, by introducing PGD into the equation -- these are just women that did have families. They didn't introduce the PGD variable, which, if anything, would confer additional sensitivity to eliminate. Women with 18 percent or fewer levels of heteroplasmy in muscle biopsies had a 95 percent chance of having unaffected offspring.

The only modeling is then implying that if one then did PGD, one would have a very, very high probability of identifying normal embryos. These are women who just went out and had children, and 95 percent of them had normal children. So presumably, then, it's not such an extension of the model to then say, if we had done PGD on them, we would have -- in fact, if anything, we might have even had a higher percentage, because presumably not all the eggs are used in natural reproduction. So that's the extension of the model.

Again, I refer you, if you want to pull it up on your smartphone, it's Helabrakers (phonetic) et al. in *Human Reproduction Update*. I think it's the most

comprehensive.

Then the other one is *Fertility and Sterility*, 2012, with Tress (phonetic) the first author, where he just had one pedigree, just one woman.

DR. ROSE: I understand what you're saying, and that's a great piece of data. But there's a lot of work that has to go into making it a clinically validated test that you can rely on for diagnosis and going forward. We have seen a lot of things that look really good based on that type of data that, when it gets out to widespread use, turn out not to be the case.

DR. KEEFE: No, I wouldn't imply that we should willy-nilly just apply this uniformly. My bigger concern about the clinical trial would be to suddenly enroll a number of women who had relatively low levels of heteroplasmy -- sort of easy hits -- who then are led into a trial without even considering the opportunity. What I have heard so far -- it's controversial, it's not clear. You're right, there's a lot more work to be done.

But if you weighed the balance of the evidence, it suggests that there is some value. In fact, the conclusion of everyone that I looked at over the last five years is that it's very promising, the idea of it -- by no means done, but promising. The concern about a trial would be to -- it's very controversial, right. So therefore come

into our trial. It would be very important to lay out that explicitly.

That's my point.

DR. EMENS: Just to add a little bit more perspective about the muscle biopsy, can you explain what is involved in that? Is it a core needle biopsy? Is it incisional biopsy? How invasive is it?

DR. DIMAURO: In our experience, frankly, there is not much difference in either pain or risk in doing one or the other. But a needle biopsy would be certainly sufficient.

DR. SNYDER: Yes, Dr. Herbert.

DR. HERBERT: Can I just make two points? One is in relation to the burden of being the chosen one, in relation to the risk to the child. In every IVF procedure, we choose one or two embryos from the cohort. So every IVF child has the burden of being the chosen one.

The other issue is, no woman would be forced to have this treatment. It is an option. It will be offered as an option to those who wish to have children, in order to reduce their risk.

DR. SNYDER: I didn't mean to imply that anybody would -- what was brought out by one of the committee members was the self-imposed psychological pressure to try to do something to minimize the risk of your kid, which is

standard in any kind of clinical trial. A mother or a family sometimes feels that they are letting the family down if they don't do something, sometimes putting themselves at unnecessary risk.

I can’t remember who brought that out, but that was one of the points.

DR. WENSTROM: When I said that, I was thinking about the MOMS trial. I was a surgeon for the MOMS trial, which was a trial of prenatal surgery for spina bifida. In recognition that a lot of parents would feel compelled to do this procedure, which was of unknown benefit and involved a lot of risk, they had to undergo a huge amount of psychological screening and counseling, and meet with an ethicist. I think this could be easily adopted for this kind of research.

DR. SNYDER: We actually have seen that in a lot of these clinical trials. As a pediatrician, I see this. The family sometimes does feel this burden. Particularly the mothers take on the burden greater than any of the other family members.

Any other aspects that we should discuss before putting closure to this question?

(No response)

Before we move on to question number 3, we want to have Dr. Steinbock discuss briefly some of the other

underlying issues that kind of attend everything that deals with the topic that we're discussing, which is spindle and pronuclear manipulation or manipulation of the oocyte and the embryos.

DR. STEINBOCK: I understand that the mandate of the FDA is safety and efficacy, risks and benefits. But I would suggest that it's difficult to talk about risks and benefits unless you characterize what it is you would be doing. There seem to be at least two conceptualizations of this proposed therapy.

There was a newspaper article. It quoted Dr. Mitalipov as saying, we're reversing them back to normal, so I don't understand why you would be opposing that.

That's one way of characterizing it.

The other way of characterizing it is to say, as it also says in this newspaper article from *USA Today*, 15 years ago, the United Nations endorsed a global agreement prohibiting scientists from altering the human genome.

We had a little bit of discussion yesterday about whether it is altering the human genome, whether it's altering the human genome in a way that's different from just ordinary sexual reproduction. How you characterize what you would be doing, I think, definitely could influence your analysis of the risks and benefits.

As a philosopher and a bioethicist, it seems to

me that it would be a good idea not to just pretend that this issue doesn't exist, but at least to lay it out, even if this is not something that the FDA feels is within its purview to resolve or settle.

DR. SNYDER: Is there any discussion of the points that Dr. Steinbock brought up?

DR. WOODRUFF: I guess I would concur with that generalization, that there are two camps here. One of the reasons I called for a consortium yesterday was different from the call for a consortium for bringing patients together and bringing research together, which is really critical. But the notion here is that there are prohibitions globally around interventions. And there are NIH restrictions, under the purview of the Dickey-Wicker. So this would necessarily stand outside of the purview of ordinary review. I think FDA would have to work within that guidance as well.

I have a hard time, as I read questions 3 and 4, even understanding through what prism we could discuss these, given those overriding, framing governmental and, even beyond that, humanist kind of view of the topic per se. There would be value in the exercise, perhaps. But I think by going down this path, we kind of move towards one of those two goals, rather than asking if this is even something that, globally, we should be even talking about.

The last sentence was really not correct. I think we should talk about it, but I think that talking about it in the context of what a clinical trial would look like is different, because the prism through which we can do this is at a completely -- it's diffracting in a very different way. Under Dickey-Wicker, under UN, under US federal law, you can't really necessarily get to questions 3 and 4.

DR. SNYDER: I think probably, with regard to Dickey-Wicker -- and officials from the FDA can clarify that -- as long as you're not using federal funds, then it's okay.

DR. WOODRUFF: Correct.

DR. SNYDER: In that sense, all of assisted reproduction violates Dickey-Wicker.

DR. WOODRUFF: Not for research, if you are doing it not in the context of research. I do think that Dickey-Wicker does provide the opportunity for research to occur if you have funding elsewhere. If the FDA, though, then gives guidance on how to do a clinical trial that includes the production of embryos for research, which -- there's almost no way you can do a clinical trial and say that every embryo is going to get transferred -- I don't know.

DR. SNYDER: Correct me if I'm wrong. If the clinical trial was funded by a private entity, then it

still would need to be approved by the FDA, but it's not using government funds, and therefore doesn't come under Dickey-Wicker, whether it's research or a clinical intervention.

DR. WOODRUFF: That's true, as long as then we decide the other issue, which is that this isn't just IVF. How do we think about moving the spindle, and where does that fit within the purview of what we have decided to do or not do?

DR. SNYDER: I guess this is where we do have to get back on topic. We decided that what we wouldn't do is talk about public policy or the ethics. I think we need to recognize -- and as many of the letter writers from the public pointed out -- and we all saw some of those -- some people will make the point that -- even though our charge is to talk about the scientific and clinical aspects of this, some of the letter writers and speakers said it's impossible to divorce it from the social and public policy and ethical aspects of it.

Having acknowledged that, I think probably what we should get back on track is -- let's assume that we will now be able to do a clinical trial, under some type of guidance and restrictions. Scientifically, what is the best way to design a clinical trial such that we get the most information with regard to safety and efficacy, while

minimizing the risks to participants?

DR. HURSH: I think we just want to clarify that the Dickey-Wicker amendment does not affect anything the FDA would do. It is true that the trial couldn't be funded by NIH, but I don't think anyone is contemplating that. Really, the FDA could be confronted with this, whether Dickey-Wicker exists or not. As I said and Dr. Witten said, we acknowledge that there are many, many larger issues, and we're very eager to see those discussed. But it doesn't get past the notion that this could come forward and we would have to make some decisions about it.

DR. STEINBOCK: If I understand what you are saying, the framing of this would be: Bracket the question of whether this is germline therapy or manipulating the human genome or conventional treatment. If you bracket that question, what would be clinical trials that would be well designed and give us the most information about safety? Then perhaps somebody else can say, regardless of the safety issues, we have to decide whether this is something we should be doing or not.

Is that what you're suggesting?

DR. SNYDER: Right. Hypothetically -- and we'll see as the discussion unfolds -- it could be that somebody says that the only way to be able to assess whether you have put the fetus at risk is to do X, Y, or Z. Yes,

that’s the ideal way to do it. We simply cannot do that. That would be the point and then the counterpoint or the caveat to that.

I think first we should probably get out the science. What would be the best-designed clinical trial? Then we can see whether that’s in any way feasible or acceptable, quite frankly.

One of the issues -- I think it actually comes up more in the afternoon, and I don't mean to link these two -- what kinds of controls do you use in a clinical trial? I think this will come up in the afternoon session. There’s a divide between how the Europeans view controls in a clinical trial versus how the Americans view controls in a clinical trial. Americans feel very comfortable, for example, with sham-operated controls. The Europeans really do not like doing that and do not include that in their clinical trials.

So there’s an example of where we can talk about the best procedure for getting the most information, then decide whether that is within our comfort zone.

DR. WOODRUFF: A point of clarification. For the clinical trial, then, are you saying that the clinical trial could be actually parsed, so that the first part, which is the intervention and the embryo quality, could be a clinical trial, without then the burden of having to

transfer any embryos. So the trial design today really doesn't have to worry about next generation. It can be bounded by just what the outcome is of the procedure itself, with the assessment of the embryo as the clinical outcome.

DR. SNYDER: It's your clinical trial, so you can design it the way you -- it could be that you feel comfortable with a clinical trial that ends right there, and Steve might say, no, I want to go for the whole enchilada.

DR. WOODRUFF: And is the whole enchilada morally based, because you think it's ethically incorrect to make an embryo to assess the clinical value of the interventions, and therefore you have to transfer? Or you think the only endpoint for a clinical trial would be a live healthy birth?

DR. SNYDER: I think this will be part of the discussion. Let's move on to question number 3. This is what a clinical trial would actually look like, which, for Steve, may include long-term follow-up of these kids until they collect Social Security, or something like that. We'll see.

Let me phrase question number 3. We'll have three discussants. I can already tell that this is probably going to bring us up to the break.

With apologies to John, I am going to read the question as originally written, but in your head you can hear the way John would prefer it be phrased.

Please discuss the following elements of the design of first-in-human trials to assess the safety and efficacy of mitochondrial manipulation technologies to prevent mitochondrial diseases in children of affected women and to treat female infertility.

There are actually five parts to this question that we have to address. Hopefully, when we go around the room, the speakers will address all of these.

The first one deals with enrollment criteria for a clinical trial. Major enrollment criteria: For example, for trials to prevent transmission of mitochondrial diseases, eligibility criteria might limit enrollment to (1) women with specific mitochondrial DNA mutations, clinical manifestations, disease severity, extent of heteroplasmy, or other factors. Selection of only male embryos to transfer might be an option to minimize the risk of transmitting mitochondrial disease to subsequent generations.

So the first part deals with enrollment.

The second part deals with controls, either concurrent or historical, that should be included in trials to provide evidence of safety and efficacy.

The second part of the question is controls.

The next is how one monitors for safety and efficacy during fetal development, in the perinatal period, during early childhood, and thereafter. In addition, for trials to prevent mitochondrial diseases, female children, but not male children, could transmit a mitochondrial disease to future generations. Safety monitoring could be extended to subsequent generations of female children.

So the third part of the question is monitoring.

The fourth part of the question is informed consent for inclusion: Any measures, including but not limited to assent or informed consent of the children, that might be necessary for the ethical conduct of long-term follow-up of the children and subsequent generations of any female children.

The last part is, how does one measure efficacy?

Just to recap, the five parts that we're hoping will be addressed when you make your comments are enrollment criteria, controls, how you would monitor, what informed consent would look like, and how you know whether the intervention has been efficacious or not.

To kick off the discussion, we have three discussants: Steve Goldman, Marcelle Cedars, and Bruce Cohen. We'll start with Steve.

DR. GOLDMAN: This one's a challenge. To design

a clinical trial in this setting, with all the variability and all of the issues we have discussed in the last day and change, is, I think, to all of us going to be quite a challenge.

To try to clarify things up front, our mandate includes defining a trial design for both infertility -- for the use of mitochondrial addition or supplementation in infertility -- as well as the use of pronuclear transfer, spindle transfer for treatment of mitochondrial disease. These are so different. We're talking about, obviously, entirely different disease indications, settings, and likely designs. At least for present purposes, I would like to break them apart and, to start the discussion off, restrict comments to the treatment of mitochondrial disease. I think the use of cytoplasmic transfer, mitochondrial transfer, in fertility is -- again, such a fundamentally different design would then be elicited in terms of a trial that that's best set aside.

Evan, I suppose it's up to you. We can then go and revisit it as a separate discussion or integrate it with comments from subsequent discussants. But I'll try to restrict my comments to potential clinical designs in the treatment of mitochondrial disease.

Any clinical trial is best done -- I should say, perhaps most easily done -- where one has a relatively

predictable disease in terms of its natural history, with relatively well-understood mechanisms, with relative homogeneity in the disease populations, and therefore some predictability in terms of age- and gender-dependent symptomatology. Of course, you would like this relatively homogeneous, relatively understood, relatively predictable disease to be fairly common so that, of course, you have large enough sample sizes in both experimental and control groups. And you would like to have very well-understood and clearly defined quantitative outcome measures.

The challenge here is that essentially none of those points is really the case in mitochondrial disease, and so we're dealing with all those as essentially suboptimal variables.

How to accommodate a design that permits the degree of disease variability, individual case-to-case variability, unpredictability, and also the protracted time course of the disease -- those really become our challenges.

To start off with, in terms of defining inclusion criteria -- because, of course, it's the study population that everything else flows from -- very often in clinical design, trial design is a question of going with relatively severe cases so that one can make a case definitively one way or the other in terms of whether something is affording

benefit, or going early in disease course or with relatively less symptomatic cases to achieve greater potential benefit, although not necessarily as easily detected. I think in this case, given all of the variability, and especially the lack of predictability on a case-by-case basis, more severe cases would really be the preferred, in that we would have a much better sense of whether or not a therapeutic outcome was achieved.

Who would those most severe cases be? How can they be defined in a setting where a trial is doable? Of course, we can look at many of the adult-onset disorders and say they may be severe, but they are, of course, very extended in time course. Do we really have the luxury of setting up a trial where we may not have any observable endpoints until 20 or 30 years out? I think most of us would agree that that's not optimal. So it's really the early childhood manifestations or those cases presenting in early childhood that would be the most appropriate.

Then, if one is thinking in terms of Leigh's or Kearns-Sayre or MELAS, essentially dealing with the most severe of these with the earliest presentations, we can start to define specific mutations that would then be essentially admitted into a trial.

If we do have that capability to say, okay, these are the mutations that are known at this point that will

most predictably yield the greatest disease symptomatology at the earliest time points in postnatal development, then I think we can at least start to define a potential patient population.

Then how to define, of course, those cases. That becomes essentially literature-based. There are so many of these mitochondrial disorders that are still being identified with novel mutations that I think it becomes problematic in terms of taking all comers based on disease symptomatology -- for example, if a given case of MELAS arises, even with siblings. Unless we have some larger basis in terms of the appearance and predictable severity of that mutation, I don't know that that would be an appropriate family.

Again I'm stressing the importance of what is already out there in terms of known mutations, with known, very early disease symptomatology of some severity.

Then how do we define appropriate cases in terms of degree of heteroplasmy? If these cases are being identified either up front on the basis of maternal pathology or symptomatology or, in sporadic cases, with the children presenting, then it becomes a question of sibling diagnosis. It becomes a question of which target cell population to look at in terms of defining heteroplasmy. Let's say, just for simplicity's sake, that we're looking

at PGD and we're going to define, for a given mutation, given degrees of heteroplasmy that will be required to make this an appropriate case.

All of those, I think, are necessary up-front definitions -- the mutation, the disease syndrome with which it's associated, the degree of heteroplasmy. I don't know, really, how many -- this is something that perhaps Dr. DiMauro and other speakers may be able to address in subsequent comments -- how many of the disorders have a sufficient patient population out there to meet those criteria. I think that will be an important consideration in terms of defining exactly what study population would be most appropriate.

Once a study population is defined, then, as the questions brought out here, do we restrict the trial to male children? That's obviously a very tricky issue in terms of sex selection in this type of setting, ethically and morally, as well as from the standpoint of clinical design. But recognizing the possibility that, in fact, this may not work, that, in fact, things may be screwed up in ways that are not necessarily readily anticipated, I think there is wisdom in restricting this to male children, simply to, frankly, minimize damage if it turns out that there are any untoward or unexpected adverse effects of the procedure.

In terms of controls, how do you set up controls for rare disorders, with high variability, with a relatively low database in the historical record in terms of what to expect, where predictability is poor? Those are all essentially rhetoric statements. It's difficult.

The level of criteria that I think we need to define the study population -- meaning exactly which mutation, exactly what degree of heteroplasmy, as defined by which tissue and with what type of family history and with what type of outcome measures to be defined -- those are so discrete and, I think, will be so comprehensive that I don't know how much we're going to find in the historical record that will be of use.

Then the question becomes, do we have matched controls? Well, how do you do that in this type of setting, where you are then effectively asking a woman to go ahead with a birth in an untreated fashion? That has its own ethical issues, consent issues, both, that I think would be rate limiting.

One could look at it from the standpoint of prospective observational controls on cases that are getting PGD and have degrees of heteroplasmy that may be ambiguous enough you permit, if you will, the woman to go ahead with pregnancy. That may provide us some perspective, but hardly a matched control by any means.

So we are going to be restricted in terms of appropriate controls. Essentially we will be dependent upon really precise registration in large population groups, nationally and internationally, in terms of those cases that, if you will, slip through, where new sporadics or, as the case may be, familial cases appear and are identified. But these cases will then have to be, in an observational sense, followed and entered into the study as observational controls with the same degree of specificity and determination of outcome measures as those who are being admitted prospectively into the treatment trial.

This is doable. There are precedents out there in other genetic disorders. But nonetheless it's very difficult and requires the establishment of large, multinational registries for diseases of such rarity.

Of course, all of that would have to be defined as a function of mutation, as a function of degree of heteroplasmy, as a function of age, as children are followed. Again, that just gets back to the necessity of having a degree of registration of these patients as they appear throughout the population that may be -- and perhaps some of yesterday's speakers can correct me on this point later -- may be beyond what's currently available. Yet I think that type of infrastructure would be really a necessity for having the population base, not only for

control purposes, but also for identification of new patients for recruitment. That's really an infrastructural point that I think is absolutely required here.

In terms of endpoints, defining endpoints here is, in many ways, the greatest challenge, because there is so much variability in disease presentation. One aspect of that variability, even for a given mutation, is the age at which given symptoms will appear and the organ system in which they will appear. The clearest endpoints, of course, would simply be, in the treated child -- the treated embryo and, of course, the resultant child -- the degree of heteroplasmy as a function of tissue. So sampling, to the extent feasible and comfortable, of different tissue sources, whether leukocytes, whether muscle biopsy, urinary sediment -- all of the things that have been mentioned in terms of accessible and acceptable sites of tissue for analysis -- establishing the degree of heteroplasmy as a function of age in treated kids -- I think those are important quantitative endpoints.

It is hard to look at something that is essentially a biologic marker, a biomarker, as a primary endpoint. Typically that's not something that is done. Usually one likes to have functional endpoints, clinical endpoints. Even radiographic surrogates can be controversial. In this case we would be looking at,

effectively, a biologic biomarker as a primary endpoint. But I think in this case that may be reasonable. But others may feel differently, and we'll leave that to debate.

The clinical endpoints would in many ways be the more difficult, establishing when a period of reasonable absence of disease, absence of symptomatology, absence of pathology in given target organ systems. At what point along the way in development, both prenatally and postnatally, does one say, okay, here we have an outcome measure that has been met successfully, where we expected with X degree of certainty to have evident pathology or symptomatology and we have none, and therefore, we have therapeutic benefit? Defining what those time points will be and for which organ system, again as a function of mutation and degree of heteroplasmy, will all be really important quantitative endpoints.

In terms of essentially establishing safety and efficacy endpoints selectively, safety is going to be a function of both, obviously, safety for the mother and safety for the child. Let's really focus on the latter. By definition, we're treating, but in this case prospectively, a disorder with known organ pathology -- not necessarily predictable in terms of time course or order of appearance. But nonetheless, on the basis of historical

controls, on the basis of perhaps concurrent or prospective observational controls being done at the same time, at least we will have some idea of what organ systems to be looking at and some idea of when.

One is looking at that point for evidence of unpredicted pathology in terms of saying that there are safety sequelae that are rate limiting -- in other words, that there are untoward effects of the procedure that are now appearing later in development. Essentially, if one starts to see evidence of organ pathology, signs or symptoms that are not expected for that given mutation, for that given syndrome, then one can look at that as perhaps a significant problem in terms of meeting safety criteria.

That, in some ways, is straightforward. What's not straightforward is if one sees an unusual pattern of presentation of disease in the organ systems that are known to be part and parcel of that given syndrome. Then one really has to rely upon comparison to controls to know whether or not that evidence of pathology that is organ-specific does reflect an adverse effect, an adverse outcome of the procedure. Is it a serious adverse event that accrues to the treatment or is it part of the natural disease process that simply has not been treated by the technique?

All these are issues that will need to be clearly

defined in terms of the establishment of what constitutes, what comprises a serious adverse event in these children after birth.

I shouldn't restrict my comments there to after birth. It's also going to be a question of following the prenatal development of these children. We'll have to consider what happens if we see evidence of either genetic -- whether on amnio or otherwise -- during the course of gestation or sonographic abnormalities. We will need to consider how to deal with these, what level of intrauterine diagnosis to require. Should these cases get relatively late genetic analysis, meaning amniocentesis? How intensively should they be followed sonographically? What would comprise evidence of a serious adverse event that would suggest the desirability or at least appropriateness of abortion?

These are all considerations that we will have to entertain in terms of study design.

Normally we think in terms of what kinds of sample sizes we need to achieve what kind of power in assessing the treatment efficacy, treatment efficacy at predefined levels of therapeutic benefit. I think that's very hard in a case like this. I don't know, other than the determination of the degree of heteroplasmy, that we need to even go there. These are obviously going to be

very limited in terms of available patients, and recruitment will be a significant issue. Trying to define up front what the statistical power would be in setting up an appropriate trial will be very difficult. It's something we don't necessarily have to deal with until we get to later stages of clinical trial and validation. But at least in the earliest phases of Phase I or collapsed Phase I/II, it's not something we need necessarily to address yet. Hopefully that's an issue that would be essentially taken care of by the concurrent establishment of large patient registries, where enrollment or recruitment would become more facile.

I think I'll leave it there.

DR. SNYDER: Great. Dr. Cedars?

DR. CEDARS: I just want to add a few things. Again, I agree that the patients with mitochondrial disease are very different than the patients with infertility. I would like to not have a discussion about the infertility at all. I'll start with the mitochondrial disease.

I agree that the patients with the more severe disease should be in these first studies, although severity is a bit in the eye of the beholder. It's also a double-edged sword, because the patient needs to be healthy enough to undergo the IVF procedure in a pregnancy. So you want the most severely affected and, when you look at a risk-

benefit analysis and you don't know what the benefit necessarily is, you want the risk to be minimal. That's a bit of difficulty.

I think you should start out with women who are homoplastic mutant, so that you really know that these are not people that have another alternative, that wouldn't have normal eggs, at least based on the data presented. I agree these should be patients where the onset is in childhood.

I also agree with restricting to male embryos for transfer, because I think if we don't know what the downstream effects might be, to expose subsequent generations to risk is particularly concerning to me. But again, if we're restricting it to male, you have thrown out 50 percent, on average, of the embryos. Again we have to think about what this efficiency of the process is and how many eggs you are going to need that are not aneuploid, how old the woman is, how many eggs you need that are only female gender. I think there are going to have to be some calculations with that.

For the controls, I think if you are starting out with patients who are homoplastic mutant, almost by definition there can't be a control, because you know what the outcome would be. So I think for the mitochondrial, which is very different than the infertility studies, you

wouldn't be able to have a control. However, as was mentioned by one of the speakers yesterday, I think it will be important to test the cytoplasm from all of those oocytes that you have enucleated from the patient affected by mitochondrial disease to actually confirm that, in fact, all of those oocytes would have been affected. I think that, in essence, could in some ways be your control, to test those enucleated oocytes.

I think we also have to think about who the donor oocytes will be and what the enrollment criteria for the donors will be. Again, given the numbers that you will need for this -- someone mentioned, obviously, screening these people to make sure their mitochondrial DNA is normal -- I think we need to look at women under 30, because you want to have as little intrinsic aneuploidy as possible. You're really probably going to need to have donors who have fairly high antral follicle counts, potentially over 20, so that you are going to get enough eggs that are going to make this potentially reasonable.

Procedures to monitor safety and efficacy: I think we absolutely need an international registry for all treated patients and all children who are conceived by these techniques. As was mentioned, the issues about preimplantation genetic testing, anatomy scans during the pregnancy -- I think post-delivery, we need to collect the

placenta. We need to collect fetal cord blood. I think we do need to do muscle biopsies on these children shortly after birth. If this is a trial, given the duration of time for development, is a muscle biopsy is predictive, then I think you are going to have to do a muscle biopsy to confirm that you don't have transmission of the mutant mitochondria.

In terms of measures and ethical conduct for the follow-up of the children, it’s very difficult. As was mentioned yesterday, these children haven’t given permission for this. I think it’s going to be important to develop informational materials for the children of progressive maturity in terms of their ability to understand the disease process and the requirement for follow-up.

Efficacy, the primary endpoint for this study -- again it’s complicated because of these disease processes, but, really, in my mind, the preclinical is required to do the embryonic studies -- that the embryo is normal, that you have looked at least from an embryonic standpoint and trophoblast standpoint for epigenetic changes, proteome. As many of the omics as you can should be preclinical.

Really, if it's a clinical trial, the outcome needs to be, at a minimum, a healthy baby. Then it gets a little dicey, because the duration of potential long-term

follow-up that would truly be required to say that this was efficacious and the reality of being able to offer this to other patients are in conflict. So I think you have to get, at a minimum, birth, and maybe you say birth, muscle biopsy, one year of development or something. But I don't think you can say “and then we want to know that this child grew into adulthood and was healthy, and we need 1,000 of those before we can do it on anybody else.” It’s just not feasible. But it clearly needs to be beyond the embryo.

DR. SNYDER: Thank you very much. Dr. Cohen?

DR. COHEN: I think I’m going to limit my comments to a clinical trial involving patients with mitochondrial disease. I’m going to start with the choice of the patient.

Our speakers yesterday told us that the mitochondrial DNA is composed of 15,569 base pairs, of which there have been 200 to 300 points along that way that have shown human mutation. But when you get right down to it, there are about a dozen common mitochondrial DNA mutations that cause human disease. About half of these cause -- it’s a bad disease. It causes blindness late in the second, early in the third decade of life. But it’s a rather restricted disease, so I think we can push that aside.

When you are really talking about common

mitochondrial DNA mutations, you are talking about two. One is the MELAS mutation, the 3243 mutation, that has a high range of heteroplasmy, meaning that you will have plenty of mothers in these families that have low enough heteroplasmy that they are probably not going to get sick anytime in the first 60 years of life, and if they do get sick, it's probably going to be something with diabetes and deafness, but have a high risk of having children with the horrible disorder of MELAS.

The other disease that you have is the 8993 mutation that causes Leigh's syndrome in babies. The advantage of choosing that would be that most of those kids who are affected are affected in the first year or two of life, and you will be able to define that very quickly in your clinical study. The problem with that mutation is that the mothers, who are often healthy at age 30, will come down with a clinical syndrome that is sort of a smoldering Leigh's syndrome at age 40 and won't be there to raise their child. That's a terrible disease.

So I think, really, what we're talking about -- and I have dozens of families. In the national registry, there are probably 100 families with MELAS. Again, these women aren't homoplasmic. Homoplasmic people with MELAS are dead by the age of 10. Most of these women are heteroplasmic, probably have percent heteroplasmy between

50 and 70 percent, maybe a little bit less, but again have a high risk of having an affected child if they go about natural methods of childbirth.

We can hear from our speakers whether they would agree with that selection process or not.

My thought about donor sperm and donor egg: Probably just stick with conventional methods, plus adding screening to make sure that there are no mitochondrial DNA mutations in the donor -- I'm sorry, typical methods of screening, then probably adding to that chromosomal microarray on the developing embryo. I'm not really sure how to screen for abnormal imprinting. That goes beyond what I'm able to talk about right now.

I think in terms of the informed-consent process -- and let me preface these remarks. When I do genetic testing on patients, my informed-consent process for a simple gene may be very quick and simple, but in general, when I'm talking about global testing, sometimes my informed-consent occurs over the course of years, to really give the patients an understanding of what genetic testing is all about. I give a talk on genetics for non-geneticists. This includes common genetic diseases, as well as the more sophisticated mitochondrial diseases and copy-number variants. I have had full professors in their fields come up to me afterwards and tell me they didn't

understand before the talk the difference between a copy-number variant disease and a point mutation disease.

So if we think, sitting around here, that physicians are fluent in this -- they're just not. Our patients can become fluent in this, but it's going to take some time.

Trying to get the point across about heteroplasmy, bottleneck, segregation, and the nuances of mitochondrial genetics is something that general geneticists who don't delve into this field on a daily basis tell me they have trouble sometimes getting their hands around. So these are not easy concepts.

So the idea of being able to give informed consent is really not one that can be done in an hour or three one-hour sessions.

I also think that parents need to realize that 3 percent of all babies have major birth defects. Trying to drive that point home simply is crucial.

I do know of a case where there was believed to be a mitochondrial point mutation disease and the couple went after a donor egg from a similar heritage-matched population. The baby was born and ended up having a nuclear mitochondrial disease, known as Alpers-Huttenlocher syndrome. Two percent of Western Europeans carry one of the lethal mutations in this disease. If the dad has the

mutation and the mom is a tall Northern European, if they go after a donor egg with that same sort of phenotypic appearance, there's a 2 percent chance that that egg may have that mutation as well.

So if we think that this is going to avoid all mitochondrial diseases, there's going to be that one instance where you are going to get caught. I think that needs to be thought about in designing these clinical trials. So maybe even more scrutiny in terms of the genetic background needs to be done.

I think selection for male offspring is one way to get around the real criticism about the female possibly passing this on to her kids. I think that's reasonable.

In terms of the muscle biopsy, when you are talking about a male baby, there's foreskin. Foreskin contains smooth muscle. Most boys get circumcised at birth. That's a neat way to test for mitochondrial DNA heteroplasmy.

In terms of following children with -- and I'm going to choose MELAS as an example, choosing the MELAS baby -- children with MELAS, even with higher degrees of heteroplasmy, can go through the first 10, 15, 20 years of life without a clinical event, and then, bam, the disease hits. If we are really going to talk about efficacy, if we don't want to rely completely on the heteroplasmy concept

as defining the disease, we probably will need to follow these children many years along. In doing so, there are two practical elements.

Number one, who is going to pay for this? Is it going to be the clinical study that pays for the follow-up or is it going to be the insurance company? Most insurance companies, when they hear about this, are going to head for the hills. That's one.

The other is withdrawal of assent. We assume the mother is going to be healthy, but what if the mother isn't healthy and the child falls into the hands of another parent? There could be withdrawal of assent.

Also when a healthy baby is born, the mother herself may break and say, "I don't give consent anymore for my baby to be enrolled in this study. I'm moving to New Mexico, where there isn't a mitochondrial clinic in sight. Come get me if you need me."

That goes into the really heavy prescreening that we need to think about.

Those are my comments.

DR. SNYDER: Great. Thank you very much.

Dr. DiMauro.

DR. DIMAURO: I in large measure concur with what Dr. Cohen said, but I want to comment in answer to what Dr. Goldman actually asked me directly during his presentation.

That is, I hope to at least partially reassure you and the panel about the existence of populations, large and uniform populations, of mitochondrial patients -- namely, patients with MELAS disease, particularly. I'm agreeing with Dr. Cohen that that will be probably the most appropriate patient to start with.

As an example, we have been following for 20 years now at Columbia over 100 families with MELAS, with the 3243 mutation, so genetically uniform. We are still collecting, but there is already a pretty rich and clear natural history of this disorder.

We are following not only the probands -- namely, the patients who have neurological symptoms, either strokes or seizures -- we are following also all their maternal relatives, and therefore carriers of the mutation. We are collecting biomarkers that allow us to recognize early enough which carrier will develop the full-fledged disease. We call them converters.

All this is to say that there is a population of patients that will be very amenable to this kind of intervention and, in fact, which desires this kind of intervention. There are many women who would ask for this intervention for their reassurance about their progeny.

You can follow these patients. You have to follow them a long time, certainly. But not all patients

manifest the disease after puberty. For example, the case I mentioned in my presentation was a little girl who died at 12 after many episodes of stroke.

So both clinically and on the basis of biomarkers, you can follow these families and have a good idea, even without muscle biopsy -- just by measuring level of heteroplasmy in other tissues and by measuring lactic acid, for example, or radiological biomarkers, which are getting more and more abundant -- you can have a good idea whether or not the procedure has been, in fact, successful.

One last point I want to make. Again, I speak from personal experience. We have tried pharmacological interventions -- for example, dichloracetate -- in this large cohort of patients, with no good results -- in fact, dichloracetate now being dangerous.

So there are no available treatments for these families. This is a good population to start with. I'm not saying they should be the only one. I'm saying that if the method clearly shows promise in this group of families, a uniform group of families, then it can be extended to other mitochondrial disease mutations that may be less common.

Certainly I agree with Bruce that MERRF would be the second group of patients that I would consider. But there are many, of course.

DR. SNYDER: Thank you very much.

Before we go around the table, do any of the other speakers want to weigh in on this or make any comments?

(No response)

Thank you very much.

As we did yesterday, we'll go around the table for comments. Two things. One, try to be as specific as possible as to exactly what a first-in-human clinical trial would look like in terms of addressing these questions. Two, if what you are about to say has already been said, there's no need to repeat that.

DR. LEBKOWSKI: I agree that for the first-in-man clinical trial, the patients with relatively high degrees of heteroplasmy for the mutant genotype should be considered.

My additional comments: I think the trial should be designed with multiple points in the trial to be able to collect information -- for instance, embryo quality or any other information that we can collect about the embryos themselves, looking at development throughout the fetal stage, looking for fetal development, normal/abnormal, what we can pick up there. Obviously important is live, normal, healthy birth, and I agree -- which was said before -- looking at probably getting a muscle biopsy shortly after

birth.

One other thing I want to bring up is a question. Will there be certain criteria for implantation of those particular embryos? Is there going to be anything special that we're going to ask for in terms of the quality or some particular characteristic of the embryo that will be required before we implant? Simply a question.

I think the only other thing new is that I do think that, although it's very difficult, some statistical modeling needs to go on here, not only to model how many, for instance, IVF procedures the mother would have to go through in order to look at if there was a difference between that and normal IVF procedures, but other things in terms of looking at potentially normal age-related disease processes versus those associated with the mitochondrial defect. So I think some statistical modeling is warranted.

That's it.

DR. DIEKEMA: I agree with most of what has been said about enrollment. I would add a couple of things. I think the general principle I have heard being propounded is that the women who would be enrolled in these trials would have to be healthy enough that the risk would be low to them and the potential children would have to be those who are the most likely to derive some prospective benefit from the procedures.

In addition, I think recruitment would need to be considered very carefully. I think you want to be attracting in general a group of women who have already decided they want to try having a child, as opposed to creating a therapeutic misconception, enrolling women in this trial who think this is the way to have a healthy baby.

As far as monitoring goes, the only thing I would emphasize is that I think it's very important that, in addition to the sort of genetic and other biochemical markers, clinical parameters be followed well, probably into adulthood, with an eye not simply to the development of disease, but also to unexpected adverse events.

Most of my comments relate to consent. I don't have a lot of those. But I would give strong consideration to some kind of -- and I'm not sure what the right term here is -- patient advocate, patient navigator, liaison -- somebody who can assure that the woman who is involved in this research really understands that it is research, that there are no guarantees, and that it's not simply a therapeutic procedure.

As far as the children go, I do think assent at some point will be required for ongoing procedures that involve their participation. If there are continued blood draws, biopsies, other sorts of interventions, I think the

assent of the children would be necessary. For need of a place to start, I would say that that would probably start at about the age of 7. And I think re-consent would be necessary for long-term follow-up, starting at age 18.

45 CFR 46 Subpart B I think probably does apply here, which means that the consent of fathers will probably be necessary. There is some, I think, potential for interpretation there, but my read of that would imply that probably the permission of the father is going to be necessary as well.

The only other two things I would mention, because they have been brought up -- Subpart B also requires that termination decisions be completely divorced from the research team. So in all cases there would need to be some person who was devoted solely to the clinical care of the woman, who would assist her in making any decisions about termination. That might be necessary because the research team is not allowed in those sorts of decisions.

Finally, there was a comment made about the use of the foreskin, which I think is reasonable. But only about 50 to 60 percent of parents in the United States choose circumcision for their children. So I think the use of foreskins would have to be as sort of a leftover tissue for parents who had made that decision for other reasons,

rather than something being encouraged or required.

DR. KEEFE: First, in terms of the goal, the goal would be reduction -- not elimination, but reduction -- in transmission of MERRF or MELAS, not elimination of disease, because we know already there are other forms of diseases. There could be some nuclear-encoded susceptibility to mitochondrial instability. So goal: Reduction of transmission of MERRF and MELAS mutations. Secondary would be establishment of the safety and efficacy of oocyte and pronuclear manipulation.

Inclusion criteria would be:

• MERRF or MELAS carrier status in the woman, established by muscle biopsy, at least 20 percent.

• At least one offspring already with a severe phenotype associated with MERRF or MELAS, so they know the disease we're talking about. If you take a woman who has never had a kid and the moment the kid bats and eyelash or falls, they're going to say, "Oh, my God, this is it." So she knows what the disease is.

• A preceding IVF cycle with PGD in which she was unable to select an embryo that was normal or below the level that we would all agree would be acceptable for transmission -- so a failure of preimplantation diagnosis -- and agrees to, in this cycle, the pronuclear transfer with PGD at the trophectoderm stage.

Sex selection: Great idea in favor of eliminating females and only selecting males is the preservation of the human germline, in the sense that we're going to stop this. Against choosing males is the data in invertebrates that there is a preferential phenotype when you do have heteroplasmy -- preferential male sterile phenotype that arises. I know there has been a lot of discussion about there being no effect of heteroplasmy. That kind of goes against the paper that's in our packet from Reinhart (phonetic) and population geneticists, who strongly argue that there's a very, very significant effect of heteroplasmy, even neutral variances, that the model of mixed races is completely different than what we're talking about. We're bypassing the kind of natural selection. We're bypassing the bottleneck through the primordial germline. We're scooting ahead. It's like having somebody run across the finish line of the Boston Marathon without having run the race.

The paper by Reinhart in our packet is very important. They argue that actually one would be especially circumspect about allowing males to go through this as being selected, because, at least in several species, the nuclear mitochondrial mismatch preferentially influenced male sterility, as opposed to female.

There may be species differences. This kind of

goes back a little bit to our discussion yesterday before that moves to clinical trial. We have to sort this out. The experts in the room here today were rather dismissive of this, and yet three population geneticists published in *Science* argue very strongly that one would avoid males.

Then it's kind of Charybdis and Scylla. Then we've got this problem, do we favor protection of the human germline or do we now introduce at least a theoretical possibility that we could be favoring male sterility in the offspring? Certainly it has to enter the consent, I would think. Before the whole thing starts, we should sort this out in some mammalian species. They say there's some evidence in mouse. I think the primate -- Dr. Molitov (phonetic) is going to be watching his male primates move into puberty.

I think, in addition, they need to agree to have the child evaluated, as discussed.

The issue of the suitability of the woman who is a carrier for MERRF or MELAS to sustain a pregnancy and to be around for much of the childhood and early adulthood of her offspring is critical. I would argue that we should not include a gestational surrogate as an option because of the further complexity. Do we have to consent the gestational surrogate? Does she have to stay involved? What would be the impact of her drinking sodas and eating

bad food on the outcome? So I would exclude someone who requires a surrogate.

Finally, I would recommend that we monitor the children as far into their adulthood as possible, agreeing that they assent to it.

DR. WENSTROM: I agree with everything that has been said so far. I think one thing we haven't touched on is our desire to understand if any unintended consequences are the result of the procedure or not. If we do this procedure and the child ends up with a birth defect or a cardiomyopathy, we're going to want to know if it was due to this procedure or some other thing. I think we have to stick in some criteria to help us sort that out.

One thing would be standardization of IVF techniques across all centers doing this. When we did the MOMS trial, we worked out every single detail, including whether you are going to put in lactated Ringer's or saline during the procedure. Then we had a monitor going around making sure there were no protocol violations.

I don't know how practical that is. My sense is that IVF labs often have their own magic procedures. But I think we would have to make every effort to absolutely standardize every aspect of the IVF procedure itself.

The other thing, which I think makes it much more difficult, is to consider excluding patients who have other

risk factors for birth defects. If a patient ends up with a child with a major heart condition, we're going to want to know whether it's because of this procedure or not.

We would probably want to exclude patients with comorbid conditions. This might be a huge problem when you consider that a lot of patients with MELAS have insulin-dependent diabetes. Insulin-dependent diabetes independently increases the risk of lots of birth defects. If that patient has this procedure and ends up with a baby with a renal anomaly, how are we going to know if it was the diabetes or the renal anomaly? So we should consider excluding someone like that.

For MERRF, a lot of those patients have epilepsy and are on medications that could independently have adverse effects on the fetus.

We would also need to do pedigrees, exclude people with a family history that strongly increases their risk of having a fetus with an adverse outcome.

I think those things would be very important, because if we do have an unintended outcome, we're going to have to try to figure out if we caused it or not with this procedure or if it was due to some other factor. Considering how rare these conditions are, if we eliminate people with comorbid conditions that could independently increase the risk of birth defects, honestly that might

limit the feasibility of this trial. But I think that's a very important thing to consider.

DR. STEINBOCK: I want to just address two things that have been said. One has to do with the need for assent from children to follow up. I think that depends on why you're following up the children. If you are following them up solely for determining efficacy -- did it work? -- then I think you do need to get their assent, because then they are being used and perhaps subjected to onerous things for the benefit of others.

But is it also for the child's benefit? Do you want to find out whether the child has a condition that needs to be treated? If that's the case, I think the parents get to make that decision. I don't kids get to decide whether they are going to be vaccinated or not, for example, or have to undergo medical procedures.

The other thing I want to address is the distinction that was made by a couple of people between using the technology for the reduction of transmission of mitochondrial disease and infertility. I wonder why that distinction is being made. In both cases, although for different reasons, the aim is to enable a woman to have a child -- in one case, any child, and in the other case, hopefully a disease-free child. It seems to me that the distinction is being made on ethical grounds that go beyond

safety to women and children, which may just sort of underscore the difficulty of bracketing the ethics. But anyway, I'm not quite sure why that distinction was made.

DR. MORAES: A few points. Regarding the comment that it should be a severe disease but the other should be healthy, that can be accomplished. There are these big families where the mutation is very severe, but there are lots of carriers that are not affected. So the women would be healthy enough. Those might be good candidates.

Bruce mentioned that maybe Leber's should not be included. Maybe we can rethink that. It's not a very severe disease. It causes blindness. But it's homoplasmic in most of the cases. In that sense, it might be a good candidate. Also there are plenty of patients around with the Leber's mutation.

Regarding the endpoints, from everything we know from almost 30 years of studying heteroplasmy, I think the success can be measured by having no mutant or very low levels of mutant. If there are health problems with this baby, I'm convinced that's because of the procedure, not because of some carryover of zero-one percent of mutant mitochondrial DNA. Of course, it's important to do long-term studies and see if there is any deleterious effect, but I think the procedure itself would be more the question mark here than solving the mitochondrial DNA problem.

Controls -- really hard here. I can't even think of what would be a control group. I think if we get rid of the mutant mitochondrial DNA, that, to me, would be enough.

Going back to which mutations should be studied, we discussed Leber's or MELAS. But in any case, even if we make it broader, it should be a mutation that has been studied and we know behaves as a recessive mutation. Most mitochondrial DNA mutations behave like that, meaning that you need very high levels to have a clinical phenotype.

PGD, of course, would be important to do in all these treatments.

Regarding the donor, one could try to match the haplotype. I think the concern of an autosomal recessive disease is not so much, because the nucleus would be removed. So having a similar haplotype might minimize any concerns that people might have of compatibility. And, of course, sequence the mitochondrial DNA of the donor.

Selecting for males -- I still can't figure out what would be the best. But in terms of the heteroplasmy causing sterility, I'm not very familiar with these papers, but there are lots of males that are heteroplasmic for pathogenic mutations that I think are not infertile. You can correct me, but I think the clinical evidence does not support this fear. So maybe it is a good idea to select for males.

I think I'll stop here.

DR. WOODRUFF: I have nothing else to add to the discussion.

MS. REEDER: Which came first, the chicken or the healthy mitochondria? I think I'm clearer today why I'm here than I was yesterday. I want to really, really stress and emphasize that I really appreciate the science. I appreciate what I heard. I think there's a point in all disease and discovery where the patient is more helpful to the doctor than the doctor is to the patient. And so it goes. That's just how it is.

When I was diagnosed 14 years ago, I made a decision that how I deal with what I deal with is to be an advocate for patients that have mitochondrial disease, adults and also their children -- families that are dealing with sick mitochondrial children.

This side of me says, for those families that deal with MERRF or MELAS or Leigh's who choose to want to do a clinical trial like this, I believe they have the right to choose that. I believe in that right. This side of me says I believe in saving life, not creating it to save it.

For the Leigh's children that I have met and the MERRF children that I have met -- if you have ever held one of those babies in your arms -- I cannot sit here in good

conscience and say that I would risk anything to pass that on. In good conscience, I can't -- it's not like the risk would be freckles and red hair. It's a chronic progressive disease. So in good conscience, I'm having a hard time with that. And I want to say I understand the science and the choice, if a family wants to try to have a baby not affected with mitochondrial disease.

I have had two muscle biopsies and a needle biopsy. The needle biopsy is less painful. I'm just throwing that out there.

I'm currently in a clinical trial. I can say that mitochondrial patients that enroll in clinical trials -- just tell them what you know. We don't show up at the door because we are looking for promises. That's what a clinical trial is, that we don't know. But many patients feel that desperate, and so they are willing to try anything, even though there is a risk. So I have signed consent forms -- this is my third clinical trial. I understand the risks. They were explained, worst-case, and the steps involved in the trial.

I think I would be more for -- and I'm not sure if it was suggested -- a surrogate rather than a mother with mitochondrial disease carrying the child. I'm not sure if that's even an option or if that was brought up.

I thought that for the criteria -- I'm trying to

think how to word this -- if this were to go through and this were to actually happen, I'm just hoping that all of the research and science, the criteria for this clinical trial, all the data is somehow shared with our doctors and researchers that are trying to find cures and treatments for current mitochondrial disease patients, if that makes sense. Although this is for a very specific issue, I'm just hoping -- again, the families that I have talked to -- we want people to know we're here. We are having our own issues about our own criteria for our own clinical trials, let alone for infertility.

I think that's all I have. Thank you.

DR. ROSE: Just a few things, because a lot has been said already.

We keep talking about informed consent. I don't remember if it was Bruce or somebody else who said that that's not a piece of paper; that's a process. Really making the families understand what this really entails is tremendously important. It's a lifelong commitment. That gets to the issue of assent and follow-up. We all know that once a person reaches majority, in fact, they can drop out. So I think that a true clinical evaluation with an endpoint early in life that you can point to is extremely important. That's where MERRF and MELAS come into play.

I think Dr. DiMauro mentioned that he has 100

families that they are following. I think the natural history, in order to be able to understand the progression of the disease, is extremely important, in order to allow an assessment of the efficacy and the potential safety.

Biomarkers are nice, but we have had too many cases of true-true, unrelated. We are going to really need a clinical evaluation that identifies a clear, measurable endpoint that you can hang your hat on for efficacy and certainly for safety.

I think using the IVF experience with respect to what should be implanted -- i.e., if you will, a bio-release assay that is validated and standardized based on experience as to what should be implanted and what the donor oocytes should look like before undertaking this -- is extremely important.

I also think truly, at least at the beginning, before efficacy and safety are proven, that this has to be done in centers that have the type of experience and expertise to be able to do this with clear standardized procedures that are followed. Once it's proven, then it could go out, but you really need centers of excellence in order to be able to do this and do it correctly. Any other way I think is just asking for potential problems. Let me put it that way.

I would say to Carlos that we are actually

working on human gene transfer for LHON that is restricted to the retina. While I understand the homeoplasty issue guaranteed it's going to happen, I think the human gene transfer part is, at least at the moment with what we know, less risky. I would hold off on that in LOHN, in this type of procedure, until we understand more about the human gene transfer studies that are being done that can address this in what is probably a less risky way.

With that, I'll stop.

DR. SNYDER: I just want to caution that we are starting to run out of time on this question. We have to devote time after the break for question number 4. For the remaining time, I don't want to limit discussion, but when you make the comments, please make them brief and succinct, and do not repeat things that have already been said.

John?

DR. GEARHART: I'll have more to say on question 4 because it impacts, I think, a lot on what has already been stated. But I want to make one additional point.

If we begin to think about only using males, in spite of perhaps the pathology that we should consider, this requires yet a second manipulation of that embryo. That is, you have to do PGD to unequivocally determine that it's a male. I think the more that this is in culture, I think the more manipulations you do, you risk a greater

percentage of time of losing that embryo. I think it's something we have to think about as far as process.

DR. COUTURE: I agree with most of everything said, but I heard a few things that I don't particularly completely agree with -- or maybe just the way I interpreted what I heard. So I just want to clarify those two points and then add one other thing. The other thing about informed consent, enrollment criteria to some degree is okay.

What I heard that I found a little troubling was the notion that we would limit enrollment to women who had already given birth to a child that had disease. I find that kind of problematic. I would not want to do that. That's the same thing as forcing a woman to give birth to a child that has disease in order to get into a trial. I think that's just unethical. I think a woman who presents to a clinic because she has disease, and therefore has high heteroplasmy for the disease or has perhaps siblings and presented to the clinic just to be sure, would be the right kind of patient to enroll in the study.

The other thing is that the issue of standardization always gives me a little pause. I hear that in these kinds of committees from time to time. I think we should not require the field to standardize. This is more of a clarification of what I consider to be the

term “standardization.” I think any sponsor that comes to the agency with a proposal to do a trial should have a robust, reproducible, well-characterized manufacturing process to do this. That, of course, implies standard processes within that clinic or set of clinics that are part of the IND. But I do not think the field should be required to come to a consensus on how this is done or any process, regardless of manufacturing process, before the agency allows anybody to go forward with it.

The last thing I want to say, just to try to be a bit pithy, is what hasn’t actually been articulated yet. It’s the antithesis of endpoints -- stopping rules. In any clinical trial, it’s absolutely critical to have well-defined stopping rules. What those stopping rules would be here -- I can’t say I necessarily would be the expert there, but I would think perhaps things like low implantation rates or low live birth rates. Certainly what I think would be a big one would be unexpected heteroplasmy in the offspring. The presumption here is that these children will essentially be either homoplasmic for the donor/mother mitochondria or whatever. But if we see some unexpected heteroplasmy, I think that would be cause for stopping the trial and reevaluating what our preclinical data was to support this trial.

I’ll stop there.

DR. LEE: Before we design a Phase I clinical trial, we need to quantify what we are trying to measure. Before we can quantify, we cannot define the hypothesis. So how to quantify the abnormality of mitochondria -- percent of mutation or DNA copy number? And also it's important to standardize the procedure. How do you standardize the oocyte from the donor? How do you do some quantification measure?

As a result, how do you confirm that the embryo created by the IVF procedure has normal mitochondria?

That's all I need to say.

DR. SNYDER: I'm going to skip you, Steve, since you already -- Taby?

DR. AHSAN: A couple things. One is to reiterate one of the things I talked about yesterday, which is that we're not treating a condition, but we're trying to deal with a probabilistic event. So I think that really having good statistical models is going to be extremely critical as we move forward with these clinical trials, just because it's different than the typical clinical trial in terms of how you will do your analysis. So some really thorough investigation and potentially even development of new statistical models will be critical for that.

I think that's it. Thanks.

DR. DAHLGREN: I agree with everything that has

been said so far. The only thing that I want to reiterate is that I think it's really important that the consent be performed by an objective advocate and not the individuals that are involved in the trial.

DR. CRIPE: I have two points. One would be the pace of enrollment. I don't think I have heard that discussed yet. What would be the criteria for the second patient. Should one patient be able to prove that they go through the whole procedure, have a child, and have that child documented to be low heteroplasmy, before enrolling a second one? I think some guidelines around that.

Then, once that's shown to actually work, do we allow another three? Whatever the specifics would be. I think that needs to be addressed.

The other question is really about limiting it to males. Just to be provocative perhaps, to me, you're pushing the science to another generation. We're losing a big opportunity to study what would happen in the female recipients. I think if the preclinical studies are sufficiently compelling and reassuring to move forward -- and we have said already that those preclinical studies need to have transgenerational studies involved -- then we ought to be able to think about including females, for the reasons that were already described. One could put in some safeguards, such as assessing prior to childbearing age

that person and counseling them as to any risks. I'm sure there will be quite sophisticated tests to assess their risks at that point in time, in addition to just sequencing the mitochondria in their muscle.

I have a little bit of a problem sort of pushing that whole thing off to another generation and missing all the opportunity to learn from that. And these women who enter these may really want to have a daughter, too.

DR. SNYDER: Thank you very much. Dr. Emens.

DR. EMENS: I agree with most of what has been said. I think the place where I disagree a little bit is in terms of the endpoints of the trial. I think biomarkers are really critical and safety is really critical. I'm kind of thinking about maybe taking a very measured approach, maybe a two-stage type of design, where you evaluate the safety to the mother, the safety to the unborn child, and then the child who is born. Thinking about the timeline of when you define that that's enough of a safety evaluation to move forward and either enroll another person or expand the patient population out to a bigger group is something that would need to be fleshed out.

But I do think that biomarkers are really important in trying to understand if the goal of altering the genetic makeup is really happening or not.

I guess the other thing that I think might be

really critical for something like this, given all the issues that we have been discussing, is having an independent medical-expert panel oversee the trial -- that probably includes bioethicists -- so that somebody completely independent of the research team is really very closely monitoring how the trial is going, what events are being observed, and that sort of thing.

DR. BUGBEE: I have just one quick comment about measurement, efficacy, and endpoint. Maybe it's a question. Would the experts tell us that if you had a sampling of the recipient and you had multiple sampling and there are no mutations -- is that a good enough endpoint to prove the concept that you safely did the procedure? If you did that three or four times and the mitochondrial DNA was stable, is that an acceptable endpoint to prove that the procedure was effective?

DR. SNYDER: If it's okay, I'm going to skip you, too -- did you want to make a comment?

DR. CEDARS: Yes, I have two comments, one in terms of the PGD and the selection for male. You are going to be doing aneuploidy screening anyway because there's an increased risk of aneuploidy with these techniques. If you're screening the chromosomal complement for aneuploidy, you're going to, by definition, know the gender. So I don't think that's an issue.

The second comment I want to make is that I don't think we're separating mitochondrial disease and infertility because one is more or less important. I think they are very different in two key areas. One is the inclusion criteria and how you define, from an infertility standpoint, that this would be an appropriate treatment. The second is that you absolutely must have controls. It must be randomized, with controls for an infertility study, whereas I think most people would agree there wouldn't be a control per se for the mitochondrial study.

I think that's why we differentiate them, and not because one is of greater or lesser importance -- although the risk-benefit ratios are different.

DR. PERA: I have two points. The first point is on the mother. It has been mentioned that the people who would be enrolled would be those that were homoplastic for a severe mutation. Currently in IVF there are regulations or guidelines -- I'm not sure if they are regulations or guidelines -- regarding the age that a woman can be and still have IVF. It's generally considered to be somewhere around 50, 52, or so. Within that consideration of the age is a consideration of the child as far as how long the mother is going to be around, to tell you the truth.

So I think there needs to be some sort of assessment of the health of the mother, even though she has

mitochondrial disease. That's consistent with current guidelines in IVF.

The second thing I would like to do is follow up on what Marcelle said on infertility and stress that, as far as I can tell, there is a need for mitochondria in the oocyte, clearly, but the link between mitochondrial dysfunction and infertility is very, very suspect. There would be no indication that I could tell from any literature of who in the infertile population would have benefit from this.

I think it's important to remember that point, because this is ultimately likely to be very expensive. So the marketing to infertile patients is something that is bothersome when a new technique arises that they will likely want to try or may want to try, and there's no indication for it. Certainly there are examples of that in the history of the field.

MS. BUSTILLO: I agree completely, and I have strong feelings about including an infertile population. I think it's a whole different set of entry criteria, controls, like Dr. Cedars said, et cetera. So I am really not in favor at all of going ahead with that, because I think it's really very complicated and very, very different in terms of the risk-benefit for the mitochondrial disease patients.

I think we have to remember that the woman who is going through this procedure needs to be the best possible candidate for this procedure, not only because of the disease that she has, but because of the outcome in terms of the IVF. So I don't think we should be including women who are 39 years old in the first group of patients that we treat. We need to look very, very carefully at the efficiency of the IVF procedure in general, even without these interventions, in terms of what we do, because again you may not want to do three, four, five procedures to finally get the first live-born and prove the concept that you now have a healthy child. The best option would be a younger patient, less than 35.

Then the other issue is whether you are going to require what Dr. Keefe said about having had her go through an IVF procedure beforehand and have testing of the embryo she has already produced, or not. In a way, I don't know if you want to do that, but if you do that, then at least you get some idea of the efficacy of that particular stimulation, et cetera, and protocols in that particular patient. So that would be an advantage.

In terms of the sex selection, I agree with Dr. Cedars. You're already going to do PGD. I'm actually in favor of not just choosing the males, because I think you are going to lose out on the next-generational benefit that

you might get. But PGD is already going to be included, because the last thing you want to do, particularly in the patients over 35 -- they have a very, very high incidence of aneuploidy, even without these manipulations, and therefore you want to avoid transferring an embryo that's going to then give you a Down syndrome baby.

DR. SNYDER: Great. Why don't we take a ten-minute break? When we come back, I'll summarize the sense of the meeting with regard to question number 3. Then we'll do the last question, which hopefully we'll complete by 11:15. If everybody could be back at 10:25, we'll complete this question. Thanks.

(Brief recess)

DR. SNYDER: We are winding down on question number 3, but before I try to summarize what the points have been, a few of the speakers wanted to make some additional points.

DR. LATHAM: On the issue of whether to restrict the studies to males, a lot of the adverse consequences of oocyte and embryo manipulation that have been seen in animal models in the literature are sex-specific. The general vesicle transfers that we did produced effects only in the female progeny. In some of the redox studies, results were only seen in the male progeny. So restricting your studies to just one or the other sex would be really

crippling your study at the outset and placing it in jeopardy for being informative.

DR. ROSE: Actually, I would say to you, eventually including females, yes. My personal view, not necessarily shared by others: Restricting it to males first for safety as a first step, and then, once you have shown you are not causing problems by the actual transfer, then getting rid of the gender issues, to me, makes more sense.

DR. SNYDER: Dr. Egli, you wanted to make a very brief comment?

DR. EGLI: Yes. I would just like to emphasize again that the genomes are not changed. There is no change in the genetic material. The mitochondrial genome is not changed. The nuclear genome is not changed. It is factually wrong to link that to genetic modification technologies. What is changed is the pattern of inheritance.

Then a more scientific comment. It would be helpful for us as scientists to determine what we need to do leading up to a clinical trial in terms of scientific evidence. It won't be possible to determine all the "omes" in human embryos, but we can do that with experimental systems. We presented that to you. Will you accept that evidence as valid if we find this is the same as in

unmanipulated cells?

DR. SNYDER: Thank you very much.

MS. BUSTILLO: I want to make a comment about the selection of the male. I think there's a very good option, because if you are going to be doing aneuploidy testing, it is done on a trophectoderm. Somebody already said that. Usually what is done is, it's biopsied and the embryo is then frozen. Then you transfer subsequently. What you could do, so that you don't have to waste at least 50 percent of the normal euploid embryos, is transfer in the first attempt the male embryo. You subsequently can use the others.

DR. SNYDER: Great. This has been a great discussion, with a lot of points. I'll try to just take three minutes to try to at least summarize and capture what the debate has been and what the sense of the meeting is, and our recommendations. Again, after I'm finished, you can correct anything that I got wrong or supplement it.

In terms of enrollment -- and I think that probably engendered the most debate, as to who would actually be included in a study like this -- I think the sense of the meeting was that we should focus -- in our discussion we certainly did -- on mitochondrial diseases and not infertility, not because there's a difference in importance, but because there would be inclusion criteria,

the types of controls that would be used are also quite different -- for example, randomized controls would be used in infertility -- and certainly the risk-benefit ratios are different. So most of the discussion focused on enrollment for mitochondrial diseases.

It was felt that in a disease category where there are a small number and a huge degree of variability, probably it makes most sense to start with the most severe cases that had the earliest onset of disease, perhaps even for specific mutations. It was brought out that some of these that have a dozen or so common mutations, such as MELAS or Leigh's syndrome, would be excellent candidates for trials, and that certainly women with the highest degree of heteroplasty or even homoplasty would be the best ones to include, assuming that they were well enough to undergo the procedure, to sustain a pregnancy, and had enough eggs to be able to do this.

There was a lot of discussion about whether or not to include males only. It was acknowledged that it would be very dicey. In favor of including only males would be that it might minimize transgenerational damage, if that were a risk. On the point of including males would be that, besides discarding about half the embryos, we might actually be working against what some evolutionary pressures against transgenerational transmission of the

problem, that perhaps we're actually increasing the risk of male sterility, and that we're also losing a great opportunity to be able to study what the transgenerational risks actually are.

Enrollment criteria should also be extended to the donor eggs. There should be, obviously, no intrinsic mitochondrial abnormalities in the donor eggs. There should be chromosomal microarray done on the embryos. Perhaps we should study diseases with specific mutations that have a well-defined tissue distribution. There should also be criteria perhaps imposed on the embryos themselves that result, that only those that have the highest likelihood of implantation should be included.

There was a debate as to whether a female should be included whether or not she requires a surrogate. Some advocated that if she would require a surrogate, she should not be included because she might not be strong enough to undergo the pregnancy. Others felt that that should not be a criterion.

There was also a debate as to whether or not a woman should already have had an affected child or whether simply having enough markers or degree of heteroplasmy would suggest that there would be some benefit from undergoing this procedure.

The exclusion criteria should include fetuses who

have other causes of birth defects or other comorbidities or a strong family history for other types of diseases, other than mitochondrial diseases.

There was also a point made on the speed of enrollment. Certainly one structure of a clinical trial has patient number two not being enrolled until one sees what happens to patient number one. That was discussed as possibly a way of approaching a clinical trial in this regard.

There was also some thought that the women who are included should be young -- in other words, less than 30 years of age.

In terms of controls, this was considered to be problematic in that there is very often a lot of variability in the diseases, often poor predictability, and then, just in general, small numbers of patients. We probably would use historical controls. The limitation in historical controls is that the registry of these patients has not been as large or as ideal as we would like. Maybe one of the offshoots of this would be having better, larger patient registries.

Some speakers talked about whether or not you could look at tissue in treated or in untreated patients, and that could serve as a control. One would also look at unexpected organ pathology. Looking at functional

assessments, both in affected and unaffected, may serve as adequate controls.

In terms of informed consent, it was felt that this can be a very difficult process. It should be stated up front that the goal of these studies is not a cure, but the reduction of transmission of, for example, MELAS and MERRF, not its prevention and not its cure.

There should be monitoring by objective people that are uninvolved in the study. Perhaps even consent should be obtained by those not actually involved in the study.

Long-term follow-up is going to be important, which means that you initially have kids involved. Getting informed consent with kids is certainly very difficult. For long-term follow-up, by about 7 years of age, one should certainly be able to get assent of the kids, for example, for blood draws, and then by 18 years of age, the kids should actually be re-consented.

Getting informed consent is difficult and is a long-term process, because the concepts themselves are very difficult. It should also be mentioned to the family members that there is already a 3 percent risk of any baby having a birth defect of any kind.

Throughout the process, perhaps patient advocate and genetic counseling should be enlisted in any study

participants, and fathers should also be involved in giving consent.

Pregnancy termination decisions also need to be divorced from the research team. Certain procedures -- for example, a circumcision -- should not be made part of the informed consent. If foreskin is going to be looked at, obtaining that material should come after independent decisions as to whether the family is going to have circumcision or not.

Finally, monitoring and assessing efficacy: First of all, it was felt that even the monitoring should involve some independent oversight which includes some ethicists. There should be some recognition that in monitoring there is variability in course. Nevertheless, a lot of these diseases do have well-established clinical outcomes, and those can be compared.

It will be difficult and it will be very important to indicate what is considered an adverse event, and an adverse event related to the procedure itself as opposed to something that is part of the clinical constellation of the particular disease. Monitoring would include looking at fetal development all throughout gestation, not just in the embryo, perhaps through serial ultrasounds, looking at the placenta, looking at fetal cord blood, doing a muscle biopsy shortly after birth to rule

out transmission of the mutant mitochondria, looking at the foreskin for mitochondrial number.

Long-term follow-up would not only be of the fetus, but also multigenerational follow-up, assuming that females are included in this process.

Biomarkers were considered to be quite important and quite useful. Other kinds of outcomes could be monitored -- for example, cardiac function, lung capacity. Statistical modeling might help in terms of being able to assess the efficacy.

It would be very important to follow up adverse events, particularly those that we think could be related to the procedure itself. Stopping criteria are also very important. What would terminate, for example, the clinical study would be a low implantation rate or unexpected heteroplasmy in the offspring.

Finally, what would be evidence of efficacy after this procedure? Again, it was brought out that efficacy would be demonstrated by low incidence of mutant mitochondria. Because we would be looking at the worst and the earliest-onset disease, whose natural history is actually fairly well known, despite how variable and messy some of these diseases can be, efficacy probably would not be hard to monitor or to assess in diseases like MELAS or Leigh’s disease.

The larger the sample size, the better. But it's recognized that there may be some difficulty.

Just reiterating what we said before, the way to assess efficacy would be clinically, which is quite important. Clinical outcome, in the hands of a really skilled clinician, would be sufficient. Biomarkers would help. Muscle biopsy, looking at foreskin, doing as many omics as possible on this material would be quite important. The follow-up should be certainly into the first year of development, but already into adulthood and transgenerational.

I tried to summarize what everybody said. What did I miss? What did I get wrong? What didn't I emphasize correctly?

DR. CEDARS: I don't think I heard you mention the use of the enucleated oocytes. I think in terms of efficacy, since there is no control group, the study of the leftover oocytes from --

DR. SNYDER: I did have that and I forgot to read it.

DR. CEDARS: Okay. I think that should be tied to the embryo that's transferred so you can also see if that oocyte was in any way predictive of success of the implantation.

DR. SNYDER: Right. I did have down to look at

all the oocytes that have been encucleated to see if they have been affected. Good. Thank you.

Anything else?

(No response)

Now we're down to question number 4. Because we're running a little bit short on time, we're going to have to try to be very succinct and crisp. I think we can do this. Now what we're talking about is probably more of a clear-cut situation. This is assuming we have launched a clinical trial based on great preclinical data, having complete knowledge of all the risks -- so a lot of assumptions. What controls should we impose over the actual reagents and the production process?

I'll read the question and then we'll have discussants.

Adequate manufacturing controls and monitoring of processes are essential to protect the safety of subjects and to minimize the risks for any children that might result from clinical trials using mitochondrial manipulation technologies. Noting that specific controls might differ for each process, please discuss controls for and/or methods for assessing the following:

(A) The source and characteristics of the mitochondria or other subcellular materials. Examples might include tests of mitochondrial DNA or spindle

integrity, quantification of mitochondria for transfer, and methods to measure the success of nuclear genome or mitochondrial transfer.

(B) Source of the oocytes or other cells.

(C) The reagents used in mitochondrial manipulation technologies. Example: colchicine, Sendai virus extracts.

(D) The methods for qualifying manipulated embryos prior to transfer, including any genetic tests.

We're going to have discussants John Gearhart and Renée Reijo Pera. Why don't we start with John?

DR. GEARHART: I think from our discussion so far, you will see that this discussion topic has to be rewritten. From the standpoint of the issues of the source and characteristics of the mitochondria, we have dealt with the patients here and what could be done in that.

The other topics, though -- I think we can handle some very easily, and Renée has the hard part.

The first is, we're only talking about a few reagents involved here, from the standpoint of doing these procedures. One is the proteins from the Sendai virus, which have to be clinical grade. They have to meet specifications. They don't exist at the moment. I don't see a problem in eventually generating these under procedures that would be clinically approved. This is not

a whole virus. These are coat proteins that are essentially isolated away from the nucleic acid.

The second is cytochalasin. That, I think, Sigma would argue, already is of a clinical grade. But that would have to be followed up as well. But there doesn't seem to me to be a major issue here of getting this approved, demonstrating the necessary steps to get the FDA approval for it.

So I don't see a problem going forward with that.

To me, a major issue here is the uniformity or standardization of the processes involved, the spindle transfer and the pronuclear transfer. How one establishes any controls or quality control of this, I think, is obviously problematic. What we are interested in is that you maintain the pronuclear structures. We're concerned about the integrity of the spindle, so that we don't leave behind chromosomes or generate a situation where the spindle's, for some reason, integrity is lost.

I don't know how you control for this, other than the expertise of the people doing that process. This is obviously a hands-on kind of procedure that would take training.

Something should be pointed out here, I think. The success that has been obtained with the spindle procedure is not trivial from the standpoint of the process

itself. I think the focus that has been demonstrated and the skill level from the investigator who succeeded with this nicely tells you that he took a lot of effort, over a long period of time, to really develop this technology, to make it work, and to make it work relatively well. How you transfer this to other individuals obviously is an issue here. Maybe we can discuss how one would go about it.

This is not something that can be done in industrial strength, I think, and have someone sitting over your shoulder.

Of concern in this -- and there must be an effort made -- is the carryover of the mutated mitochondria and how that will be assessed or analyzed. Obviously it's a major issue. Could there be ways developed that, in a temporary sense, the spindles or maybe the pronuclear material could be -- I hate to say this -- cultured or placed in some situation where you would in some way eliminate any mitochondria associated with them? I don't know that, but I think it's something that should be considered. And, obviously, how you monitor for that is an issues.

To me, those two topics are of concern, and how we can standardize the process and monitor for carryover of the mitochondria. Obviously one measure of the spindle issues would be the PGD associated with looking at the

karyotypes of these cells, which would have to be a standard procedure.

Those are my comments.

DR. SNYDER: Renée.

DR. PERA: I was assigned the second and the fourth to look at, the source of the oocytes or other cells. The source of the donor oocytes for the mitochondria would follow the general guidelines that are used in many IVF clinics or donor programs. Looking it up on the Web, the kinds of criteria that are used include the age of the donors -- generally, between 18 and 34 -- physically healthy, normal BMI, non-smoker, regular cycles, not using contraceptives, having both ovaries, psychologically healthy, devoid of genetic disease in their family, not using any drugs, no history of substance abuse, willing to take injections, and then having a process that includes counseling and informed consent.

In addition to those, there may be others that are used in some programs. This application would seem to suggest that we should promote the use of a muscle biopsy to determine that they don't have mitochondrial disease.

On the third one, I think it has been brought up that currently there is a need for Sendai virus in this procedure. That still seems problematic to me, to include Sendai virus in the reagents, but someone else can talk

about that a bit more, if that is of value.

Finally, the method for qualifying the embryos prior to transfer: That's difficult, if you ask me. The embryos can be grown to blastocyst stage and the trophectoderm removed. There are some standard criteria that can be assessed, like the absence of chromosomal abnormalities, the absence of other genetic mutations that might be associated with disease. But I'm not sure how reliable the assays are for mitochondrial disease at the trophectoderm level. Certainly if we're talking about very well-characterized or well-known mutations, that won't be so difficult, but it would be difficult where the disease would be much less well described.

Then, of course, the tests can determine if it's a male or a female embryo, and so one could choose to transfer male or female.

There are some other things that have been developed over the years, like oxygen consumption, re-assaying media. There is time-lapse imaging. There are different things that may contribute to the success of implantation. But they are more generalizable assays, and so they may or may not be used in this context.

DR. SNYDER: Thank you very much.

Do any of the speakers have any comments?

DR. SIRARD: Concerning the evaluation of embryo

quality, one thing that could be done -- if we would have a biomarker of mitochondria function in terms of adequacy of the blastocysts, we could use a part of the blastocyst biopsy to do PCR for specific gene expression factor -- not necessarily do the whole transcriptome, but look for a specific marker that would tell us, whoops, there's a problem here. That would come from research.

DR. MITALIPOV: I agree that there are some specifics of the skills that are required to do the procedure. Even in my laboratory, I have postdocs that do it routinely in the mouse. Maybe they produce 100 live mice, but they are not qualified to do it in humans. So they would not get that approval level to do it with human oocytes.

If the clinical trials proceed, of course, these would be the people who already have expertise, who have at least done it *in vitro*. Those people would be doing it, presumably in our clinic in Oregon, or if we have to do it off-site where the patients are, we would fly there with our team, bring not only the reagents, but some specific microscope types equipped with laser, with a spindle imaging system that has been also part of this procedure, which is not standard in most IVF clinics.

In terms of how you evaluate the quality of the embryos, a lot of that work has been done. There are two

studies we published, our group and Dieter. We already know what to look for. I mentioned about these problems with fertilization. You could have extra pronucleus, and that's very important to watch out in this procedure. That's what my embryologist would do that all the time.

We could efficiently, of course, the trophectoderm biopsy, which may not harm the embryo, but any extra manipulation is undesirable. What the trophectoderm biopsy can do? We can sample maybe 10, 15 cells, but you have to figure out what you are going to do with that small amount of the material you have. You could do CGH. We have done CGH. Unfortunately, we found that today's CGH approaches have a high error rate. For example, we knew this embryo was triploid because it had triple nuclei, but when we did CGH, CGH showed it's a normal. We derived stem cells from the ICM and we showed it's triploid. CGH failed to detect it.

In terms of defining the mitochondrial carryover, it can be done. We have a pretty good test. But you have to choose. If you use it for mtDNA, you cannot use anything for CGH.

DR. SNYDER: Thank you. Any other comments from the speakers?

(No response)

Why don't we quickly go around the room? Try to

keep the comments sharp and to the point.

DR. LEBKOWSKI: Just two comments. The product in this particular case is the manipulated embryo. Therefore, there should be some release specifications for that particular product and criteria that you would use to implant into, in this case, the mother. There should be some release criteria that are important.

The second comment is that the operators -- in this particular case, as John was saying, it's a very labor-intensive procedure and dependent on the individual operator. The individual operators should be qualified, using some particular test, and shown that they can reliably do this procedure, whether it be with animal embryos, whether it be with animal oocytes, et cetera.

DR. KEEFE: Just two quick comments about the technology. Before I do that, a disclosure. I'm actually the U.S. patent holder on Oosight, which is the device that's used for enucleation. But I have completely signed off. I receive no licensing revenue. It's all signed off to Woods Hole Marine Biological Laboratory, where my lab was, and also Woods Hole, so I have no interest in that.

It's now used by over 500 IVF centers worldwide, so it has a wide usage. It appears to be safe. It's approved by the FDA for use in IVF. It has very low levels of light. But we set the swing -- it's a parameter of

polarized light -- to optimize spindle visualization. This is apropos to John’s question about whether you could find some noninvasive way to track lagging chromosomes. Chromosomes, too, exhibit birefringence. Therefore, if you tweak the oocyte or use the other model that isn’t so optimized to look at the spindle, you should be able to also use polarized light to look for lagging chromosomes.

The second issue, with regard to looking at oxygen uptake -- I also have a US patent on the use of the noninvasive self-referencing oxygen electrode. Again, I don't receive any licensing revenue. It’s through Woods Hole. It’s now commercialized in Europe.

A word of caution. We had a very difficult time getting that to be quantitative. There’s a big impact on how close the electrode migrates to the embryo. It uses the fixed equation to look at diffusion of oxygen through the media. Knowing the diffusion constant and measuring oxygen in two locations, you can self-reference. But there’s a lot of noise, a lot of problems with that. So I would be cautious about using something like that.

DR. WENSTROM: I would just add, in the interests of avoiding unintended consequences, to donor screening, to do more of a detailed genetic evaluation, maybe microarray using a prenatal chip or CGH, just to make sure that we’re not inadvertently introducing an unknown adverse genetic

problem.

DR. WOODRUFF: I have a question. It's listed as Sendai and colchicine. Are those the only things that are under consideration? I know the Columbia group was doing electrofusion.

DR. SNYDER: I think it would be any reagent. Those were just examples.

DR. WOODRUFF: I think there would be different procedures if you are going to electrofuse, which is not a manufacturing issue, but the quality of the embryo in terms of the other things that have been identified -- how long between divisions for the embryo and other metrics of size and numbers and mass.

DR. SNYDER: Sharon?

MS. REEDER: No comment, thank you.

DR. SNYDER: Steve?

DR. ROSE: No comment.

DR. SNYDER: John?

DR. COUTURE: I just have a couple comments, first on the Sendai virus. I don't have a particular problem with Sendai viruses being used in a lot of different applications, including making iPSC and whatnot. It's also being considered as a gene therapy vector, and so I know the agency is probably already familiar with some of the issues around Sendai virus or some of the concerns --

not concerns, but considerations.

What I will say, though, is that I read through all the literature, looking at materials, methods, exactly what people are using, and I think it's not clear exactly what people are using. Some people talk about an inactivated Sendai, some Sendai extracts, some people Sendai proteins. You look at the couple of companies that actually sell it, and it's really not clear exactly what they are selling, but it appears to be an inactivated Sendai preparation, which is not the same thing as recombinant proteins from Sendai virus.

So that's something that has to be sorted out as a reagent. But the agency is very well equipped and understands how to look into those kinds of reagents and ensure that the quality of the material is sufficient for the stage of the trials, et cetera. So I'm not really concerned about it. I have no doubt the agency would apply that to any reagent that came along.

I will only say, though, that, unlike making an iPS cell line or something else, this is not an upstream manufacturing process for the viruses involved. It's almost essentially the same as direct injection of material into a human. It goes right into the embryo and the embryo goes into a patient. So there are potentially some abstract, maybe hypothetical considerations around

immunogenicity, et cetera, et cetera, including repeat fertilization of the female. I don't think those are particularly big issues, just something I have no doubt that the agency will at least consider with the sponsor.

In terms of the manufacturing process -- I said this yesterday -- I consider what we heard today to sort of transcend standard IVF technologies. This is actually manipulation well inside the oocyte itself. It's moving chromosomes and whatnot around. That, to me -- and I suspect it's why we're here -- would raise this to the level of an IND and ultimately a BLA, and not just a process that is carried out around the country.

That means that the manufacturing process really has to be a qualified manufacturing process. It doesn't have to be the same from sponsor to sponsor to sponsor, but it has to be well qualified by the particular sponsor that's going to use it.

I don't see that as a problem. I think that's something that one can do with either abnormally fertilized human eggs or other eggs. But I think there are going to have to be a fair number of process controls and a demonstration that, at least by particular operators in a particular location, with particular equipment -- all defined by standard operating procedure -- the process is reproducible and has certain failure rates, or not, based

on whatever criteria are applied.

I think everything else -- the assays, the tests down the road -- has been covered well enough, and I don't have anything to add there.

DR. GEARHART: Evan, just to make a comment, at least to address part of what -- from what I know, the preps that are available of this have no nucleic acid in them at all. They are just protein. Whether they are HA, F -- how many components, I don't think there's an issue with it being inactivated.

DR. COUTURE: I didn't mean to imply that there shouldn't be RNA left in the prep. I think, whatever the prep is, it just has to be characterized and qualified as any other raw material that's used, factoring in that it's not a far-upstream material that gets washed out. It's right there in the egg.

DR. SNYDER: Dr. Lee?

DR. LEE: I would just like to emphasize again that the discussion and presentation yesterday so far look to me more qualitative than quantitative. Unless we have these quantified, I don't see how you can do sample size power calculations or stopping rules, because those are the things I usually do. We need quantified data. Thank you.

DR. GOLDMAN: To Jane's point about the release criteria, there are actually several stages of release

here. Thinking in terms of some of the discussion earlier in terms of occult genomic mutations that might then become apparent, one stage of release would be, whether PGD or otherwise, the initial oocyte donor. We may want to suggest some screen of known mutations that would be of concern -- this, of course, becomes ethically debatable as well -- some screen of known mutations that would be of concern in the spindle or pronuclear DNA to be transferred. That presumably could be at the PGD stage, but before oocytes are set aside for potential donation. That would be one set of release criteria at the stage before transfer is actually accomplished.

DR. AHSAN: I want to reiterate a few of the important points that were already discussed. One is standardization, which Larry brought up, which I think is very important. Along those lines, I think quality control at various steps during this process, not just release criteria at the end, but, as Steve said, at various points, which include the recipient oocyte, which may include also nuclear testing of the donor, just to make sure that we don't complicate it with additional pathologies -- p art of this is going to be really important to have nondestructive testing and monitoring throughout the process.

The other thing is, there was some mention in the

briefing document about contaminating mitochondria that move with the spindle or the pronuclei. It's important to evaluate what kind of adulterating components are being part of that transfer as well. It may not be that it has to go to zero, but it needs to be well defined and there has to be a set threshold for that.

DR. SNYDER: Linda?

DR. DAHLGREN: I have nothing further to add.

DR. SNYDER: Tim?

DR. CRIPE: Nothing to add.

DR. SNYDER: Renée? You're good. Carmen?

MS. BUSTILLO: The only thing that I think we haven't talked about is, in terms of the source of the donor eggs, I agree, and I think obviously you have to do all the things that we need to do and additionally test the donor, et cetera, et cetera. But if we're going to also use vitrified oocytes because of the difficulty in coordination of the two cycles, then that's going to be a little bit problematic, because the success rate might really be affected by that. In our program, the success rate from donor egg with vitrified eggs is about 10 percent less than it is with regular. So that's another issue.

DR. SNYDER: Okay, great. I think this will be fairly easy to summarize. I don't think there was a lot of controversy on this.

Basically, these are manufacturing controls. In terms of the source and the characteristics of mitochondria and the entire process, it was emphasized that this requires an enormous amount of skill and that only those well versed in the art should really be participated in this, particularly assessing spindle integrity and actually involved in its transfer -- should only be done by specialists who have been qualified, and in specialized centers, at least initially.

Assessing the degree of carryover of mutated mitochondria is tricky. One might be able to do it by culturing or by polarized light.

Every stage in the manufacturing process needs to be monitored -- the operators, the equipment, the preparations -- and ongoing quality control at each one of those stages. These should be quantified if possible, not just based on quality metrics. Failure rates should be well established for the centers that do this.

In terms of the source of the oocytes, the only additional criteria to the routine standards that are imposed on oocyte donors would be perhaps a muscle biopsy or some other way to rule out preexisting mitochondrial disease, a microarray of the donor to rule out any other genetic diseases that could confound interpretation, and recognizing that vitrified oocytes could influence the

success rate.

Looking at the reagents, it’s the standard procedures that would be imposed on looking at any kind of reagent in any kind of clinically applicable procedure.

There was a little bit of a discussion as to using the Sendai virus extracts. There was expressed a desire perhaps to be able to eliminate that from the process. It was also brought out that it’s inactivated and has never really posed a problem.

Finally, release criteria should be established here, as in any procedure, and release criterion for the product in this case is the embryo. Releasing the criteria for transfer would include, first of all, the standard procedures that are used in terms of grading the embryo. It was admitted that checking for mitochondrial status is not a well-established routine, and probably some work needs to be done on that. Perhaps looking at the trophectoderm, perhaps a blastocyst or embryo biopsy might help in this regard.

It was thought that maybe other ways of monitoring the embryo prior to transfer might help -- for example, looking at oxygen consumption, though that’s difficult to quantify, time lapse. It was also acknowledged that if sex is going to turn out to be one of the criteria as to whether or not one transfers, whether or

not you include males or females, that can also be determined and be a release criterion at that stage.

Anything that should be added to that?

DR. COUTURE: Just a question to maybe the experts that do this. I heard you say something that I didn't pick up, and that is requiring an oocyte donor to subject themselves to a muscle biopsy. Is that likely to actually happen? Wouldn't that pretty much just kill oocyte donation? I'm not sure that --

DR. SNYDER: No, no, no. That was brought up only for this particular clinical trial, not routinely.

DR. COUTURE: I understand, but even for the clinical -- it's a question. My gut response is, it's never going to happen.

DR. SNYDER: It was brought up at one point as to whether --

DR. PERA: I imagine that they would still be paid quite a bit. I'm trying to think. The severity of a muscle biopsy versus oocyte donation itself -- I think the muscle biopsy might be easier.

DR. SNYDER: The point that was brought up was some way to rule out preexisting mitochondrial disease. It doesn't need to be a muscle biopsy, but some tissue that is informative, which you would not usually require from the routine oocyte donor, so something in addition.

MS. BUSTILLO: I heard urine sediment today. Maybe that's a good option.

DR. COHEN: Dr. DiMauro's lab has shown that that has been a very sensitive measure.

DR. SNYDER: The point that was brought up was that, in addition to routine oocyte donation, which is very well established, there should be other screening criteria, for example, making sure that there are no other genetic problems or preexisting mitochondrial problems.

If urine sediment -- I think probably the FDA would love to hear that urine sediment is adequately sensitive and specific.

We're right on time. Have we answered your questions with regard to the four questions?

DR. WITTEN: Yes, you have answered the questions. I would like to take this opportunity to thank the committee for the discussions over the last day and a half, which are really helpful to us. I want to thank you now because I know, for the afternoon's topic, not everyone is going to be here who was here for the last day and a half.

We really appreciate the committee's discussion of the topic, as well as the input provided during the public comment session. There is no vote. This wasn't intended as a decisional meeting. But the meeting provided

valuable information that will help inform the FDA's deliberations in the event that we have a clinical trial of one of these technologies proposed.

I really appreciate it. It's a complicated topic. We heard lots of perspectives, scientific and other viewpoints. That will help us as we go forward with this. So thank you very much.

DR. SNYDER: Great. Thank you very much.

We're actually moving on to topic II. Even though some of the people around the table are not involved in what topic II is, it was asked that you just sit around and wait until lunchtime, which will be around noon. So if you can hold that for about 45 minutes, that would be great.

Agenda Item: Topic II – Update of Guidance Documents Issued by Office of Cellular, Tissue and Gene Therapies, CBER, FDA

DR. SNYDER: Topic II is an update of guidance documents issued by the Office of Cellular, Tissue and Gene Therapies. I guess Dr. Rachael Anatol will do a presentation on that.

Agenda Item: Guidance Update

DR. ANATOL: Good morning. For the next several minutes, I'm going to speak to you to give you an update about guidance development in OCTGT, the Office of

Cellular, Tissue and Gene Therapies, and present some of our latest guidances.

I'm going to talk about our good guidance practices, cover some very brief guidance basics, go over the guidances we have issued since 2009, which was the last time we gave an update to this group, and go over our 2014 guidance agenda.

FDA's good guidance practices were mandated by the Food and Drug Administration Modernization Act of 1997 and are described in the Code of Federal Regulations. These regulations are policies and procedures for developing, issuing, and using guidance documents. Our good guidance practice regulations require the FDA to publish a yearly guidance agenda, both on the Internet and in the *Federal Register*. This describes a list of topics we are considering developing guidance on or revising guidance on over the next year.

The regulations also describe how the public can participate in guidance development. I think the primary way the public participates is by commenting on our draft guidance documents. Generally, we issue a draft guidance document, and at this time, we're really hoping to get stakeholder and public input on the content of the document. Once we receive those comments to the docket, we consider all comments and move towards finalizing the

guidance.

But in addition to this, the public can also comment on final documents. They can propose topics for us to consider guidance development on. They can comment on our guidance agenda. They can submit draft documents, proposed documents, for FDA to consider. They can also suggest that FDA revise or withdraw specific guidance.

In addition to voluntary public input, FDA may also solicit public input. One way we do that is by holding public meetings or advisory committee meetings on certain topics during guidance development. This can happen before a draft guidance is developed or after a guidance has been developed. Of course, this committee this afternoon will be providing recommendations on our draft guidance, “Considerations for the Design of Early-Phase Clinical Trials for Cell and Gene Therapy Products.” In the past, the committee has provided recommendations on other topics, including investigational applications for products intended to repair or replace knee cartilage, our guidances on cord blood applications, and our guidance on cell therapies for cardiac diseases.

The regulations define guidance documents that are prepared for FDA, applicants or sponsors, and the public that describe FDA’s interpretation of or policy on a regulatory issue. Guidances are the only form of

communication we may use to communicate new agency policy or to describe a new regulatory approach to a broad public audience for the first time. Guidance documents represent our current thinking on a particular topic, but they do not legally bind FDA or the public. Because guidances don't convey regulatory requirements, stakeholders may choose to use an alternative approach to what we have outlined in a guidance. But, of course, this has to comply with all relevant statutes and regulations, and we would recommend that anyone come in to talk to us before going forward.

The regulations define what topics guidances generally cover. These include the design, production, labeling, promotion, manufacturing, and testing of regulated products, the processing, content, and evaluation or approval of submissions, and inspections and enforcement policies. The regulations also specifically say what is not a guidance document. These would include agency SOPPs or reports. They would include general communications to consumers or health-care establishments. They would also include things like warning letters or individual communications to sponsors or persons.

On this list you can see the draft guidances we have issued since our last update to this group in 2009 that have not yet been finalized. I think, as you can see, all of the draft guidances in this bucket were published in

2013. We are going to be very busy this year moving towards finalization of those guidances.

This slide contains a list of the guidance documents we have finalized since our last update in 2009. I'm not going to go through them, but on the last slide I have links so you can easily access each of these guidance documents.

Finally, this is the list of guidances that OCTGT has included on CBER's 2014 guidance agenda. This was just published in January and will be updated again in June. These are the guidances that OCTGT and CBER have committed to publishing by the end of 2014.

Our contact information is included on this slide. I would like to draw your attention to the bottom bullet, which is the OCTCT Learn Webinar Series. This series contains a large number of presentations by OCTGT and FDA staff that cover topics relevant to the products we regulate.

Finally, this just gives some links for you to easily access parts of the FDA website particular to CBER. I want to draw your attention to the second, third, and fourth links, which are where you can find our guidances on cellular and gene therapy topics, our guidances on tissue topics, and then all the guidances CBER has issued in the 2014 agenda.

That’s all I have for today. Thank you. I'm happy to take any questions.

DR. SNYDER: Are there any questions?

(No response)

The next part of our agenda is recognition of committee services. Dr. Karen Midthun will acknowledge the service of those that are rotating off the committee.

MS. DAPOLITO: Dr. Snyder, some members have called in. Drs. Galanis, Dubinett, and Hornicek, are you on the line?

(No response)

We’ll have to proceed, I guess.

Agenda Item: Recognition of Committee Service

DR. MIDTHUN: I get to do the fun part. I would like to take this opportunity to thank those committee members who have finished their terms or who are about to rotate off. We recognize the tremendous dedication that this service that you provide to us entails and also your generosity in giving of your time and your expertise.

You have advised us on many novel products and their development, including the licensure of cord blood products used to reconstitute hematologic or immunological cell populations and patients with certain conditions. You have provided us with a lot of advice on numerous product development processes and also on guidance documents. You

can see where the office has been very, very busy in developing guidance documents that are really so important in trying to facilitate the development of novel products. We really thank you for that as well.

Many of you have also assisted us in the site visits to our laboratory-based research programs, which have also been very, very important to us.

I had wanted to acknowledge those who were to join us by telephone, Drs. Dubinett, Galanis, and Hornicek, but unfortunately we have had technical problems. But I would like to go on and recognize those who are here in the room with us today. I would like to call each of you to the podium so I can give you your letter of appreciation. Unfortunately I don't yet have the plaques, but they will be forthcoming in due time.

I will start in alphabetical order.

(Letters of appreciation were presented to Dr. Couture, Dr. Dahlgren, Dr. Goldman, Dr. Lee, and Dr. Snyder.)

Without much ado, I think you can go to lunch, but I'll let Dr. Snyder and Gail Dapolito speak to that.

DR. SNYDER: According to the agenda, yes, it is now time for lunch. Normally we only have an hour lunch, but unless Gail has any objections, I think -- why don't you tell me whether we should reconvene at 12:55, as

scheduled, or before that?

MS. DAPOLITO: How about an hour? I want to make sure there's enough time for discussion for this afternoon's topic.

DR. SNYDER: All right, we'll reconvene at 12:30 and start the afternoon session.

(Recess for lunch)

AFTERNOON SESSION

DR. SNYDER: We're ready for an entirely new topic, even though, as Celia pointed out, a lot of people connect the two. I think in her introductory statement, she will indicate why this should not be connected with the topic of the prior day and a half.

With that, Celia, do you want to give your introduction?

Agenda Item: Topic III - Draft Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products

FDA Introduction

DR. WITTEN: Thank you, Dr. Snyder.

This is just a brief introduction. I would like to welcome the members of the Cell, Tissue and Gene Therapies Advisory Committee and their special government employees who are staying for the presentation and discussion of this second topic, as well as members of the public, and to thank the members of the FDA who planned this second day's discussion.

This afternoon's discussion will focus on the draft guidance entitled "Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products," which was issued in July 2013. The advisory committee's consideration of the draft guidance is a

separate and independent discussion from the discussion of mitochondrial manipulation technologies that just concluded over the previous day and a half. The draft guidance document is intended to help direct development of any early-phase clinical trials of gene and cell therapy products that are regulated by our office and addresses a number of questions that have come up over the years in our discussions with sponsors who are working in this area. FDA will consider the advice from this afternoon's advisory committee discussion in preparing the final guidance document.

This afternoon we will begin with John Hyde, from the Office of Cellular, Tissue and Gene Therapies. Dr. Hyde will provide backgrounds and an overview of the scientific questions the committee will be discussing. Over the rest of the afternoon, the committee will discuss the FDA questions on this topic and provide any additional comments they have on the guidance in general.

Now I turn to Dr. Hyde for his presentation.

Agenda Item: FDA Presentation

DR. HYDE: Good afternoon. I'm John Hyde, from the Office of Cell, Tissue and Gene Therapies in the Center for Biologics.

The purpose of this section of the advisory committee meeting is to discuss this draft guidance

document, “Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapies.” I will be presenting an overview of the draft guidance and the discussion topics for the committee.

As you might expect, production of a draft guidance requires the efforts of a number of people. Listed here are the FDA staff that contributed in various ways to the guidance document.

The draft guidance document is available through the CBER website. The link is listed here. The draft guidance document includes information on submitting comments to the docket, and the number is listed on the slide.

On July 2 of last year, the draft guidance was published for public comment. Today, February 26, we are presenting the draft guidance to this advisory committee for discussion, as well as to further publicize its availability and call for public comment. The comment period has been extended from the date originally published. May 9 of this year will be the end of the comment period. Then we plan to finalize the document as soon as feasible after the comment period closes.

Let me first say a few things about the motivation for producing this guidance. Cellular and tissue therapy products have distinctive features compared

to small molecules or some other biologic products, such as monoclonal antibodies and therapeutic proteins. Therefore, the design of early-phase trials is often different from that of other pharmaceuticals. This guidance is intended to provide perspective to improve early clinical trial development in cell and gene products. The intent is primarily educational, to make IND sponsors aware of issues to consider when proposing early-phase trials and provide them with recommendations for ways to address those issues. The hope is that this will help IND sponsors in the design of their early-phase trials and enhance their interactions with the FDA.

I want to stress that the guidance does not set forth any new requirements on IND sponsors. The guidance is intended mainly to provide advice.

The intended scope of the guidance is the biologic products for which the Office of Cellular, Tissue and Gene Therapies has regulatory authority. In particular, it applies to early-phase trials in cell and gene therapies. The guidance therefore does not cover tissue-based products regulated solely under Section 361 of the Public Health Service Act, Devices, or the biologic products that are regulated by the Center for Drugs.

The scope of this guidance is also limited to clinical trial design, and design of the first few clinical

trials is only one aspect of getting a clinical development program going. There are also the important issues of manufacturing the product, conducting the preclinical or animal studies. IND sponsors often have questions about those areas, too, but those topics go beyond the intended scope of this particular guidance document. However, we certainly recognize the importance of those other issues, so it should be pointed out that our office has produced other guidance documents that address manufacturing issues and preclinical aspects of product development for cell and gene therapies. I have included links to those other guidances on this slide for reference.

I will not be discussing those documents here, and we are not asking the committee to comment today on the topics covered by those guidances.

The bulk of my talk will be an overview of what's contained in the guidance document. Here I have the outline, from the table of contents. The real meat of the guidance is in sections III and IV, where we talk about special features of cell and gene therapy products and how those features impact the clinical trial design. I'll describe each of these sections, but my talk will focus mainly on the material in sections III and IV. Finally, I'll go over the topics we're asking the committee to discuss.

The introduction goes over the purpose and the scope, much as I have just described. Section II provides historical background on issues that have arisen and the early experience with cell and gene therapy products. The background section also provides a quick overview of the special features of cell and gene products.

Now I'll say a little more about the two major sections.

Section III sets the stage by giving more specifics about the features of cell and gene therapy products that could impact the design of early-phase trials. General features include the relative novelty of these products. There is a relative lack of clinical experience compared to the vast experience of many small-molecular pharmaceuticals or even monoclonal antibodies or enzyme replacement products.

Also, importantly, it's not at all unusual for a cellular or gene therapy product to need invasive administration to get to its target. Common examples are cardiac catheterization, injection in the central nervous system, or other procedures that might require surgery to get the product to where it is intended to be.

Cellular products may require a donor to obtain the cells. This can be the subject who is going to be treated or the donor might be some other people who is not

getting the treatment. Cells might also have the potential for differentiation into other tissue types. Cells may undergo migration from the site at which they are initially placed.

Gene products present issues of uncontrolled or poorly controlled expression that could interfere with other biologic processes. There could be the potential for genome alteration. Genes delivered by viruses or other microbes raise the possibility of vector shedding, which refers to the possibility of transmitting the vector to other people or releasing it into the environment. And, of course, gene-modified cell products, which involve the administration of cells that have had their genes modified, can have features of both the cell and gene products.

Other features of cell and gene therapy products result from the complexity of the manufacturing process for certain of these products. In some cases there may be limits on the range of concentrations or doses that can be manufactured. Logistics can play a role. For example, a product may have a short shelf-life. In other words, it may need to be administered shortly after it’s prepared in order to maintain its potency.

Some products might be made only for a specific subject, such as a product using autologous cells -- that is, the subject’s own cells. There could be considerable

variability in the product from one subject to the next -- for example, due to variation in the number of cells that are harvested.

Also, if manufacturing is long and complicated, there could be a significant delay between when a subject is enrolled and when the subject is treated. The subject's condition might change substantially in the meantime.

Finally, there are special considerations regarding the role of preclinical or animal data. Conventional pharmacokinetic, or PK, studies such as are routine for small molecules usually simply are not feasible for cellular and gene therapy products. Preclinical studies for cellular and gene therapy products may be harder to interpret than those for small molecules as far as extrapolating the findings to humans. This may be due to species specificity of the cell type or the gene or because of cross-species immunogenicity. So for several reasons, extrapolation of preclinical information to humans has the potential to be especially challenging.

As I mentioned earlier, there is already another guidance that addresses cell and gene preclinical issues in detail. We're not asking the committee to comment on those topics today.

Section IV of the guidance document talks about how the specific issues I just discussed might affect the

way early-phase trials are designed. Section IV also makes some general recommendations about approaches to addressing those issues. The subsections include objectives, choosing study population, control group and blinding, dose selection, treatment plan, and then monitoring and follow-up. I'll talk about each of these sections in turn.

The primary objective of early-phase trials, especially first in human, should be safety. But there are often additional objectives. These includes not only dose exploration, which is common in Phase I for many types of products, but also a preliminary assessment of feasibility regarding some of the logistics issues of manufacturing or delivery and some initial assessment of bioactivity, in many cases using some kind of biomarker, to see if the product is actually present and showing at least some of the expected physiologic or pharmacologic effects.

Choosing a study population is a complicated issue and will depend greatly on the nature of the product and the disease being targeted. Here the draft guidance mainly tries to identify the considerations that should go into making that choice, and it provides some general advice. The potential of the product or its effects to persist or even be permanent, along with often significant uncertainty about the totality of risks, usually means that some potential for benefit may be necessary to make the

risks acceptable. The need for potential benefit often makes healthy volunteers not a suitable study population.

One approach that is sometimes proposed is to enroll subjects with the most severe or advanced disease, on the assumption that using this population is a way to make the risk-benefit more acceptable. However, these subjects may also be more vulnerable to adverse effects or less likely to be in a position to benefit, or the background of severe illness may make results harder to interpret, so the trial might not be that informative. Therefore, the guidance makes the point that the use of subjects with severe or advanced disease should not be an automatic choice for early-phase trials.

Finally, there are specific regulations regarding research on pediatric subjects. The guidance provides an overview of those regulatory requirements. Of particular note is the fact that cell and gene therapy trials almost always pose more than a minor increase over minimal risk to pediatric subjects, so there needs to be a prospect of direct benefit to pediatric subjects who participate.

Control groups can be valuable in early-phase trials for safety and preliminary assessment of activity. However, some cellular and gene therapy products require an invasive administration procedure, and it can be challenging to decide what constitutes an appropriate

control group for trials of those products. For a product that needs an invasive administration, an invasive control might be necessary for a Phase III trial in order to have an effective blinding needed to make the efficacy results more persuasive. However, in early-phase trials, the objectives are only to get a preliminary idea of the product's effects. Therefore, rigorous blinding can be less critical for early-phase trials than for late-phase trials. In fact, rigorous blinding may not be desirable for early-phase trials if the blinding can't be done simply and with minimal risk to control subjects. For example, if the risks of the invasive administration procedure are substantial, then rigorous blinding with an invasive procedure in the control group might not be appropriate.

However, having some control for the study is still valuable, and the use of a concurrent control group that does not undergo an invasive procedure may be an acceptable approach in such situations.

For small molecules, there are widely used methods for scaling up to human dosing from animal studies. But for cell and gene therapy products, the conventional allometric scaling may be less precise, which can make it difficult to establish a safe starting dose. Previous clinical experience with similar or related products can be useful to consider in the starting-dose determination.

With cell and gene products, it may be challenging to decide even how to describe the dose, because different attributes of the product may be responsible for different effects. In other words, efficacy may depend on one attribute, safety may depend on a different attribute. For example, cellular products may be a mixture of cell types, and different cell types may contribute differently to the product's effects.

Gene transduction rates can be highly variable for a gene product, and vectors that do not contain the therapeutic gene, which would not be expected to contribute to efficacy, might be relevant to safety.

Due to the possibility of extended duration of activity, the dosing regimen is often a single administration or a one-time dose, and repeated dosing might not be an acceptable risk in early-phase trials.

Most first-in-human trials of cell and gene therapies will involve staggered administration, which means that rather than treating several subjects at once, an individual subject or a small group of subjects is observed for a specified period of time before the next subject is treated. This might be done for the first few subjects in the trial, for the first few subjects after each dose increase. The guidance explains some staggering schemes and considerations for picking the observation time

between subjects.

For dose-escalation trials, “cohort size” refers to the number of subjects used to evaluate the dose before going on to a higher dose. The size should depend on the considerations of the risks. A 3-plus-3 design is a common scheme in oncology, but that might not be appropriate for other therapeutic areas.

Manufacturing issues or disease prevalence also sometimes influence cohort size. When product delivery involves complex administration or specialized devices, operator training or skill may be an issue. It may be important to specify a required level of proficiency. It’s important to record and evaluate administration procedures. One might then be able to identify modifications that need to be made to the administration procedure.

If the product is subject-specific, such as a product that is made using cells harvested from the subject or a matched donor, then the trial design should have contingencies for such things as manufacturing failure or for a change in the subject’s condition while waiting for the product to be manufactured.

The primary objective in the early-phase trial should be safety, and so general types of safety monitoring would be appropriate for an early-phase trial. Such general safety monitoring would include routine exams,

routine labs, possibly some targeted testing for adverse effects of concern or that are relevant for the disease being investigated.

As mentioned previously, looking for evidence of some sort of physiologic effect or bioactivity may also be an objective. When looking for bioactivity, one should anticipate that the effects of cell and gene products might develop slowly or be delayed relative to the traditional time course of small molecules. The monitoring should take that delay into account.

For certain cell and gene therapy products, it may be appropriate to consider including more specialized testing to address issues that are particular to these products. Such testing could include testing for immunogenicity, for persistence of product or activity, for migration of cells, for shedding of microbial vector used to deliver a gene. For pediatric subjects, the potential for protracted effects may mean that there could be a need to have assessments of growth and development.

Follow-up may need to be extended in cell and gene therapy products. In general, the duration of follow-up should be designed to cover the period of time during which the product might present safety concerns. Follow-up for a year or longer is appropriate for most cell or gene therapy products. There is already an existing FDA

guidance document covering recommendations for follow-up for certain gene therapy products, but there is no corresponding guidance for cellular therapy products.

Some cell or gene products that use harvested cells may require some sort of pretreatment of the donor to facilitate harvesting the cells. As an example, stimulating factors might be used to enrich cell populations in peripheral blood. For products where there is cell harvest using pretreatment, there may be a need to have follow-up of the donor after the harvest, even if the cell/gene therapy product is not given to the subject.

As mentioned previously, special concerns about the effects in pediatric subjects may call for long-term monitoring to assess growth and development.

It’s important to note that if extended follow-up is needed, it usually would not need to be as detailed as the follow-up schedule and procedures used in the main part of the study. It’s also important to note that even if long-term follow-up is needed, it is often not necessary to complete that follow-up before the next study can begin, so that subsequent trials can proceed based on support from shorter-term interim data.

This guidance includes a subsection discussing considerations for stopping rules and explains the reason behind them and how they operate. Stopping rules stipulate

events of a certain type or occurring with a certain frequency that will lead to suspending treatment, pending a review to determine if it's safe to continue. Stopping rules are valuable for products for which there may be significant uncertainty about the nature, frequency, or severity of the adverse effects that might occur. The role of the stopping rule is to limit the number of subjects exposed to an unexpected safety problem. Depending on the event that triggers the rule, the event may call for a modification to the study, such as change in enrollment, dosing, administration procedures, or monitoring plan in order to mitigate the risks, rather than necessarily terminating the study. So a stopping rule is not a study termination rule.

Section V of the guidance makes the point that we very much encourage sponsors to have interactions with the FDA, even before they submit an IND. Section V also lists about a dozen clinical topics as issues that might be appropriate to discuss at a meeting with the FDA.

Section VI points to additional information about submitting an IND. The section is relatively short, and it's not intended to provide comprehensive instructions on how to go about submitting an IND. It's mainly limited to citing regulations and other FDA guidance documents that are concerned with the information that should be provided

in an IND submission.

The section also provides some brief general advice and suggests that sponsors consider the overall development plan early in a product's development.

That concludes the overview of the draft guidance on early-phase trial design. Section VII is references, and references are references, so I won't be commenting on that section.

Now I would like to go through the discussion topics that we have chosen for this advisory committee meeting.

Sections IV.B.1 through IV.B.3 of the draft guidance suggests the selection of study population for early-phase trials. The draft guidance states that the use of healthy, normal volunteers does not provide an acceptable risk-benefit profile for most cell/gene therapy trials. But it also makes the point that the most severely affected subjects are not necessarily the best choice for early-phase trials either.

Specific topics in these sections include study of healthy volunteers, disease stage or severity, and the availability of alternative treatment options for subjects.

The committee is asked to discuss this section, which addresses the principles of choosing an appropriate study population in early-phase trials of cell and gene

therapy products, and we ask that you identify any revisions or additions you recommend for this section.

Section IV.B.4 of the draft guidance addresses the use of pediatric subjects in early-phase clinical trials. The section is largely an explanation of the existing regulatory requirements pertaining to the use of pediatric subjects in clinical research.

The committee is asked to discuss any revisions or additions that they recommend for that section, and we ask you to please consider how data in adults could support the initiation of pediatric studies.

Section IV.C of the draft guidance addresses the choice of control group for early-phase trials. For example, a concurrent control group may facilitate preliminary assessments of product efficacy in early-phase trials, particularly when the natural history of the disease is not well characterized. Some cell and gene therapy products require invasive procedures for administration, but an invasive procedure might not be reasonable or necessary for control in an early-phase trial. So a question that commonly arises is the advisability of using a control that involves an invasive procedure as opposed to using a sham procedure or simply standard of care.

The committee is asked to discuss the section

that addresses choice of control groups, and we ask that you identify any revisions or additions you recommend for this section, particularly with regard to the need for and selection of an appropriate control in early-phase trials if the cell and gene therapy product requires an invasive procedure for administration.

Section IV.F of the draft guidance presents considerations for monitoring and follow-up. For certain types of gene therapy products, the FDA has issued guidance on the recommended duration of follow-up, but no comparable guidance has been issued for cellular therapy products. Topics in this section of the draft guidance include monitoring for both expected and unexpected safety issues, special monitoring considerations -- e.g., for malignancies or graft-versus-host disease for cell and gene therapy products -- and the duration of the follow-up.

The committee is being asked to discuss the principles that should be used to decide the duration and nature of safety follow-up for early-phase trials of cellular therapy products.

Finally, in addition to the topics 1 through 4, our office is interested in obtaining input from the committee on any other sections of the draft guidance. We are asking you to comment if you have any recommendations for any topic in the draft guidance that the draft guidance

did not address in sufficient detail or if there are important topics that the draft guidance omitted. We ask that you please identify any revisions or additions you recommend.

Keep in mind, however, that the intended scope of this draft guidance is limited to clinical trial design and that manufacturing and the preclinical issues are addressed in other guidance documents.

In conclusion, we published this draft guidance in hopes of facilitating early-phase clinical development of cell and gene therapy products. We're looking forward to receiving public comment on the docket, and especially to the discussions of this advisory committee, in order to make the guidance as useful as possible.

That concludes my talk. I'll be happy to take questions. While I do, I want to leave up the slide that shows how anyone who is interested can provide comments on the draft guidance. Comments should refer to the docket number, which is on the slide. The docket will be open for comment until May 9 of this year. If there are questions about the comment process, those can be directed to, at the bottom of the slide there, the Office of Communications, Outreach, and Development, using the contact information on the slide.

Thank you. I'll be happy to take questions.

Agenda Item: Q&A

DR. SNYDER: We're open to questions directed to Dr. Hyde regarding his presentation. Larry?

DR. COUTURE: Just sort of a procedural question. Is the intent to get suggestions and whatnot, and then issue a new draft for public review again or is this for suggestions that would be in maybe a future version of the guidance document? How do you see the outcome of this meeting affecting this particular --

DR. HYDE: Let me refer back to Dr. Anatol's talk at the end of this morning. The standard process is that we issue a draft guidance, put it out for public comment. The usual process, unless there are a lot of issues, is that we consider those comments, whatever revisions we might need to make to that. Then usually we put out a final draft at that point. As she said, one can still comment on a final draft, but at that point we consider it our final version.

DR. LEE: This morning or yesterday, I have problem visualizing how the data is quantified. The main reasons are we need to do dose escalation in Phase I, as mentioned in your slide. When the procedure is not -- I don't see how we do dose escalation if we don't have this measurement quantified in the procedure.

DR. HYDE: The guidance is really issues for

considerations. We don't give answers to any of these, although we do recommend some approaches, or at least things to consider in trying to formulate or address those issues.

DR. SNYDER: Maybe to answer Dr. Lee's question, it might be helpful for you to give a standard protocol for how one might do a dose escalation, in your experience. For example, you talked about the 3-plus-3 design.

DR. HYDE: In oncology, where you are sort of expecting toxicities as part of the effect of the product, a 3-plus-3 design is sort of standard, where a small cohort of three is done. If there's no problem, you escalate the dose. If you get one limiting toxicity, then you might expand it with another three. Depending on the results, you may go up or down or stop. That's a widely used protocol in many oncology applications, but not all.

Sometimes we have seen protocols that sort of apply that oncology algorithm in areas where they really don't seem to be terribly appropriate. If you are not expecting a lot of toxicity, you're mainly concerned about a threshold of efficacy. Also if you have a very small population to deal with, an extremely rare disease, you may want to think about how to do it, other than that sort of standard thing.

The guidance is just to try to expand horizons in

people’s thinking about how to do dose escalation, and not simply doing some automatic algorithm that might be popular.

DR. SNYDER: One of the things we may consider -- question number 5, I believe, is things that are not spelled out as well in this document. It sounds like, for legitimate reasons, dosing in these products is very, very difficult. There is very little guidance. Maybe that can be topic number 5, something that needs to be spelled out. How would one start with dosing?

So why don't we make that the topic of question number 5, which hasn’t been explored as well in the document, and not covered by the previous questions? I think it’s a very good topic.

DR. HYDE: We certainly welcome that. Our questions haven’t covered every aspect of the guidance, only those where we thought issues were a little harder to resolve. We certainly welcome comments on any aspect.

DR. SNYDER: And it is a conundrum. Having dealt with cell products a lot, it may be the one aspect that stymies the researchers trying to do an early-phase clinical trial more than anything else. So we’ll make that one of the discussion topics.

DR. COUTURE: Without getting into number 5 and all the other things, you mentioned several times that you

haven’t come out with guidance documents for cell therapies -- long-term follow-up. Is that because you don't intend to or you are looking for us to help put together what those long-term follow-up guidelines should be?

DR. HYDE: I’m not sure I can answer that. It depends. Certainly with the gene therapies, we perceived issues and a need that we needed to address with that. It’s a little less clear what needs to be done and how we might deal with that. That’s why we are using this venue to raise that issue: Is there something that we need to think about more in that area?

DR. COUTURE: So it would be helpful to the agency for us to have a discussion about long-term follow-up for cell therapies?

DR. HYDE: That’s certainly one of our questions.

Again, the intent of the guidance is not to answer those questions, but at least to raise the issues to the point where sponsors think to address them when they have a submission. That may lead to additional actions on our part, too.

DR. SNYDER: Thank you very much.

We’re doing really well on time. That means we’ll be able to get into the questions, and maybe, after an hour into the questions, we’ll take a break and then

finish.

Agenda Item: Open Public Hearing

DR. SNYDER: We now are at the part for open public hearing. I have to read a conflict-of-interest statement.

Both the Food and Drug Administration (FDA) and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include the company's or group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement,

it will not preclude you from speaking.

So far we have registered one member of the public who would like to make a statement, Rafael Cassata.

MR. CASSATA: I'm Rafael Cassata. I'm deputy director of regulatory affairs at the Center for Cellular therapies at AABB.

I do not have any financial conflicts of interest to disclose.

We would like to thank FDA for bringing this topic for discussion to today's advisory committee meeting. We would also like to commend FDA for developing this draft guidance document, which, when finalized, will serve as an instrumental tool in contributing to the design of many Phase I clinical trials for cell and gene therapy products.

AABB has developed preliminary comments to the draft guidance document, which will be submitted to the docket before the end of the comment period.

In general, we think that the specific sections, Sections IV.B and IV.F, highlighted for today's discussion are of the most concern for AABB's membership. Specifically, we would like to iterate a few issues relevant to today's discussion.

We recommend including geriatrics to the list of the study population groups listed in Section IV.B. Geriatrics often have comorbidities and concomitant

therapies that may interact with the investigational cell and gene therapy product. These age-associated issues may not be observed or extrapolated from the traditional adult population.

Additionally, in Section IV.F.3 on monitoring and follow-up, FDA recommends that long-term monitoring not be designed as a separate protocol. However, for academic centers or any other organizations, federal funding will not allow carryover grant money to cover long-term follow-up. Additionally, there are logistical challenges with keeping a database open, especially if the clinical development of the product will progress to Phases II and III trials.

Thank you for this opportunity. We look forward to submitting our complete set of comments before the end of the comment period.

DR. SNYDER: Thank you very much.

Do any members of the committee have any questions you would like to pose to the public speaker or additional information?

(No response)

Is there anybody else in the public who would like to make any comments?

(No response)

Then I think we can move on to the next agenda

item. We're really quite good on time, so what I would suggest is, let's begin tackling the questions, and after an hour into that, we can take a break and then finish up the last three questions or whatever.

Agenda Item: Committee Discussion of Questions

DR. SNYDER: I think it might also be worthwhile -- question number 5 is a bit of a wildcard. It means that any topics that should be fleshed out in this guidance document that are either not going to be discussed explicitly in the first four questions or that maybe emerge as a result of discussion of the four questions can be tabled to there. That will be a group discussion. I can chair that.

What I would suggest is that we keep track of items that might be worthwhile discussing in question number 5, before we adjourn. The three items that I took notes on that could be included there were:

- The issue of dosing.
- Then, brought up by the public speaker, the inclusion of the geriatric population, which is probably as unique a population as talking about the pediatric population or a standard population.
- The issues of long-term follow-up and what we mean by that.

If anybody else -- you don't have to tell me now,

but when we get to that, issues that should be part of our discussion that might be included in the document.

Let's start with discussion topic number 1. I'll read it into the record. Dr. Cripe will be the first discussant. Then we will, as we typically do, quickly go around the room for any additional comments.

Topic number 1: Please discuss Sections IV.B.1 through IV.B.3 -- as if you can remember what those really were -- which address the principles of choosing an appropriate subject population in early-phase clinical trials of CGT products. Please identify any revisions or additions you recommend for this section.

Basically, I think this will be talking about, within the adult population, the use of severely affected patients and healthy patients.

Section IV.B.4 of the draft guidance addresses the use of the pediatric subjects. That will not be included in this particular -- this is just dealing with adults, severe versus healthy patients.

Dr. Cripe.

DR. CRIPE: I actually prepared most of my answers to discussion topic 2, since that's pediatrics and what I was thinking I was being assigned.

Just briefly on topic number 1, I agree completely with the sentiment that healthy volunteers,

although they may typically be the subjects for Phase I studies in general, are most likely not going to be appropriate in most cases of these kinds of higher-risk gene and cell therapy products. So I really don't have any revisions for that.

In terms of disease stage and severity, I applaud the FDA for already identifying the fact that these patients that are typically included in Phase I studies are often the highest-risk patients with the shortest expected lifespan, particularly in our field of oncology, and they therefore may not be the most appropriate targets. What I would recommend perhaps is some discussion about the possibility of what we would call window therapies that we have used in pediatric oncology to address this issue -- that is, without inhibiting or preventing subjects from getting standard of care, beginning with a short window therapy, trying a new agent for safety. In some cases in our field, we have been able to incorporate that window therapy in their future standard-of-care therapy if there is efficacy in that short window. Usually it constituted a few weeks of a novel combination of drugs or whatnot to see if in a given patient there was any response.

It’s a little bit harder to imagine how that might play out in terms of cell and gene therapies because of the longer-term effects in that, but I raise that as a

possibility for discussion, rather than wholesale moving everything up earlier in the course of the patient's disease, which then changes the risk-benefit ratio and may make it less feasible. It's just an idea to throw out there to think about.

I otherwise don't have any significant additions to this section.

DR. SNYDER: Let's quickly go around the table and see if there are any other thoughts.

DR. LEBKOWSKI: On this question, I polled colleagues from industry, the Alliance for Regenerative Medicine, from BioSafe groups, and no one had any particular comments on this section, but just to reiterate, really appreciated the flexibility, and the adult population that may be the most severely affected isn't necessarily the best patient population in which to start these trials. So it was positive reinforcement.

DR. COUTURE: I just have a couple of comments. It comes from experience in doing a lot of these cell and gene therapy trials. Two things are not really highlighted in here -- if I can remember what they are.

The first is that there was no discussion about ensuring that you can actually enroll the patients you are selecting for the trial. We see a number of trials that end prematurely simply because enrollment just isn't

possible -- and, quite frankly, could have been predicted to not be possible up front, if just the institutions that were doing the trials were polled. I think the agency should say that sponsors should at least consider the likelihood of success of the trial. Otherwise, you're wasting patients' time. They are at risk, with no real benefit if you end up doing one or two patients.

The second is -- we have also seen this a fair amount -- what could have been predicted to be reasonable standard-of-care treatment of the patient during the ongoing care of the patient that could impact your product. For example, immunosuppression might be added to a standard of care down the road, and if that were to happen and you had some product in there that would be adversely affected by that, it might make a difference.

I think those two things are things that are not adequately covered in the guidance document.

DR. ROSE: I think, first off, the FDA is to be commended on the flexibility. I agree totally. I'm in a slightly different situation, in that we're doing eye research, so we are in a very limited area. The issue is making sure it doesn't get out.

Part of the issue here is, ensuring safety first may be something to do in people with more limited vision or further along in the disease, but the ability sort of

gets to the dosing issue and who the population is. Moving down to a less affected population is certainly something that is allowed in here and something that provides the flexibility that's needed as we go forward.

DR. LEE: How to define dose is very important. That's my only comment.

DR. GOLDMAN: Just a point that will come up later, to reiterate Larry's point, the likelihood of success as something to potentially consider up front, not only in regards to success in recruitment, but in terms of in a Phase I design whether or not some elements of Phase II should be incorporated in terms of Phase I definitions for cell therapeutics. This is something we can get to a little later.

DR. SNYDER: That certainly comes up a lot. Taby?

DR. AHSAN: A couple of comments. One would be about minority and health disparities, thinking about certain socioeconomic groups or ethnic divisions and how that plays in. For certain applications, maybe they are more of a target because they have a greater prevalence of the disease or the pathology. Those need to be, I think, carefully considered. Also vulnerable populations include aging, and taking that into account.

The other thing is, in regard to the most severe

cases, as we start moving towards autologous and personalized medicine, there is a morbidity sometimes associated with a primary harvest site. Whether or not they can tolerate that might be an important issue to consider. The worst-case scenario is that you start the clinical trials and you can't enroll enough patients, which means that the people that did enroll were adversely affected, potentially, for no reason. That's one thing to think about.

Also for safety, if you are looking at the most severe cases, with some of these cell, tissue, and gene therapies -- we'll get to this a little bit later about monitoring and follow-up -- if the safety follow-up is for extended periods of time and they don't actually have an extended prognosis, then we may not get the safety information from that demographic that we actually need.

Those would be things, I think, to consider when we talk about subject population.

DR. SNYDER: Linda?

DR. DAHLGREN: Nothing further.

DR. SNYDER: Dr. Emens.

DR. EMENS: I would just like to emphasize this idea of window therapy. In oncology a lot of times we test new drugs very late in the disease process. I think people are starting to come around to the idea that earlier may be

better. You can approach that as a window of opportunity, where the patient is really not get standard therapy because the window is truly there, or you can approach a trial design and selection of a patient population by considering the potential interaction of the agent with standard therapies, provided that there is preclinical data supporting a combination type of approach.

DR. BUGBEE: In my field, which is often arthritis, the best population for these treatments would be, paradoxically, the least affected. So I think, as has been mentioned, some consideration of that. The early arthritic patient, for example, would be probably a better study population than the late. These patients might be the type that would otherwise choose no treatment. So some consideration of these as maybe not an alternative, but as a new therapy versus simple observation.

I'm sitting next to oncologists. Probably most of the subject populations that would get this, frankly, would be non-life-threatening diseases. Understanding the risk-benefit -- consideration that most people might be treated -- for example, arthritis would be non-life-threatening. So the risk-benefit of that should be considered.

DR. SNYDER: With regard to question number 1, I think this is pretty simple to summarize. By and large,

the committee seems pretty happy with the topic, recognizing that, at least for Phase I, healthy volunteers are probably an unacceptable risk-benefit. For severe patients, it's recognized that they certainly are a population that is willing to accept the risks or probably in the greatest need and probably can tolerate any adverse effects better. On the other hand, they are less likely to have a success and perhaps may be too sick to respond. Even for the intent of a Phase I study, either they may not survive long enough to be able to look for long-term risks of the procedure or they may be so sick with other comorbidities that any kind of risk attributable to the procedure or the GTC product may be uninterpretable or confounded by so many other comorbidities that it would not be useful.

I think the consensus was that you should pick the patient population that gives you the best interpretability of outcome data. It doesn't necessarily mean -- the most severe should not be your knee-jerk reaction. And be cognizant of the need to include minority patients or patients in which the disease may have a disproportionate amount of representation and assess the risk-benefit.

Any other modifications of that summary or anything else?

(No response)

Now we can move on to discussion topic number 2: Please discuss any revisions or additions that you recommend for Section IV.B.4. In the discussion, please consider how data in adults could support the initiation of pediatric studies.

I'm the discussant on that. This basically addresses the inclusion of pediatric patients in clinical trials. This is actually something that I am somewhat passionate about, mostly because I'm a pediatrician, but also because in the field of regenerative medicine in which I work, the pediatric population is vastly ignored. That's for all kinds of reasons. Their diseases, as we talked about, are often very rare. Typically nobody has heard of them. These kids often have such lethal diseases that they do not survive long enough to be a Michael J. Fox or a Ronald Reagan -- to be the face of a particular disease. So then you depend on parents that are famous, some of whom want to hide the fact or shield their kids.

So kids seem to be ignored, and they should not be. They obviously need additional protection.

But I would make the argument that they shouldn't be an afterthought. First of all, many of the diseases only manifest in the pediatric age group. For some of these therapies, the CTG therapies, they tap into --

particularly the stem cell therapies -- developmental programs. That's what they do. Stem cells are part of development, and it's the developing system where they are most likely to have their greatest effect, early on in the system, in fact, harnessing developmental processes.

Any of the pediatricians around the table will know this. There typically is a pediatric version of almost every adult disease. The advantage is that the cell types or the genes or the pathophysiologic processes are actually much better defined. Parkinson's is an example of that. Familial Parkinson's helps you study Parkinson's disease much better than sporadic Parkinson's disease. The same thing for neuromuscular diseases or certain dementias, lysosomal storage diseases, things of that sort.

So not only is there a need, but they may also inform adult diseases. What I would emphasize is not what tends to be the case, which is trickle-down therapy -- let's try it in adults and let it trickle down to the kids -- but, rather, bubble-up therapy, to preferentially approach some of the pediatric diseases and learn from that and let that inform the adult diseases.

Obviously the kids need very, very careful protection. One, they are not old enough in many cases to give informed consent. The adults have to give informed consent.

What was brought out in the document -- and this is quite good -- is that you are dealing with a developmental system. Everything is developing -- the nervous system, the bones, the teeth, the psyche, cognitive function -- which means that certain systems that would not be attended to in the adult absolutely need to be attended to in the kids. This requires very long-term follow-up, including aspects that might be not initially thought to be relevant to the organ being treated. For example, if you are trying to treat cystic fibrosis, which is a lung disease, or a pancreas disease, one might not think about looking at short-term memory development or language development. But you should. We still don't know a lot of the off-target effects of cells or genes or various things of that sort.

With that, in general, I'm pleased that pediatrics is included. Except for the nuances I just brought out, I think the guidance document is pretty good.

We can go around the room again.

DR. LEBKOWSKI: This is an area of a little controversy, not so much as to the document itself, but as to whether you start with pediatric patients or you start with adult patients in indications where there are patients of all ages that are qualified for the clinical trial. The biggest issue, as Evan brought up in the discussion, was

informed consent and the difficulties in getting informed consent from kids or from parents of pediatric patients. Some of these trials and some of these types of therapies are quite invasive and can also be very, very, very new, and the outcomes there are not known.

Under those circumstances, there seems to be a favoring that if there was an adult population that is a candidate, you start there and do the trickle-down, as opposed to the bubble-up.

Overall, the group pretty much felt that this is an indication-by-indication consideration. If you can make a case for the adults or you can make a case for the pediatric populations, you do that.

Again, mixed feelings, everybody, with each individual product, thinking about the various complications of using pediatric versus adult populations, and most of it, again, concerning informed consent.

DR. SNYDER: Larry?

DR. COUTURE: I don't have anything to add.

DR. ROSE: I would agree with what you said, Evan, and what Linda said. In our cases, which are retinal diseases, we have found that going to the pediatric population pretty early, actually, is extremely important. Rescuing and preserving vision is one thing. Not getting the disease to begin with is really the holy grail of where

you want to go.

We have found the FDA to be extremely flexible in this, working with the investigators in ongoing human gene transfer trials, which is extremely important.

I just want to say, a lot of them are not life-threatening. I think, without a doubt, we're at a different stage in the human gene transfer than we are with the cell therapies. I think that eventually that will catch up, but certainly treating earliest to prevent the disease is obviously the holy grail of where we want to go. I think the FDA is being very good at this. I just ask that, as things more forward, the flexibility and ability to allow going younger earlier be kept in mind.

DR. SNYDER: Dr. Lee?

DR. LEE: No comment.

DR. SNYDER: Steve.

DR. GOLDMAN: I just want to pose a question. This is a bit the reverse of what we have been discussing. I think all would agree that for many of the life-threatening pediatric disorders where cell or gene therapeutics will be assessed in a very age group -- neonates, infants, or young children -- parental consent, properly informed, is sufficient.

But I wonder about the flip side. A couple of years from now, when we have cell and gene therapeutics

that are proven effective, and very specifically in life-threatening diseases of the pediatric population -- when we get to that stage where we have unequivocal success with rescue of otherwise fatal disorders, what happens when a parent does not give consent?

Some of this, of course, impinges upon the ethical issues, on a number of levels, depending upon what cell therapeutic or gene therapeutic one is discussing. But I think this could be alluded to for a later date. But I do wonder what happens when we get to the point where these types of instances come up and we have to decide whether this is equivalent to withholding therapy in cases where it would be generally medically recognized as appropriate and called-for, or whether or not, even after the point of demonstration of efficacy, we will be looking at these as fundamentally experimental therapies that are subject to consent.

DR. AHSAN: I have a couple of comments here. Clearly in the pediatric population, the potential for good is tremendous with this, because they are so early in the trajectory in growth and development. But, of course, we also have to be careful about the contrary to that, which is having long-term adverse effects.

I wonder if in pediatric populations potentially, even if we do the trickle-down, extended or longer-term

monitoring is necessary. That might be something to really consider when we start thinking about the pediatric population.

Then, actually, I had the same thought that Steve did. Maybe there needs to be, especially as we are forward-thinking about therapies in the future, advocates that try to play into helping with decision making about which therapies certain children would be eligible for or should be involved in, just because of familial dynamics being very complex, especially in very sick children, where there are a lot of things happening in the family. That might be something to think about -- especially in heritable diseases, as well.

DR. CRIPE: I have a few thoughts. Again, I was pleased also to see this included in the document. But basically it's a reiteration of 21 CFR 312 Part D, which boxes us in pretty much in terms of what we can put into this guidance. Namely, the prospect of benefit is required for studies with more than minimal risk.

However, I would submit that there might be some things we could encourage the FDA to add in here to encourage developers of these therapies to be more pro-pediatric. Let me just frame the question a little bit with some observations from the field.

As you indicated, children are not smaller

versions of adults. They have distinct PK and PD, different tolerances of drugs. And it's not just one age group. Pediatrics isn't just an age group, of course. Babies are quite different in their physiology than prepubertal or postpubertal age groups. Maybe some encouraging words could be used to define the age group they are targeting and do studies specifically in those groups or models of those groups. In that regard, it really doesn't have to be trickle-down or bubble-up. It could just be for that population.

Although many of the adult-type diseases do appear in pediatrics -- and that was, I think, the intent of the PREA, the Pediatric Research Equity Act that would require companies to test pediatric indications for those that are shared. That may be good for asthma or other kinds of shared diseases, but in terms of cancer, for example, companies don't develop a drug for cancer. They develop them for breast cancer or colon cancer or lung cancer, prostate cancer. Kids don't get those. So that rule doesn't really benefit pediatric patients who have neuroblastoma or rhabdomyosarcoma or medulloblastoma. Although I think that's an important act to have enacted, I think it could go further.

It has been said that children die from their diseases just as efficiently as adults die from their

diseases. Our kids should be able to benefit from our research.

I think experience in other clinical trials has taught us a number of lessons. One is that usually kids tolerate drugs a lot better than adults. They have fewer comorbidities. The doses that we can dose-escalate in Phase I studies in kids with cancer are typically higher than those that adults can tolerate. In fact, the risk-benefit ratio may be different and it may be favorable for companies to study things in children.

In addition, there are different risk profiles. Drugs, for example, that may put an adult at risk for myocardial infarction -- that may be due to comorbidities that adults suffer from. That risk may not even be present in children.

I really think that the current paradigm of the way we conduct trials in pediatrics is not working well for drug development for children. There are many fewer patients, so accrual is often slow, which requires pediatric centers to open a lot of trials that don't accrue any patients, at their cost, if we want to capture those patients as much as possible. We need to encourage either legislation or guidance to keep the number of patients required as small as possible.

We often have to wait for the results of adult

studies before starting pediatric studies, and that slows progress.

What's more frustrating in the last several years, especially with targeted therapies, has been that drugs are often pulled from clinical trials if they fail a particular indication in a Phase II study in adults. So we may be in the middle of a trial in kids, Phase I, and the company decides it's not working in their primary indication in the adult population, and they pull the trial. That throws a wrench into the pediatric trial that may be in the middle.

Therefore, with this trickle-down, we're sifting everything through the adult diseases, and we're probably missing a lot of effective drugs for pediatric diseases by ruling them out because of the experience in adults first.

The other thing that has been typical in pediatric cancer trials is to start doses at 80 percent of the adult maximum tolerated dose. In fact, that reduces the number of patients who have a prospect for benefit, because we're starting at usually a lower-than-effective therapeutic dose, when in fact most drugs are tolerated better by children. One proposal might be to allow starting at the maximum tolerated dose for adults in a given study.

I agree that, for most companies, pediatric

development of drugs doesn’t make business sense. I would encourage this document to refer readers of the guidance to the Best Pharmaceuticals for Children Act and the PREA, to encourage them to look at the possibility of developing pediatric indications and the benefits that may come from that, such as patent extension.

When it comes to cell and gene therapy issues, we do need to consider age-specific effects on gene expression patterns, on cell differentiation, and hormonal effects through puberty. Those do pose extra potential risks in these populations. The years of life that are potentially affected are quite different. Is 15 enough? Do we want to follow patients for 70 years? Should there be some criteria where, if a given subject that has undergone treatment passes after a certain number of years, they could come off follow-up?

The point that was already brought up by others about who pays and how we get grants or academic institutions to pay for that follow-up is an important one that I want to reiterate.

No model will be predictive of the effect. So I don't think the answer is to just test in more and more models and get more and more data. Ultimately these reagents need to be tested in humans. But I would encourage us to think of not just a risk-benefit ratio, but

a risk-risk ratio. What is the risk of the patient undergoing the procedure versus the risk of not doing it? For patients who are terminally ill, the risk of not doing something may be greater.

I tried to think of what kinds of solutions we might be able to encourage or things that there may be flexibility on. I don't know whether all of these would be constrained by existing laws:

• Perhaps encouraging drug companies to go lower than the standard age of 18 to a lower postpubertal age, 14 or 15, with some of their adults might help.

• I think starting Phase I doses at 100 percent of adult maximum tolerated dose, for those that are doing trickle-down.

• Perhaps not even requiring adults first, particularly, obviously, for those diseases that are exclusive to children.

• There ought to be a mechanism for the use of products that are not approved for therapy, but where substantial experience has been gained. What we found in some other kinds of treatments -- for example, I-131 MIBG, meta-iodobenzylguanidine, therapy for neuroblastoma -- it has now been used for over 20 years. There’s a preponderance of data on its effectiveness. But no company has stepped forward yet to want to take it to licensing.

So any institution that wants to start that therapy for children with neuroblastoma has to get an IND and, under that IND, cannot recoup the costs of that reagent, unless it's for a compassionate-use IND, in which case they can't collect the data for research.

It provides a conundrum for us in the field, without having something in between where we can use a product where there's a preponderance of data, but there is no drug company that wants to invest in taking it to licensing.

I would propose that we do modify this section some, referring the readers to the BPCA and the PREA, perhaps think about ways we can reduce the number of patients required, going beyond the 3-plus-3 design, and perhaps at lower doses, only requiring one patient, for example, before dose escalating.

Also the prospect for benefit, I think, is a bit vague. I'm a little worried that an industry sponsor would read that, be thinking, well, we have to prove that this is going to cure this patient's disease before we can test it in children. So we might want to define that a little bit more. Is temporary disease stabilization a benefit? Is just feeling a little bit better a benefit? Certainly in the cancer Phase I arena, we are now considering prolonged stabilization of disease a benefit.

So I guess one of the questions is, where does the bar fall on that, since that's an important element of considering pediatric studies? In fact, by the rule of the law, the prospect for benefit could be just generalized knowledge, and not necessarily curing that patient.

I appreciate this section, but I do think there is some room for improvement.

DR. SNYDER: Leisha?

DR. EMENS: I agree with the vast majority of the discussion to date. I guess the only thing that I slightly disagree with is the idea of including kids or young adults between 14 and 18 in adult trials. It seems like it might be better to have trials that focus on adults and trials that focus on kids of the appropriate age for whatever the intervention and the disease indication is so that the data stays a little bit cleaner. If the adults get into trouble with toxicity where the kids might not, it might mess up how the trial goes. So it might be better to keep them separate.

That's really the only additional thought I had.

DR. BUGBEE: In support of my colleagues here who treat pediatric patients, I support the idea that it may be important to put something in this document that recognizes that you may initiate studies in the pediatric population, and really look to how institutional IRBs will look at

this. Right now, if you say “cell and gene therapy” and “pediatrics” in the same sentence, it’s typically a nonstarter for many institutional IRBs. So perhaps an acknowledgment that we recognize that this is unique therapy and it may be appropriate in a pediatric population rather than this trickle-down effect that Dr. Snyder alluded to -- that might be useful for a study sponsor to help inform the local IRB or something like that.

DR. SNYDER: Bruce?

DR. COHEN: Nothing new to add.

DR. SNYDER: Again, not a whole lot of controversy here. I think a key point that came out of this particular question was that everybody was fairly happy that pediatrics was addressed in a positive sense in the industry guidance statement. In fact, it was said that kids should benefit from our best science. Even though they are a vulnerable population, and that was acknowledged, certain diseases are best treated early on and in the pediatric age group, and some diseases only are pediatric diseases that may be amenable to therapy. There may be a good risk-benefit ratio. The risk of not doing something may be worse.

It was brought out that prevention may be actually better than trying to do repair or regeneration or reconstruction. This would be particularly the case in any

life-threatening, progressive diseases. Many of these diseases in kids are not static. They are progressive. So getting in as early as possible would be good, and going younger earlier might be encouraged.

IRBs and companies should not think of kids as the third rail in regenerative medicine. There are certain extra degrees of attention that need to be paid when you do include kids. First of all, there's certainly the developmental component. Two is defining what benefit means in this age group. Is it stabilization? Is it cure?

There may be age-specific effects, which means that maybe pediatric groups should not be clustered together as all kids. They should be broken down into more discrete groups -- for example, premature babies, newborns, school-age, infants, adolescents. That would be important.

If one simply does trickle-down therapy, you may miss certain effects. If one simply goes by adult dosing, for example, and picks 80 percent of that dose, you may actually miss a therapeutic benefit because kids may tolerate some drug doses better than an adult. Perhaps, in terms of doing the dose-finding studies, we should be able to tolerate fewer patients at the lower dose that may be ineffective.

The other degree of vulnerability that was acknowledged was that this is a group of kids that cannot

give their own informed consent very often, so informed consent has to be done very carefully. To echo one of the discussions from the morning, because one will need very long-term follow-up, at about 7 years of age, perhaps the kids need to give certain kinds of consent to blood draws or to X-rays or to imaging, and at 18 years of age, maybe they should be re-consented.

Not pertinent necessarily to guidance in a Phase I study, but for longer-term considerations would be who pays for long-term follow-up. If this ever did become standard of care, what position should health-care professionals take in encouraging parents to enlist their kids in these kinds of therapies? Might there -- and I think this is both positive and negative -- be undue pressure for a rare pediatric disease for a family member to feel obligated to include their kid in even a Phase I clinical trial?

DR. ROSE: I just want to make the plea for the non-life-threatening rare inherited diseases. As I said, we deal with blinding eye diseases. Going blind is the second most feared condition, besides cancer. We have found in talking to companies and development groups that they really focus more on the life-threatening diseases. We just think that if there’s some way of acknowledging that it’s not just life-threatening, that’s really where

this needs to be.

DR. SNYDER: That's a really good point. You're talking about quality of life as well. That's as important as --

DR. ROSE: You are talking about a lifetime of -- even though there's a TV show on at the moment with a guy driving a $100,000 car, the bottom line is that blindness is not without its challenges throughout the rest of your life.

DR. BUGBEE: And I would concur. In the orthopedic world, the same thing.

DR. SNYDER: I think those are very good points.

Okay, I think we're ready to move on to question number 3. I'll read it into the record: Section IV.C of the draft guidance addresses the choice of control group for early-phase clinical studies. For example, a concurrent control group may facilitate preliminary assessments of product efficacy in early-phase trials, particularly when the disease's natural history is not well characterized. Some CGT products require invasive procedures for their administration. But rigorous control of a trial might not be as critical for early-phase trials as for Phase III confirmatory trials.

A question that commonly arises is the advisability of using a control that involves an invasive

procedure as opposed to using a sham-procedure control or simply standard of care.

Discussion topic number 3: Please discuss Section IV.C, which addresses choice of control groups. Please identify any revisions or additions you recommend for the section, particularly with regard to the need for and selection of an appropriate control in early-phase clinical trials if the CGT product requires an invasive procedure for administration.

Bruce Cohen is going to discuss this.

DR. COHEN: My first comment pertains to this, as well as all the other questions in this section. We're going down a new line of therapy. We are not trying to provide another treatment for high blood pressure or diabetes, where the rules of the game are known. My comment is that whoever is initiating the trial would have maybe even a closer relationship with the FDA in terms of advising this than would be otherwise. I know the FDA really tries to work with new treatments to make sure that the trial is going to go in the right direction, but even a closer relationship.

If the answer to this was obvious, we wouldn't have to have this discussion. I came up with a couple thoughts. One would be a vector-only trial. That may be a randomized trial, receiving vector versus vector plus

product. In a trial for an injectable into, let's say, a muscle or even an eye, one could choose left eye versus right eye or left biceps muscle versus left biceps muscle. I know that in some of the earlier muscular dystrophy trials, the muscle was used.

The other is to go outside the disease itself as part of the control group. We do no-benefit trials all the time in the United States. If you have to obtain spinal fluid so you can investigate whether a new metabolite is worth measuring or not, you're going to have to do spinal taps on people who are healthy control volunteers. Even if we talk about Phase I clinical trials in cancer, the purpose of a Phase I trial is dose escalation, and sometimes the dosages that we start out with, we know in our heart of hearts, will provide no benefit to the patient. When we do informed consent, we tell our patients this. The discussion goes: We know you're here because you want to get this new drug, but you're going to be entered into cohort 1 and cohort 1 is receiving one-tenth the dose that we think is helpful to treat cancer in animals.

We really do no-benefit trials all the time. So maybe we can consider a control group in certain circumstances being someone who may be at the end of life with another disease process, but would be a good volunteer

for one of these trials.

Finally, I think, in terms of how this may affect children, parents have been good proxy decision makers on pretty much all medical investigation that I have seen in my career. When we look back at bone marrow transplant in the early days, that was a horrendous therapy. It's now less horrendous in terms of the effects on the kids. But when we look back and learn from our past experiences, I think that has been a positive story.

DR. SNYDER: Thank you very much. Jane?

DR. LEBKOWSKI: Several comments here again. The choice of the control group -- again, not to be wishy-washy, but the group that I have been communicating with basically said it's really indication-specific. For instance, you were talking about an ocular application. The control eye might be just the other eye that doesn't get treated. Similarly if you are looking at treating a limb or something like that.

On the other hand, the thought is, in many cases, there isn't that kind of an opportunity and that, at least for very early-stage clinical trials using invasive methods to deliver, a strict control group that gets the product with vehicle through an invasive method is probably not something that should be pursued -- in a very early-stage clinical trial.

That being said, the thought is that there could be some other ways to control -- for instance, looking at subjects who might not choose to participate in a clinical trial, looking at those individuals who decline participation, but using them as a concurrent follow-up, as a control. It's not a strict control, but it's something where you might be able to get an idea of the natural course of your particular indication.

There was lively discussion about how you eventually incorporate a control into a later-stage clinical trial that is being conducted for one of these particular indications -- a lively discussion about how you could do that and, again, about the robustness of outcome measures, et cetera, et cetera.

Again, the thought here is for early-stage clinical trials really to look at -- if you can get some sort of control group, it's advisable, but we might need to be flexible in what that particular control group is.

DR. COUTURE: First, I would like to say that I think the agency has handled this issue well in the guidance document. That's what we're being asked to discuss. I think it is handled well.

I agree with almost everything Jane had to say. We can talk a lot on what controls we should use in whatever sense. But I think the issue is, in early-phase,

Phase I, clinical trials, the use of controls for cell and gene therapies -- not cancer chemotherapeutics, but cell and gene therapies -- is somewhat questionable. Pulling a gene out of an engineered T cell and infusing that into a patient with virtually zero chance of benefit, but the risk of immune responses, cytokine storms, et cetera, et cetera -- you can go on to just about every other cell and gene therapy trial we have done, where the potential risk to the therapy is in some cases very high for the patient.

Doing that as sort of a controlled -- it's not the same thing as a PBS control or water or sham or something. We're talking about a completely different set of therapeutics.

It's rare where we look at a Phase I trial and seriously contemplate any sort of control group for that trial, until we have those first patients in just to assess the overall safety of the material. We're not looking for efficacy very strongly, just safety. Once we have some safety, then the question starts changing about how we can control and make sure that, in fact, it is the transgene, not just the cells or the virus or whatever it is. That's what I think Jane was talking about as well. As you move down, we need to start thinking more carefully about what those control groups could be and whether or not it's justified in a particular setting.

Again, I think the guidance document adequately addresses this. They are not typically used in Phase I trials, for good reasons. But they may be required by the time you get to Phase III or licensure of the product.

DR. ROSE: I would agree. I think the agency has handled it well.

I think one of the things that is mentioned, actually, in the guidance is diseases for which the natural history is not well characterized. I think if you have a well-characterized natural history, that, in and of itself, can serve as a control, compared to, in our case, the fellow eye or whatever.

I agree that one of the conundrums we run into is, as you get further out of Phase I -- and I have to say, for the most part, at least in our area, for human gene transfer, it's a combined Phase I/Phase II. It sort of gets to this dosing issue and moving on. It's not just a straight Phase I. But I think a good natural history and a good cohort of that is extremely important in the early trials. As you get further on, I'm not sure -- and I have to take exception to injecting empty capsid. You just don't know what the immune response -- even though in our case, the eye is supposedly immune-privileged, not as immune-privileged as everybody thinks it is.

A lot of thought has to go into it, but I think

flexibility there as you go out is important.

DR. SNYDER: Dr. Lee?

DR. LEE: No comment.

DR. SNYDER: Steve?

DR. GOLDMAN: I agree that the guidance has a tremendous degree of flexibility, and I think we all appreciate it. It certainly permits relatively uncontrolled and open-labeled trials in Phase I.

But I wonder, frankly, how wise that is. When one talks about potentially invasive controls and how to regulate them, that, on some level, begs the issue of the extent to which efficacy should be incorporated at the level of Phase I to, on some level, prevent the inefficiency of progression to trials that then require much more stringent and often invasive controls.

When I was looking over this specific issue -- in my own field, adult neurology, of course, there have been a number of cell therapeutic trials in Huntington's disease, Parkinson's disease. This is an issue that, as many of you are aware, was quite contentious in the design of trials for Parkinson's disease some years back, and more recently, in the design of trials for gene therapeutics in Parkinson's disease. There were several trials with cells and then several with the genetic vectors.

Looking at these papers, they essentially all did

use -- and this came about in an evolutionary process -- relatively invasive sham controls that included, at the very least, burr hole production in the skulls of patients getting these therapeutics or sham. So the sham surgeries involved burr-hole drilling and often dural invasion, in some cases intracerebral catheterization. These are, I think, about the most invasive controls any of us would consider.

What came out -- there was a retrospective analysis of the control groups by Karl Kieburtz's group just last year. Out of six trials that included sham controls, the bottom line was that every one of those trials had gone to trial because of favorable Phase I safety data. Essentially these Phase I's were all open-label, and so there was some suggestion of efficacy. Every one of them failed once they were compared to control.

So the inefficiency of that process, I think, is manifest to all. I think it raises the point whether or not the issue is not so much the degree of invasiveness of control that we should be considering -- I think that's still a fair topic of debate -- but rather, more importantly from my own perspective, whether or not some more rigorous criteria for establishing at least potential efficacy with some sort of acceptable control should be part and parcel of Phase I in these, especially, cell but

also gene therapeutic trials.

DR. AHSAN: This idea of this multistep process in terms of thinking about the controls and when they can be incorporated -- that does sound very attractive, but I'm not quite sure how that is going to be executed. When I think about safety, I think about risk. When I think about risk, I think about risk-benefit. As soon as I think about benefit, I think about efficacy. So now it's a different set of controls again. Especially in the non-life-threatening arena, that becomes a little bit difficult.

It does seem nice to have this kind of incorporating of controls over different steps, but I think that needs to be done with real care about, in part, the efficiency and the number of patients that need to be enrolled in order to achieve, because with the increased number of patients you have to enroll for the different stages or the different steps, you then essentially are increasing the risk for an adverse event. I think that needs to be thought about with care as we move forward.

DR. DAHLGREN: I don't have anything greatly additive to say. I did feel like the paragraph read well. I do think that it's important, in order to be able to go forward with the trials, that they not be hampered by the potential for not being able to include enough controls. In other words, if there is a plan to have X number of

controls and nobody wants to consent to being in that group, and that's going to impact the ability of the whole project to go forward, then there needs to be that flexibility.

DR. CRIPE: I think there are a couple ways it could be done to minimize the number of controls. Perhaps in the guidance it should state something like, the FDA encourages creative thinking regarding keeping the number of controls to a minimum, should controls really be felt to be needed, without compromising the scientific integrity of the study, such as alternate ratios of randomization. It wouldn't have to be one to one, but maybe three treatments to every one control, or crossover designs, where the control is given and then a treatment is given later, with a period of observation in between.

DR. SNYDER: Leisha?

DR. EMENS: I don't have anything to add.

DR. BUGBEE: Nor do I. I think everyone has said the important points.

DR. SNYDER: Bruce? You're good? And you're good?

Okay. Again, most members of the committee seemed fairly comfortable with the guidance as written with regard to control groups. Some members thought that there could be a minimally invasive type of control -- for

example, using an empty capsid or using an unaffected limb. Other members of the committee felt that, for simply an early-phase Phase I, where one is simply looking at safety and nothing else, a control group of that particular kind is not safety. One is simply looking at safety risks, and not really with an eye towards efficacy. Therefore, anything invasive or placing any kind of risk may not be warranted in early Phase I, though it clearly is going to be necessary for later phases.

It was thought that control groups obviously are the basis of science. Noninvasive control groups could be including age-matched and disease-matched controls who declined to participate in the trial, those that are just getting standard of care, if standard of care exists, or, if there's a well-characterized natural history, comparing it with the natural history.

Of course, that would mean that those patients who are not being treated also need to be enrolled in the trial to be followed very carefully, contemporaneously, perhaps with the exact same tests. The key here would be to be able to enhance the signal to noise. In this case, signal would be any type of safety risk.

One point that was brought up is that in this field now with CTG products, there is an increasing burden that Phase I not just look at safety, but also look at some

degree of efficacy. If that's going to be the case, and given the fact that in certain interventions there has been a huge placebo effect -- for example, in the clinical trials in Parkinson's disease -- somehow that may need to be addressed, perhaps not immediately in the document, but recognition that the scope of Phase I may be expanded. If that's the case, then placebo controls of some sort may need to be included.

Controls should be kept to a minimum, if included, such that the scientific rigor of the study -- diminished to a point, but not such that the scientific rigor of the study is compromised. Crossover designs may address that kind of concern.

Anything else that we should include?

(No response)

What I would suggest -- we have been at this now for an hour. We only have two more questions left. We're due now for a 15-minute break anyway. I suggest we take a 15-minute break and come back to do the last two questions.

Just before we do the last two questions, for question number 5, which is our wildcard question -- so that we can all think about it during the break -- is there anything that answering the prior three questions has suggested should be included in that? The topics I have that should be addressed in question 5 are how to address

issues of dosing, issues of long-term follow-up, and the inclusion of the geriatric population in some of these studies.

Anything else that we should address in there?

DR. CRIPE: I have two. One would be the use of reporter genes and constructs, and the other would be Section IV.B.3, lack of other treatment options and defining that more precisely.

DR. SNYDER: I'm sorry, I missed what you said. Lack of what?

DR. CRIPE: There's a brief paragraph about lack of other treatment options. I think that ought to be discussed a little bit.

DR. SNYDER: Leisha?

DR. EMENS: Some brief discussion maybe added about the use of novel trial designs.

DR. SNYDER: Okay. Anybody else have things we should include in the wildcard category?

(No response)

If anything comes up when we hit question number 5, just chime in.

We'll take a 15-minute break now. We should be back at 2:30.

(Brief recess)

DR. SNYDER: We're up to question number 4. I'll

read the question: Section IV.F of the draft guidance addresses considerations for monitoring and follow-up. For certain types of gene therapy products, the FDA has issued guidance on the recommended duration of follow-up -- guidance for industry, gene therapy clinical trials, observing subjects for delayed adverse events, from November 2006. But no comparable guidance has been issued for cellular therapy products. Topics in this section of the draft guidance include monitoring for both expected and unexpected safety issues, special monitoring considerations -- for example, for new malignancies or graft-versus-host disease -- for CGT products, and duration of follow-up.

Please discuss the principles that should be used to decide the duration and nature of safety follow-up for early-phase trials of cellular therapy products.

Appropriately, Steve Goldman will lead the discussion.

DR. GOLDMAN: Going through the guidance, it covers a lot, and it does so, I think, very well. Fundamentally, it tries to lump lots of very, very different conditions, implicitly so, in that the nature of recommendations for establishing safety -- setting efficacy aside for now -- for cell therapeutics is going to be very, very dependent upon what cell type one is discussing and

for which disease indication and in what settings those cells are being introduced, as a function of disease, as a function of age, as a function of organ.

The guidance is, of course, intended to cover all of those bases, and as a result -- it's very well done, but generic from that standpoint.

I suppose a question for the group and for FDA is, how specific should it be as a function of the obvious of the obvious differences in organ systems, cell types, et cetera, that come up as one discusses different disease targets?

In that context, much of what we look at as cell therapeutic, especially in the current age and years to come, falls into the rubric of regenerative medicine and, as we just discussed, in the context of pediatric targets, cells that very often are taking developmental paths, even if you are going into adults, but certainly when they go into kids -- very much so. These are cells that are being used to reestablish and recapitulate developmental pathways and essentially to recapitulate the construction, on some level, of the organs into which they are being placed.

I'm being fairly specific here in terms of cells being used for regenerative therapies, but that does comprise, I would suspect, a large proportion of the disease targets and bases that we're looking at at this

point, and to which the advisory is supposed to be directed.

So how to assess safety for cell therapeutics in regenerative medicine becomes, I suppose, the more restricted mandate.

There are a number of issues that come up in terms of how long to follow patients after given cell therapeutics have been delivered. Those are necessarily going to be, again, cell type-specific and disease-specific. But they do have some commonalities.

Any cell that is put into a patient from the standpoint of having to recapitulate and to reconstruct a given lineage -- it's going to take time for that to occur. Depending upon what stage of a lineage one is putting into a patient to generate a given cell population, that may be actually a quite prolonged process -- in many cases, months to years. So that, of course, is going to dictate the period of time that one has to follow a given patient and, unfortunately, dictates the amount of time that's required to really establish safety.

Then the issue becomes how to establish appropriate controls, as we discussed before, but in this case, controls to assess the effects of concurrent manipulations that also impinge upon safety. Very specifically, here we have to think in terms of immune

suppression. At least in the setting of allogeneic grafts, when patients presumably will have to be immunosuppressed on some level for some period of time, how do we assess how long those periods of immunosuppression need to be? Of course, there's urban legend out there in terms of immune-privileged organs, but in practice there has been very little, I think, evidence that even the brain or the eye is as immune-privileged as long past studies suggested.

It's a reasonable expectation that we're going to have to immunosuppress patients for long periods of time. Are those periods of time going to be congruent with the periods of time that the given lineages take to develop fully? In other words, if we put a cell population in that takes a year to regenerate a given portion of tissue or organ, is the period of immunosuppression throughout that period, and therefore are immunosuppression controls required to assess safety and to distinguish the safety pertaining to that immunosuppression regimen versus that of the cell therapeutic? How does one distinguish the two as any serious adverse events are noticed?

Then, of course, once there is the generation of mature phenotypes and the reconstruction, let's say, of a given tissue by virtue of a cell therapeutic, in what organs can immunosuppression be stopped? In what organs does it have to be continued?

All of that is really fundamental to the issue of safety, because in many cases ultimately the immunosuppression regimens may turn out to be as much an issue of potential concern as the actual cell therapeutics.

A flip side of having to wait a long time, potentially, for given cells to have effects and to have to essentially follow patients very closely during that period and await essentially the asymptotic effect of a given cellular manipulation is that we'll need to know, once cells have been introduced and once they have integrated into a given organ, how durable they will be, how long-lasting they will be. That will also vary as a function of disease and cell type. If those implanted cells turn out not to be durably integrated and to, at some point along the way, die off, what are the effects of that die-off? And does that become a significant safety issue?

Those could be very late events. Those could be late events, for example, dependent upon the withdrawal of immunosuppression. There could be very late toxicities accruing to late rejection.

All that is part and parcel of, I think, what we need to consider in terms of potential safety issues.

The flip side of that potentially long ramp-up time to get to the point of therapeutic integration is that it can take that long for toxicities to be evident. Of

course, in a very generic sense, when we think in terms of cell therapeutics, of course, we're thinking in terms of the potential for immune reactions and graft-versus-host disease, if one is talking about immune cells that are being donated or inadvertently introduced, as the case may be. But depending upon the organ, one is also concerned about the formation of heterotopias, the formation, obviously, of neoplasms. Those events are going to be functions of cell type.

So When we talk about cell type, I would suggest that the advisory needs to be perhaps more discrete in terms of distinguishing cell- and tissue-derived, and obviously autologous versus allogeneic -- but, fundamentally, tissue-derived, whether immediately isolated from tissues or significantly manipulated or expanded, with particular attention being paid to the degree of expansion and how long cells have been expanded *in vitro*, and then, of course, if not tissue-derived, whether or those are pluripotential cell-derived, and if so, again, of course, whether they are derived from embryonic stem cells or induced pluripotential cells and what the provenance of those cells had been beforehand. With iPS technologies, it's going to be a function of exactly how the cells have been de- and reprogrammed, and what vectors they may or may not be carrying.

All of these potentially yield different toxicities or different relative indices and frequencies of toxicities. Those will all be potentially different depending upon disease context.

I wonder just how discrete we may need to be in the advisory in terms of just how many of these -- lumping versus splitting, right? -- how many of these considerations to introduce into the guidance or how generic to keep it. But I would suggest that there may be significant differences in the level of concern regarding toxicity, safety, regarding tumorigenesis, whether one is talking about tissue-derived as immediately isolated versus tissue-derived after significant *in vitro* manipulation and expansion, versus embryonic stem cells, versus induced pluripotential cells.

These are the major donor sources of cells, at least for solid organ transplants that are being considered. Yet their toxicities may be significantly different, and therefore the period of time that they have to be looked at, that patients have to be followed may be quite different. If one is taking, say, a tissue-derived phenotype that was immediately isolated from a normal individual and putting it back into another patient in a disease setting where one does not necessarily expect induced expansion of that phenotype, then one can imagine

that, within a relatively short period of time, you are going to know whether or not that cell has any associated toxicities in a recipient.

On the other hand, if one is taking, say, an embryonic stem cell population from which a given phenotype has been isolated, purified, after differentiation, and then transplanted, of course, the concern is always for residual undifferentiated cells or for cells that, in the setting of iPS, may go back a step in terms of differentiation capability or differentiated state, and at much later point in time, potentially become tumorigenic.

Those different situations, I think, suggest very different periods of time for follow-up of what is happening to the implanted cell population.

Again, it gets back to the period of time during which patients are being evaluated, but if one is then constructing a trial around all this, then I think that translates into what the lead-on times on during a trial, how many patients can be introduced at a given point in time, how long one has to wait until then introducing the next cohort of patients, recognizing that you are still following that first cohort, and following it intensively. How many times can you go through that cycle and be following successive cohorts of patients, perhaps in a dose escalation, perhaps just adding on patients to increase

sample size? How many more cohorts can one introduce while one is still fundamentally looking for trouble in the very first cohort?

I think those are fundamental issues that I don't see addressed very specifically in the monitoring section of the guidance.

I think everything else that I would have to say really follows from that. The duration of follow-up is going to be a function of the potential period of time during which toxicities may arise. One could argue that that's just never-ending, but I think, in a realistic sense, we have to say, given the risk-benefit considerations, how long one look intensively for signs of trouble, signs of serious adverse events? Then how does one do that?

These days, at least for most of the solid organs and certainly the nervous system -- but I think for most solid organ recipients -- imaging endpoints are first and foremost. Then the question becomes, how sensitive are those imaging endpoints? That's going to be a function of tissue and a function of disease state. Then to what extent can we utilize those as reliable surrogates? In which setting have those been validated as such and in which cases not -- in other words, as validated surrogates for potential heterotopic cell expansion in a recipient

organ?

That is something that we may want to consider addressing in a bit more detail in this section covering duration of follow-up, because fundamentally it's not just the clinical setting. If a patient has an adverse event that manifests itself clinically, that' going to be potentially obvious, depending upon what organ system one is talking about, what disease state. But the surrogates may not be so obvious. Presumably we're going to include surrogates as a means of early detection, whether biomarkers, whether radiographic. To what extent do those have to be validated? Then, when trouble appears, what to do about it? Under what settings do they become stopping points? Under what settings does trouble look significant enough to halt the trial?

I think, again, the advisory does attempt to deal with these, but in a necessarily generic fashion. There are such strong differences across organ systems and across cell types that I do wonder whether it would be advisable to parse that out in a bit more detail.

I'll leave it with that.

DR. SNYDER: Thank you very much.

Just for the nervous system -- for the brain, let's say -- do you have a number that you would give, a concrete number of follow-up, long-term follow-up or time

before enrolling the second patient after doing the first patient?

DR. GOLDMAN: Again, it depends on cell population and disease state. I guess, distilled, the question becomes, what's the reasonable period of time to assess the possibility of neoplasm or heterotopia formation in a brain after a given cell donation?

That's going to be a function of the cell dose and of the phenotype, and how differentiated or relatively undifferentiated that phenotype is. Let's say one is putting in a neural stem cell population or a somewhat more differentiated -- and this might be, I think, perhaps the better example -- glial progenitor cell or, as the case may be, a still mitotically competent neuronal progenitor population. In animal models, typically one will pick up readily tumor formation, whether we're talking about tissue derivatives, expanded lines, or iPS. One will pick up tumor formation histologically relatively quickly -- six to eight weeks, certainly. But the issue becomes, in a patient, how long can a tumor cook along before it becomes clinically apparently? The answer there is, years, if it's not a highly malignant neoplasm. That's certainly the experience in clinical neuro-oncology.

That being the case, how can we speed up detection? Then it becomes a question of reliance on

surrogates. If we have radiographic -- let's say serial MRIs -- then one would hope -- I mean, it becomes a question of the sensitivity of the MRI and the detection technique, but if one, say, is using a 3-tesla MRI and is using diffusion tensor imaging and focusing very specifically in the areas that have been implanted -- in other words, very high-sensitivity techniques for picking up potential neoplasm -- reasonably, one should be able to pick that up in a just a few months, two or three months. So one could argue, then, that, let's say, every four months, a follow-on group could be added.

But there are lots of ifs there. I could reasonably put together a protocol and say, okay, we're going to do three or four patients every four months, with hard MRI criteria. But one could still go through a couple of years of patient recruitment to a reasonable Phase I before one has the sample size required. By that point, you have, conceivably, a couple dozen patients entered. Let's say there is a late tumorigenesis. It doesn't take much. It could be a cell that remains quiescent for a long period of time and then is activated in the setting of whatever the disease is that the patient is being treated for.

This is something that is a concern in the demyelinating diseases, lysosomal storage diseases, as you

well know.

So let’s say one goes into a given organ -- in this case, the brain -- and you are going in at a quiescent period of the disease, but then the disease activates at a later point in time. That immune stimulus -- what does that do to the implanted cell population? Is there a possibility of it activating that pool to yield a transformative event?

I think the jury’s out. The animal data I don't think is going to be informative, because we really don't have animal models for many of these disorders, and certainly none that can be followed with the periods of time that we’re talking about in terms of clinical use.

DR. SNYDER: Let’s go around the room. I’m going to put you on the spot, since the FDA is on the spot, to actually give -- even if it’s wrong -- a precise number also: How long to follow up? How long between enrolling each patient? When you would gavel the Phase I shut as being safe, to then move on to the next phase, to say, we’re okay to move on to Phase II and then Phase III?

DR. LEBKOWSKI: Right, gotcha --

DR. SNYDER: You could be wrong, but I just want you to commit yourself.

DR. LEBKOWSKI: I will echo what Steve is saying. It does depend on the cell type that you are administering,

whether you expect that cell to be persistent or not. For cells that are probably not persistent, we would be looking at shorter periods of time.

So let me address thoughts about the cells that are thought to be persistent. The appropriate time is probably anywhere from five to 15 years, probably not the lifetime of the person.

I think another thing to consider, especially in regard to the patient population that you are studying, is, is the patient population going to be alive for a very, very long period of time? Some of the indications that we're looking at are for people who are in the latter stages of their lives. In other cases it's for younger people. I think you have to take into consideration how long the patient population is going -- their expected lifespan.

But I think the other thing to consider is, especially for the longer time points, how frequently you are going to monitor. For some indications, it can be a challenge for people to come in every three months. In other cases a year follow-up might be appropriate. Especially if you are looking at monitoring for tumor formation, et cetera, et cetera, yearly follow-up might be appropriate.

So I think, again, looking at long-term safety is

appropriate. What is appropriate long-term safety? When do you go to the next patient? When do you go to the next cohort? If you're looking at having very long-term follow-up for a year to two years, even, before the next patient or the next patient, the clinical trial is not feasible, from any perspective. Yes, you have to follow for tumor formation for a long time, but if you have to wait for a year to two years in order to make the decision to go/no-go, it is not feasible. So there has to be some reasonable compromise, looking at the toxicities that are associated with, first, maybe the implantation of these cells, the biodistribution of these cells, et cetera, et cetera, the metabolism of these cells.

But then there are some things you just have to wait to look at, as Steve was indicating. If you have to wait for the long-term follow-up for everything, then the studies become really infeasible.

I think everyone is in favor of long-term follow-up, but I think the idea really is to look at what the appropriate timeframe is for the particular population and the frequency of those particular visits.

There was one other comment that there was a concern about in the groups that I discussed it with, which is including the long-term follow-up in the primary protocol. That, I think, was echoed by someone in the

audience. It's more from a clinical operations point of view, being able to summarize and collect the data after a one- or two-year follow-up and looking at the long-term as a separate protocol. Both protocols, obviously, might be mandatory that someone sign at the time of enrollment in the study, but the concern really being that clinical operational-wise, that was a nightmare, to look at a 15- or 20-year follow-up in a single protocol.

DR. COUTURE: It's no easier for me to answer the question. I kind of agree with everything Steve outlined really, really well. Pretty much I agree with everything Jane had to say.

I want to sort of underscore that I agree that these cell therapies are going to have to be treated differently, depending on the nature of the cell type and the source of the cells and how much they have been manipulated or, in the case of embryonic or pluripotent cells, how much they have been differentiated or not, I think as Steve also pointed out.

When we look at these cell therapies and think about what kind of staging we're going to do and what kinds of time points we're going to look at, quite frankly, we look at them very much like a gene therapy. Depending, I guess, on the indication, we look at very early time points and then take those out to about a year, which we consider

to have basically covered the early part of the trial. We usually look from a couple of days to a week or two weeks, then a month, three months, six months, and a year. That's usually the intense kind of testing we'll do. With some things we'll think about much less testing. We always follow up with a patient about a week later, then a month, then maybe six months and a year. But it's always some chopping up of a year and a few months or a few weeks. After that it usually becomes a little bit more difficult for us to decide exactly what to do.

But I would tend to agree with Jane. Usually, in the worst case, if we think there's a cell therapy or a gene therapy that is going to persist, it's something on the order of a yearly basis for some finite period of time, preferably not end of life. For some patients, end of life occurs before these longer periods. In many of our cases, that's the case. Otherwise, it will be five to 15 years, just as Jane put it.

In terms of staging, I have essentially the same comments. We would typically think about, if it's a very high-risk technology -- and we're thinking about this with some of the embryonic stem cell things -- proposing, again, because there is no real direct guidance from the agency at this point -- treating one or two patients -- not necessarily just one, but a very small number -- and

letting them go for about three months before we start the next round. But not necessarily just one patient, because we're not sure that's going to tell us a lot.

We might stagger the first patients by, say, a month, a month, a month, then stop for, say, three months and wait and see, and then pick up and start going from there. Not until we had some number of patients in the protocol -- and I can't put a number on that -- would we just start treating patients as they came in the door until we finished up enrollment.

We kind of like the idea of getting more than one patient in -- I don't think one is really informative -- staggering them a little bit to get them into the trial, stopping for a bit, letting those patients run the course for a while, making sure nothing untoward is happening, maybe out to around three months, and then we would start picking up the second cohorts.

Again, I'm probably wrong, Evan, but those are just some numbers.

DR. ROSE: I agree with Jane and Larry, a lot of what Steve said. I think it depends on how accessible the imaging would be, to be able to detect what biomarkers could be used to see if something is going wrong. If you go in the liver and you begin to see elevated LFTs that don't go down, hey, there's an issue. We have the imaging

in the eye.

I happen to think -- I think a bit different from Steve -- that flexibility is the real answer here. The more you try to corral different types, the more you are going to get into trouble. I think it's going to be a case-by-case basis, based on cell type, disease, and what your markers are that you can really look at.

DR. GEARHART: I will comment on this. I agree with a lot of what has been said, but I don't think it's practical. Our experience in grafting cells into literally thousands of animals at this point, from fish to mice to rats to pigs to nonhuman primates, for a variety of targets, tells us exactly that everything is highly variable at this point. With some things, we can come in and immediately begin to screen whether grafts are doing something. With others, with our monkeys, we are waiting months. These are, as you know, the Parkinson's models there.

I'm in favor of having a document like this, in the way it is already constructed. I think it addresses the issues. I think it serves as a guide. It is generic. It's flexible. I think anyone coming into the FDA seeking an IND would have to address all the kinds of things that Steve and Larry have mentioned. It's going to be specific for the target you are doing.

I know this is all preclinical I'm talking about, but this is the experience. When we have to make a decision, for example, with the nonhuman primates, when it costs us hundreds of thousands of dollars per animal, this is a very practical thing: When do you start another cohort based on information you are trying to derive from those that you have already done? So it's a little bit similar -- difference in issues and safety.

It's extremely variable. I think we all appreciate that. There are a lot of ifs in this, a lot of parameters to look at. I like the way this document is written. It gives that flexibility. Obviously we recognize -- and maybe this should be introduced -- with the different targets, as pointed out, the different sources of cell types, these all have to be addressed on a specific target.

DR. SNYDER: Dr. Lee?

DR. LEE: No comment.

DR. SNYDER: Taby?

DR. AHSAN: I'm not going to answer Evan's question directly. No one else has either. But he's outgoing chair, so we feel okay to disobey him for the last moment.

I think this is so clearly application-specific that that's the difficulty in giving a generic answer at

this moment.

Also I do believe, to answer in the context of stem cell therapies, which are closer to my purview, it depends on the mechanism of action. Are you relying on these cells to release trophic factors and to have very short-term engraftment or do you actually expect them to engraft and differentiate and actually start to maintain the tissue? Those are two very different things, so the monitoring and follow-up would be very disparate for those different conditions.

I think that really needs to be taken into consideration: What is the mechanism of action that they are proposing? In that case, what are the metrics and the frequency that make sense?

Of course, we're always thinking about these unintended consequences or inadvertent side effects. With cells, especially stem cells -- and, of course, if we're starting to talk about personalized medicine and iPSCs, where they at one point had pluripotency -- the question becomes, where do they end up? Do they end up in the lung? Do they end up in the bone in an inadvertent fashion?

So where we actually monitor is also, I think, very important, and not the site of implantation or delivery, but also throughout. And that needs to be strategic, because clearly we're not going to do disruptive

testing on every tissue. That's not feasible.

But I think we really need to think about the mechanism of action, what the preclinical data had indicated in, potentially, the appropriate animal models about where to monitor, what the most vulnerable tissues are for deposits of inadvertent cell or gene therapies. I think that really needs to play into both the frequency and the type of monitoring that we do.

DR. DAHLGREN: I don't feel like I can put any timeframes on it because of the diversity of what might be getting addressed. Long enough to know. I don't know what that means, though.

DR. CRIPE: I think the ideal goal is to not monitor too little and not monitor too much. I think it has to be individually based. I agree, a lot of these cells disappear, and if the sponsor/investigator has data to suggest they are gone and writes in that the patient will meet certain parameters -- if this is hematopoietic engraftment and we don't detect chimerism after six months, we should be done.

DR. EMENS: I'm going to go out on a limb and give some timeframes, presuming that there is an intervention that leads to the persistence of something. I think early on, for deciding when to enroll additional patients, you have to base that on acute and subacute

toxicity, and that's probably going to vary depending on the intervention a little bit, so anywhere between four and eight weeks, depending, for that phase.

So that's sort of in the active phase of the study. Then I really think long-term follow-up has to be separate from the primary protocol. Maybe there will be near-term follow-up in the primary protocol and then have people transition into a long-term follow-up protocol.

To go out on a limb, I would probably look every three months for two years and then annually for 15 years after that for the emergence of long-term toxicities, like a tumor or autoimmune disease or something like that.

The other value of long-term follow-up is looking at the stability of the bioactivity or the clinical effect of the intervention. That gives you a chance to collect that data as well and assess the need for repeat treatment, if necessary.

That's all I have to say.

DR. BUGBEE: I'm going to say that I read the first three paragraphs carefully. I'm not sure I could improve the wording, because they do make a point to say if there are any risks, such as integration, then make the number 15 years, which sounds like a reasonable number to alert sponsors that, if you worry about that, you have an obligation that's far beyond the one- to two-year thing

that we are all used to. It gives wide guidance.

I don't think long-term follow-up in orthopedic trials for nonfatal disease is reasonable. Nothing would ever happen in this field.

So I think the document is pretty good, with all the considerations we made.

DR. COHEN: Given the known variability and that this is going to be a trial-by-trial consideration, I think, especially in trials that require dosing, a cohort of three to six and then a second cohort immediately to follow at something like 75 percent of the dose of the first cohort. That way, while you are collecting safety data on cohort one, you enroll cohort two at a lower dose. You don't have to wait to do that. Then you have six to 12 patients, and you can dose-escalate from there. It's just a trial design that has worked in the past.

But not all these trials are going to be dose-dependent. Having said that, I think all the other comments seem to be reasonable to me.

DR. SNYDER: Some people took my bait, some people didn't. But it's okay.

With regard to the document as stated in terms of follow-up, I think the consensus was that, in broad strokes, it was pretty acceptable, and even prescient. There was some initial concern that perhaps it was too

generic and that true guidance would need to be organ- and cell-specific, disease-specific, age of recipient-specific, and that the risks for the different cell types are also different and require different kinds of follow-up and for different durations. Somatic stem cells may give rise to a certain kind of neoplasm, like proliferation of the primitive version of that, whereas pluripotent stem cells have the risk of giving rise to teratomas in appropriate cell types.

Given this, then some people on the committee thought that there was no way for the document to be that overly prescriptive, so maybe it needs to be generic and every case needs to be decided on a case-by-case basis, based on the disease, the recipient, and the strength of the preclinical data.

That seemed to perhaps come full-circle, though perhaps a little bit more specific guidance may be offered.

What might help is, in general -- still being generic, but providing some guidance -- if it’s a cell, is it designed to be a long-persistence cell or a short-persistence cell. For example, umbilical cord, mesenchymal stem cells typically are not meant to be long-persistence, so their follow-up may be shorter. Long-persistence cells that are designed to reconstruct an organ, like in the heart or, definitely, the nervous system, may need longer

follow-up.

There was concern that even the short-term-persistence cells, because they are very migratory, may wind up in unanticipated organs. For example, the mesenchymal stem cell, even if designed for transient influencing the nervous system, may get stuck in the spleen or in the bone marrow or in the lung.

It was thought that during the follow-up, particularly because tumors, for example, can be smoldering for many, many years, surrogates would be useful, that imaging surrogates in real time would be quite helpful, somehow being able to sample the organs. Then, of course, we have to figure out what organs to sample. Other surrogates besides imaging surrogates could be looking at liver function tests or other biochemical markers. And recognizing that the actions of the cells are manifold, one would have to look at various kinds of outcomes for risk.

How often one would do this -- it was suggested that maybe not all patients get enrolled at the same time and that they be enrolled maybe in pairs or one, two, or three at a time. When precise numbers were given, it was suggested that perhaps a cohort be monitored for every three to four months for about a year, and it might be safe to roll in the next cohort of patients if things seem to be okay after three or four months.

Acute problems -- just from the procedure itself, for example -- could be detected in the first four to eight weeks. Follow-up might be the first week and the first month and the first six months, then the first year, and then yearly, either by imaging or by biochemical assays for surrogates, up to 10 to 15 years.

It's a little bit unclear how long you wait before then gaveling the Phase I shut, saying it's safe, and being able to move on to Phase II. It was brought out that you can't wait 10 to 15 years before starting your Phase II. At some point, you have to be bold and pull the trigger, but continue to follow your patients.

The other part of follow-up that was brought out was knowing, if it's a cell, how long there is a risk for an immune response, because that will influence how long you follow up your patients on immunosuppression. When will that become an issue?

I'm not sure if I missed anything that was brought out in the discussion.

DR. GOLDMAN: If I could add a point? This gets back also to the earlier discussion about controls, and severity thereof. In terms of the follow-on time required before the jump from Phase I to Phase II, these are really overlapping discussions. If there were a mechanism which was more formalized in terms of a collapsed Phase I/II

design and recommendations thereof -- that's a design that's not used often in drug trials, but for cell and gene therapeutics, especially for cell therapeutics, at least personally, I would like to see more in the guidance that would give some clarity in terms of what kinds of criteria would permit that, what kinds of efficacy measures could be incorporated into Phase I, in a collapsed form, with dose escalation, so that that would be viewed by FDA as achieving real efficacy information, in the setting of a collapsed Phase I/II.

DR. SNYDER: I did forget to mention one thing. It wasn't explicitly brought out here, but has been put forward at various times when this is discussed: the recognition that sometimes not only safety, but efficacy is not seem for a very, very long time. For example, if you want to reconstruct a neural organ, it takes time to reconstruct, to make connectivity, to even see whether you are going to have a seizure focus or something like that.

Sometimes it has been mentioned, would there be some built-in suicide mechanism so that if you saw the cell doing something bad, it could be eliminated? Certainly in certain organs, it's quite easy to eliminate something that looks nasty -- for example, in the eye or in any of the orthopedic indications.

That may influence the kind of follow-up. If you

can reverse the process, that may make one feel a little bit more comfortable about the follow-up.

Just anecdotally, one of the issues that has been brought up in the neural disease field is what went on with the clinical trials in Parkinson's disease, the old fetal tissue trials, with which many people here are familiar. These were patients that initially did quite well with their Parkinson's disease after receiving fetal tissue, perhaps for the first year or two, and then went on to start developing dyskinesias.

It was a problem that did not manifest itself in the first one or two years, not even seen in the monkey preclinical studies in the first year, and then became an issue and put a halt up to this day on future cell-based therapies for Parkinson's disease. So that's always a cautionary note.

Anything else?

(No response)

I guess we're ready to move on to our wildcard topic. The way this question reads is, in addition to the discussion topics 1 to 4, OCTGT is interested in obtaining input from the committee on other sections of the draft guidance. So topic number 5: Please comment if you recommend modification in the draft guidance of any topic, if the draft guidance did not address a topic in sufficient

detail or if there are important topics that the draft guidance omitted.

Why don't we do them in the order in which they were brought to our attention? One of these was dosing. Are there practical ways to guide industry -- and this is an industry guidance -- on how to appropriately find the right dose for cells? I think we have experience with drugs. Is there a way to do this with cells?

Since there's no designated speaker, why don't we just go around the table.

DR. LEBKOWSKI: This is obviously a challenge, the challenge again being dependent on the route of administration and where the cells go after administration. Again, I would just recommend that the dosing is dependent, really, on the site of administration, the volume of the tissue, and how you want to distribute those cells amongst the different tissues. That again is a case-by-case basis.

DR. COUTURE: I'll just be succinct. I don't think we can actually define what dosing is going to be for any particular product, because they are so varied. In fact, in most cases, it's max feasible dose that we're running up against. This is not a small molecule. It's a completely different paradigm, a different model for how we dose.

There's some dose escalation, of course, based on

animal modeling. We tend to start low and we move up. Again, typically, almost always in some of these cell therapies, it's max feasible dose that limits us. We often get there, in some cases, before we get any sort of efficacy.

It's all case by case.

DR. SNYDER: Just to be provocative, to drill down and try to be as specific as possible, let me put out a straw man. All of these have to be based on careful preclinical data that has been accepted, and many of them involve a large-animal model, often a primate. Start with the effective dose in your large animal model as dose X, and then you can decide, do I want half X, two X, three X?

Is that a reasonable recommendation? That's case by case. Or does that still miss something?

DR. COUTURE: That's kind of how it's done. I completely agree. We usually hit what we think is an effective dose on a per-kg basis in most cases. Sometimes it doesn't scale that way, but that's usually how we look at it. Then we usually come back, with guidance from the agency -- encouragement sometimes, pressure sometimes -- come down from that, sometimes a half-log or a log, and then move back up in the patient trial. So I completely agree.

DR. SNYDER: That still makes it case by case,

but it gives something concrete to guide somebody who wants to try to do this.

DR. ROSE: Certainly the preclinical data has to inform that. I would say a couple of things.

One is, if you are trying to replace a cell population, do you have an idea going in what number of cells you have to replace in order to get the function that you're looking for? But then are you going to run up against the top end of what you can actually put in? But if you have some idea -- again, I have to go back to what I know, which is the eye. I know there are a certain number of photoreceptors that have to be there in order for a certain amount of acuity. If I'm going for that, what is it going to mean to put in half of that? What's it going to mean to put in three times that? That has a potential influence.

If I'm trying to produce a particular molecule, a neuroprotective or a signaling molecule, if I can get any idea from preclinical studies, cell studies, pathway studies as to what amount of material is needed -- in nanogram, picogram, picomolar, whatever -- what are my cells producing? What is the potential for them to give me enough to be able to actually do what it's supposed to do?

Definitely case by case. Definitely very dependent on the preclinical data and the results from the

models. In a lot of cases, there aren't large-animal models. You're sort of stuck with the rodents in a lot of cases, and we all know scaling from rodents is almost non-useful.

DR. GEARHART: I obviously agree with the two gentlemen to my right. When you think of working with a heart attack in a mouse and you look at the mouse heart and it's the size of the fingernail on your small finger, and you're thinking of the human heart, which is larger than your fist -- and when you can measure a heart attack, you have lost about 4 billion cells -- you're not about to replace that. You do the best you can. It's a delivery issue, and also how you keep them in place.

With many of the things we have done wonderfully in mice, we have never been able to go the next step to a larger animal. It's the issue of scale.

As much data as can be obtained from working in the pig heart, for example, or even nonhuman primates, they are not that large sometimes compared to us. So it's difficult to predict how many cells should be put in and how they should be delivered.

It can be informative, there's no question. The urge now is to, as much as possible, as much as your NIH grants can afford, work on large animals, which are expensive. But this is where we're going to get informed

as to then how to go to the human.

DR. LEE: I just read this *New York Times* report. What did we learn from those four monkeys they created? I think that can be giving us some information from the animal data about what to do.

DR. SNYDER: Steve, did you want to weigh in?

DR. GOLDMAN: Sure. Before a longer comment, just a point that came up in terms of large-animal models. I think it's disease-dependent. There are some things that are disorders, effectively, of gross structure where you are trying to replace on a stoichiometric basis, cell by cell. There large animals are appropriate and needed. In other cases where the disease modeling is much better in rodents and where that necessity for stoichiometric replacement isn't there, I think rodents are fine. So it's going to be very disease-specific.

I would just caution against any generic point that large-animal models are required for any of these studies.

But the point I want to make is in regards to the scalability issue that was raised. I don't think we can think about cell therapeutics, especially the safety issues, in dosing in the way that we typically think of pharmacokinetics for drug therapy. Many of the toxicities accruing to cells have to do with how many population

doublings they have gone through and what their degree of expansion has been. If anything, I can make a fine argument for the lower cell doses being potentially more dangerous, because if one is putting in a mitotically competent phenotype that’s going to fill out a given organ, then it’s going to have to go through many more divisions and more population doublings in order to get there if you are starting with a low dose, whereas if you are starting at a high dose, in most somatic tissues, that higher dose translates to fewer cell divisions before that cell population has integrated in a terminal fashion to the organ. It’s certainly what we see with the brain.

We have actually started to worry more about the toxicities accruing to low dose than high dose. The risk of tumorigenesis, I think, is substantially higher with low-dose injections than high-dose.

That potentially, I won’t say changes, but at least informs the paradigms that we traditionally use in starting at low doses and going to higher doses. In cell therapeutics of adult organs with mitotically competent progenitor populations, I don't know whether that paradigm really is wise. I think we have to accommodate the possibility that, with greater cell expansion accruing from lower doses of mitotically competent cells, we might actually see a higher incidence of toxicity in that

setting.

DR. AHSAN: A couple of comments, maybe about nonlinearity.

One is, as we scale across species, clearly cell size does not scale in the same way that weight does, or mass or volume. It's not an easy question to think about this in terms of how we move from species to species.

Also dose itself, even within a species, may be nonlinear, and the fact that 1X and 2X is not necessarily 1X/2X potency. As you were talking about, there might be this threshold effect about toxicity, where just the entry-level amount of dose would have some toxic effects. You might have diminished increased toxicity with increasing the dose. But, conversely, the same thing about potency.

I think that's really important. And there is a potency guidance document as well that I think ties in very closely with this dose issue. I think that's something to think about.

Really, dose is clearly a much more complex problem when we talk about cell-based therapies and gene therapies than when we talk about pharmaceuticals. I think this nonlinear aspect needs to be incorporated into the preclinical studies that help inform these decisions. That might be something that might be expected, that we need some dosing data in the preclinical studies as well, to

help inform these decisions as we translate.

DR. DAHLGREN: My only comment on dosing is that I do think the preclinical data is important, and I think it's important to remember, depending on what species is used preclinically, that there is a lot of individual variation -- and I'm sure this must be true of people as well -- as far as response from one individual to another. I don't have any idea how to account for that, but it certainly is problematic in the clinical studies that I do. The variation from one horse to the next is huge. Somehow that has to get taken into consideration. The route of administration is going to impact how much variation occurs there as well.

DR. SNYDER: I think people are almost as complex as horses.

DR. CRIPE: That scares me.

There are a number of issues that come to my mind in the field of viral therapies and repeated dosing for cancer patients and the requirements for preclinical data. Particularly about dose escalation, do you go up in log doses or half-log doses? Should there be any regulation about that?

In the viral therapy field, when we give an IV virus, a lot of studies have gone up in log doses, and then you will see someone design one with half-log doses. They

are going up over 4 or 5 logs, so they may have twice as many patients in there than they really need to.

Again, I think the idea of trying to minimize the lower-dose numbers -- then the question about intra-patient dose escalation comes about. One of our paradigms is that you don't do that. Yet that might be a way to minimize the number of patients that are treated with subtherapeutic doses, to do some sort of intra-escalation.

DR. SNYDER: It's probably harder for a cell therapy, though.

DR. CRIPE: Yes, but I'm thinking of viral and gene therapy with repeated dosing, not necessarily difficult at all.

I guess I would like to see some guidance about those issues.

DR. EMENS: I agree with everything that has been said. I guess the only other thing to guide dosing is, if there's some kind of biomarker of either toxicity or efficacy that's an early indicator that you are kind of there for your particular indication, building that into the trial would be extremely helpful.

DR. BUGBEE: Maybe I have a question of clarification of something you said and then Larry said.

Larry, you said that it's typical to start with what preclinically was the effective dose and then go down

from there. You said perhaps it may be appropriate that you double the dose. You said you go half-X or 2X. So whatever the maximum preclinical dose was, it's acceptable to double that when you go to early clinical?

DR. SNYDER: I think we're only bringing out the point that obviously the preclinical will not be humans. It's a place to start. Inevitably, that's your guidance, and you are going to be making a guess as to what's appropriate for a human. That may be off, so --

DR. BUGBEE: So the FDA would be silent on that.

DR. SNYDER: -- half that dose, perhaps, double it, triple it, as dose finding. I think that's what Larry and I were both saying.

DR. BUGBEE: I got it.

DR. COHEN: Having written down dosing in the wrong place, which is why I said it for topic 4, one advantage of sitting at the end is that there's nothing else to say.

DR. SNYDER: All right, let me just summarize. There was a feeling that maybe some guidance with regard to how to define the dose for cell products was not as clear as it should have been in the guidance document. It still is difficult, and you can't be entirely precise. When one is talking about cells -- and I think, of the CGT products, cells are probably the hardest. There is at least

experience with that. It was brought out that in a drug you talk about maximum tolerable dose. Maybe with cells, it's the maximum feasible dose.

While it varies from case to case, organ to organ, cell to cell, and all that, since every group entering a Phase I trial will have had extensive preclinical data, that's at least a place to begin, starting with what seemed to be both safe and effective in your preclinical animal model, perhaps halving it, then doubling it, then tripling it.

Finding whether or not you have reached the best dose may not only depend on how the patient does in terms of safety and efficacy, but it would be great to have some biomarkers to know when you have actually done that.

What's considered to be successful can vary from region to region. It may simply be that you replace enough cells until you return function. I can say that in the nervous system the little rule of thumb that we have always used is that if you replace 10 percent of normal, function will be restored. So that's what your target is. That's the dose you're shooting for. Will that persist? Maybe, if you want a persistent reconstruction of your organ, you have to shoot for larger, maybe 50 percent, or you have to entertain something that wasn't discussed at all, which is redosing -- giving a dose at point A, waiting a few years,

recognizing that maybe you need to redose with the cell.

It was brought out that dose and potency may not be the same thing, that they may be different things, and potency may not be linked directly to dose. Also increasing dose and increasing safety risk may not be directly correlated. It was pointed out that sometimes they can actually be inversely correlated, so that the lower the dose, the increase of the safety risk, particularly if you allow for excessive uncontrolled proliferation.

Anything that we should add with regard to dosing?

(No response)

The next topic that was felt was not entirely covered -- but I'm wondering whether we have now covered it -- it was brought up that the precision of long-term follow-up was not entirely covered. But I think we have now covered that. The issues that were left unaddressed I think still cannot be addressed in a guidance document, which are the logistical problems of following up your patients long-term and who is going to fund it. I think that probably is beyond the scope of a guidance document.

Now we come to the inclusion of geriatric patients in clinical trials. I think we can probably deal with this pretty expeditiously. Jane?

DR. LEBKOWSKI: Clarify the question. I think geriatrics should be in clinical trials. In fact, some of the indications that are being developed are specifically designed for geriatric patients -- especially since 80 is the new 60.

DR. SNYDER: So you're in favor of geriatric patients.

DR. LEBKOWSKI: Yes.

DR. COUTURE: I agree. I have nothing to add. I think they should be included and they should not be excluded in the guidance document. They should be put out there just like pediatrics as something to consider.

DR. ROSE: It just depends on confounding comorbidities, but there's no reason to exclude geriatrics at all per se. It just has to do with health and potential for getting information out and potential efficacy.

DR. GEARHART: Sure. Self-serving. We'll be there someday.

DR. SNYDER: Dr. Lee?

DR. LEE: No comment.

DR. SNYDER: Steve?

DR. GOLDMAN: I'm all for the elderly.

DR. SNYDER: Taby?

DR. AHSAN: No comment.

DR. SNYDER: Linda? Tim? Leisha? Bill? Ruth?

(No response)

So I guess a panel of aging investigators have all endorsed the inclusion of geriatric patients in future trials.

The only thing that I would add is that the geriatric population has also, to some extent, some of the concerns of the pediatric population, in the following way. We have to make sure that they can give informed consent. If you are starting to deal with a dementing illness in a geriatric population, they may have caregivers, they may have relinquished their ability to give informed consent, and one has to be cognizant of that, the same way as with kids.

The second thing is that there are comorbidities that have to be taken into consideration, and organ function is not the same in a geriatric patient as it is in your standard adult patient. Renal function may be compromised, cardiac function, pulmonary function. Even if that's not the target of the clinical trial, that has to be taken into consideration, the same way as in a pediatric population, we take into account dosing by weight and function and things of that sort.

But we're all in favor of old people.

The next topic: reporter genes. Do you want to take that, Tim?

DR. CRIPE: I can speak to that. Most vectors have reporter genes in them when they are being tested in the preclinical setting. I hear a lot that people went to the FDA and they said they need to excise the reporter gene. Maybe it's in another guidance document, but I guess I would like to see some guidance about what the thinking is on that.

I know there are some vectors out there in clinical trials with reporter genes in them. How did those get through and others have to be excised? If you are using a vector that is not totally gutted that is expressing a bunch of viral genes, why is the reporter gene any different than the foreign viral genes?

In addition, in some of the preclinical data, the reporter gene actually has some efficacy. Some of the reporter genes, in the cancer field anyway, are a little bit toxic to cells, and that may be playing a role in what generates the preclinical data. If you take those out, things may not be exactly the same. So do investigators really have to go repeat everything with a reporter gene excised?

In addition, the reporter genes may have some utility in the clinical setting for monitoring biomarker efficacy.

So I would just, like I said, like to some

guidance or a reference to some other guidance surrounding their thinking.

DR. SNYDER: All right. We don't have to go around the table. Does anybody have any additional comments to add about some guidance on reporter genes? Basically, what you are saying is that if you have demonstrated safety and the reporter gene is in the construct, then you don't have to redo the whole experiment excising the reporter gene. Safety is safety.

DR. GOLDMAN: If I could just add to that, not so much reporters per se, but it came up before, a couple of times, in terms of the use of suicide genes. A number of similar issues come up in that setting. Of course, the suicide genes, whether TK or otherwise, are being tonically expressed, so it becomes an issue. But I think, more so, I worry about if one actually uses those. So in the setting where it usually comes up, in TK in acyclovir addition -- but there are other -- cytidine deaminase -- there are other ways to skin that same cat -- in each case, you are presenting the possibility of an acute wipeout of a given integrated cell population. So I actually worry about that being in some cases more profound a disturbance than whatever it is you are trying to kill that cell population to get around. As we see in immune reconstitution syndrome, what happens if a given cell population in the

brain is suddenly wiped out? That, in and of itself, can be fatal.

So the use of suicide genes, as they have been so frequently brought up, is not necessarily a good thing. It's something we may want to consider in the setting of the safety criteria that have been suggested for some of the cell populations that we have been discussing.

DR. SNYDER: Right. I think I would make that a completely separate category, apart from reporter genes, because those are really bioactive and the reporter gene is presumably not bioactive.

That actually comes up a lot. I would agree, that comes up a great deal. I think Malcolm has dealt with that issue a number of times, people coming to you and wanting to know -- cells very often have GFP in them, which is necessary for the preclinical trials and for scaling up. They will often want to know, do they have to repeat all of the preclinical data with a cell that no longer has GFP or does that invalidate their preclinical data?

I think you have given a lot of good guidance with regard to that, Malcolm, saying safety is safety. But it might be important to give that kind of guidance explicitly in the guidance document. Maybe you hear that a lot, Jane, too. That provides an enormous amount of confusion, when people are planning their preclinical

studies with the anticipation of moving on to Phase I.

The next topic Leisha brought up. You wanted to address the question of novel therapeutic design.

DR. EMENS: Just briefly, I think a lot of times, as people begin thinking about a trial, you think in terms of standard Phase I, II, and III. But there are novel designs that you could think about using that may be appropriate, depending on the intervention and the patient population. Inter-patient dose escalation is one example. Accelerated titration in a situation where you expect the toxicity risk to be quite low might be another, with appropriate stopping guidelines built in. There are interesting trial designs to look at interactions between things, if you have two things that you are putting together. Earlier a Phase I/II or II/III collapsed trial design was mentioned.

I just think encouraging people to think a little bit out of the box to accelerate clinical development is not a bad thing.

DR. SNYDER: That actually segues to another topic that we felt should be addressed a little bit more. Steve brought this up. That’s the notion of being parsimonious between clinical trials -- in other words, allowing perhaps some crosstalk between trials, if there’s a really relevant control group from one clinical trial, to

have it also be used to do double duty for a second clinical trial.

Did you want to flesh that out a little more?

DR. ROSE: Yes. And I know the agency is under confidentiality and you need all sorts of paperwork to allow different sponsors to use another sponsor's data. But I think if there is a way for the agency to -- you can't make it happen, but the question is, can it be somehow, with the original -- if you see something come in where you go, hey, that control group actually has applicability to something else we're seeing, is there some sort of leeway or something that can be done to somehow try to make the first group, let's say, aware that that's the case, without giving out the store.

I know it's a fine fence here, but reinventing the wheel every time is just slowing stuff down, costing dollars, and preventing things from moving as fast as they possibly can. There just needs to be a way. When we are sponsoring or funding trials that have that potential, we definitely talk to the investigators that are involved in both trials about it -- now, separately. I mean, we don't pull them in the room and gun them. But bottom line is, it's extremely important, and it's something that I know could definitely be a positive for moving fields forward.

DR. COHEN: To the extent that the FDA would

currently look at, let's say, data collected outside the United States on a trial, in an open-label fashion, or published data, would that be something that would be sort of applicable to what you are talking about?

DR. ROSE: I think that, at least in the ones I have been involved with, published data or data that's in the public domain goes into the IND package as supporting information. But there's a lot of data that is not in the public domain that really could have an impact on trial design, measures of efficacy, controls, all sorts of areas. And I know there are groups, like us -- it was talked about at FasterCures -- that are beginning to collect placebo data from trials that they are sponsoring to put into a database to be able to use for future trials.

DR. COHEN: One of the things that Dr. DiMauro was commenting on was NAMDC, North American Mitochondrial Disease Consortium, which is building a database for the purpose of allowing for this sort of thing. Maybe the proposal would be to consider public domain databases.

DR. ROSE: And I realize that FDA can't say, thou shall. I think it's up to those of us who are working with sponsors, those of us who are sponsoring, those of us who are funding to do it. Again if there's some way the agency can say, okay, I can't make you do it, or whatever, but this would really be good for the field -- just a thought.

DR. SNYDER: Great.

Another topic -- and I apologize, I can't remember who brought it to my attention -- is discussing lack of other treatment options.

DR. CRIPE: That was me again. This might be a little bit picky, but Section IV.B.3 says lack of other treatment options and basically says CGT trials sometimes enroll only the subsets of subjects who have not had an adequate response to available medical treatments or have no treatment options.

We always have some option. The question is, how good is it? We have a lot of different salvage chemos that we'll try on relapsed cancer patients, but it may only work 10 percent of the time. Is that a treatment option or not?

Maybe there could be a little more specificity there, that there's no standard, acceptable, reasonable, more likely than not, option that will work for this patient.

DR. ROSE: But where there is absolutely no treatment option as of the moment, where there's an unmet need, there's nothing that can be done, because there's even nothing in trials in some cases.

DR. CRIPE: Then it's obvious. But I'm thinking about patients where there are things we could do, but they are probably no better than a clinical trial. But we do

them anyway because it's all we have.

Would this verbiage box those patients out? There is something I could actually give the patient as an option. It's maybe not a very good option. Maybe 10 percent of patients will have some stabilization of their disease. Is that good enough to box them out of a potential trial? It's not a complete lack of options.

DR. SNYDER: So your recommendation is that that category be clarified a bit more in the guidance document, some modification of what "other options" means, like less than ideal options or marginally effective options.

DR. CRIPE: Right.

DR. SNYDER: Okay. The last topic that we thought maybe we should discuss was mentioned by Jane, and that's perhaps some guidance as to how one can transition -- maybe its own document, maybe not in this document -- how a group of investigators transitions from the end of Phase I into Phase II.

Do you want to flesh out what you were thinking?

DR. LEBKOWSKI: Yes. This was a comment that was made to me, which would be, maybe at the end of the guidance document, to put together a paragraph or a couple of paragraphs that might foreshadow what the next guidance document might be, which is on later-stage clinical trials, so looking at what types of things the investigators need

to narrow down and figure out before you take the leap into that next later-stage clinical trial.

That was one recommendation.

DR. WITTEN: As you go around on this question, I would actually be interested in people's comments on that -- not what we should write, but if we were going to write something, what they think investigators should be learning from this in order to decide to go to the next phase. I don't know what we would put in exactly. I would be interested in people's comments on what they think we should put in if we are going to take your idea.

DR. LEBKOWSKI: Unfortunately, there is not a lot of discussion about that, but I think in terms of questions on follow-up, questions on selection of dose, selection of outcome measures, selection of trial designs, things like that.

DR. WITTEN: That you think people should have learned from this.

DR. LEBKOWSKI: Yes, or should have at least thought about it as a result of doing the trial.

DR. SNYDER: Basically, the question is, after you have finished Phase I, what knowledge should you have to be able to move on to Phase II? What data should you have abstracted by that? You're saying you should already know the dose, you should know the route of administration,

you should know what the potential toxicities could be, what to look for.

DR. LEBKOWSKI: Exactly. You might need to expand upon the dose, but some ideas about what your next dose cohorts would be.

DR. SNYDER: Larry, do you want to add anything?

DR. COUTURE: Yes. In agree with Jane in principle. I'm not sure this is a separate guidance document. I think what it is -- because once you move to Phase II and III, ostensibly different people might get involved, especially in a lot of the trials they are starting. Phase I's often are academic or small companies.

I think what the two paragraphs are that Jane is getting at, and Celia as well, are, what should one learn from a Phase I clinical trial? That is not in there at all. It's just sort of a kick-starting out the door -- go do something. But there's no real guidance on what you should really be trying to achieve in a Phase I.

I want to add along those lines -- I think what Dr. Lee was maybe trying to get at yesterday -- nowhere in here is there any discussion of statistical relevance of the trials or the animal studies that go into these trials. It is a problem. We see this happen a lot. Certainly a Phase I 3-plus-3 kind of -- whether that's statistically relevant or not is debated. But there's no treatment of

what an investigator should be thinking about in terms of statistically powering a trial to really inform or to permit a larger-scale Phase II or Phase III, whether that statistical powering takes place in the Phase I or Phase I/II or not until the Phase II. Again, there's no real guidance to investigators on how to think about that issue.

I hope I didn't misspeak, Dr. Lee. You raised the idea in my mind.

DR. ROSE: I would agree. It's more, I'm done. What do I need to think about that's next? That's all.

DR. LEE: In cancer clinical trials, usually, after a Phase I trial, when we are satisfied for the safety, efficacy, and toxicity study, then the investigator needs to decide how to design a Phase II trial, which is different from a Phase I trial. At that time, the hypothesis has to be clearly defined, sample size, power, and treatment arms. From this two-day study, it seems to me it's too early to consider a Phase II trial at this point, because you need a lot of data to justify that you can move on to a Phase II trial.

DR. SNYDER: Do you want to comment on this, Steve, this particular question, transitioning?

DR. GOLDMAN: Just to reiterate the points that have been made and to get back to the point of perhaps blurring the lines between Phase and Phase II.

To Celia's point, one thing I would want to know is whether something looks like it actually has a chance of working. I would like to see some sort of efficacy measures in Phase I incorporated at least sufficiently to justify logically, if not statistically, going ahead to a larger-scale trial. We have seen so many, at least in CNS disorders -- what I'm most familiar with -- both gene and cell therapy trials that have gotten through Phase I, but there was never any reasonable expectation of efficacy, and, of course, they failed in Phase II.

Having a little bit more by way of hard efficacy endpoints incorporated into Phase I -- therefore, making it, on some level, a Phase I/II -- I think would be a good move in terms of the advent of cell therapeutics.

DR. AHSAN: I think one of the issues with these types of guidance documents is exactly that, that it's so broad that you can't be specific about what the certain applications are. In that vein, even in the transitioning from Phase I to Phase II, in the document, meetings with OCTGT are at the end of the document. In order to maybe emphasize that all of this needs to be in conversation, so the goals of Phase I need to be agreed upon early on, maybe that section should be at the top of the document. Then the rest of it is, these are some things to think about, but, really, you need to come talk to us. The "come talk

to us" should be first.

That might be something to think about. There might be some unintended consequences there that I'm not aware of, but it seems to me, in the spirit of let's build this idea together about what we think our endpoints are and what we're trying to accomplish, the conversation element of it might be at the top of the document as opposed to the bottom of it.

DR. BUGBEE: I actually do have a comment here, because I think this is particularly important in my field, this idea of taking efficacy data from a Phase I trial and using it -- this collapsing or novel therapy. I think in orthopedics there's a perception that cell and even gene therapy is less risky, and therefore there is a motivation to do one trial and try to get the safety out of the way, because it's a lesser order, theoretically, and then take that efficacy data to go on to others.

Back to the question of topic 3, therefore, the document says it may be okay not to have a control group in Phase I, but if you take that to heart and then you take the data and use some efficacy data, as has been suggested, to go forward, then that study wasn't powered properly. Frankly, in orthopedics there are a lot of researchers who don't understand any of that. They just carry on.

I think, therefore, if we're talking about that,

this document is unbalanced. It should have some verbiage that says, if there is any consideration of using secondary endpoints in the safety study for efficacy, then the discussion of control group, placebo effect, and all that should be reconsidered in a completely different manner. I think that's an important thing to balance the document out.

DR. GOLDMAN: If I could respond to that, I agree, implicit in the idea of a collapse of I and II is having a control group that is informative in the initial trial. I'm looking at it, of course, from the perspective of neurologic, and especially rare neurologic, diseases, where one of the things that comes up in some of these Phase I's that have been done is that the affected patient population is exhausted in a safety trial, so that it then takes several years for new patients to accrue for the next trial to be done, with no efficacy data having been obtained the first time around.

So I look at it more from that standpoint of getting the most information out of a given rare patient cohort and, at the same time, potentially being able to do some good for those patients.

DR. BUGBEE: Just study arthritis.

DR. COHEN: I think there are certain disease models that lend themselves to Phase I/Phase II trials.

Others -- just picture a drug that works great in lab animals and is highly toxic, where you would probably really want to spend your money defining your maximum tolerated dose before bringing it to a Phase II, especially in a common disease like glioblastoma, for example, where it may make more sense to do a true Phase I and then a Phase II.

So I think it really depends on the disease model.

DR. SNYDER: Was that helpful, Celia? Okay.

Go ahead, Dr. Lee.

DR. LEE: Actually, these gene therapies or genetic therapies might consider first the Phase 0, these pharmacokinetics. These things have to be done first, like on cells, instead of directly to go to patients -- a Phase 0 trial, to make sure of the safety/toxicity before to do Phase I.

DR. SNYDER: Wouldn’t that be part of the preclinical work, though?

DR. LEE: Yes, preclinical work or some other animal studies.

DR. SNYDER: Presuming really good preclinical work before ever moving on to Phase I.

These are all the topics that have been brought to my attention that were in our wildcard category. Are

there any other things that we should recommend that the guidance document include or describe better?

(No response)

I guess, if that's the case, then our work here is done. Is there anything else that we can provide in terms of guidance?

DR. WITTEN: No. I would like to thank you, in particular, and the whole committee and our SGEs for your assistance with this topic.

DR. SNYDER: Thank you all and have a safe trip home.

(Whereupon, at 4:10 p.m., the meeting was adjourned.)