

U.S. FOOD AND DRUG ADMINISTRATION

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PEDIATRIC ETHICS SUBCOMMITTEE

OF THE

PEDIATRIC ADVISORY COMMITTEE

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MEETING

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TUESDAY,  
JUNE 10, 2008

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The subcommittee convened at 8:00 a.m. at the Holiday Inn/Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, Maryland, Norm Fost, Subcommittee Chair, presiding.

PRESENT:

- NORMAN FOST, M.D., Chair
- JEFFERY BOTKIN, M.D., M.P.H., Consultant
- AMY CELENTO
- LEONARD GLANTZ, J.D., Consultant
- STEVEN JOFFE, M.D., M.P.H., Consultant
- ALEXANDER KON, M.D., Consultant
- THERESA O'LONERGAN, M.A., Consultant
- GEOFFREY ROSENTHAL, M.D., Ph.D.
- ELAINE VINING
- BENJAMIN WILFOND, M.D., Consultant

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Health Coordination, Office of the  
Commissioner

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CELIA WITTEN, Ph.D., M.D., Office Director,  
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P-R-O-C-E-E-D-I-N-G-S

8:03 a.m.

DR. FOST: I think we're ready to convene. Good morning. I think renewed introductions are not needed. I take that back; we do have a new guest from FDA. Maybe we should just go around and just re-introduce ourselves briefly, so everybody knows everybody. Steve?

DR. JOFFE: Steve Joffe, Pediatric Oncology from Dana-Farber Cancer Institute, and Boston Children's Hospital.

DR. FOST: Leonard?

DR. GLANTZ: Leonard Glantz, Boston University.

DR. KON: Alex Kon, Pediatrics and Bioethics at UC Davis.

MS. O'LONERGAN: Terry O'Lonergan, biomedical ethicist, Children's Hospital in Denver.

DR. BOTKIN: Jeff Botkin, pediatrics and bioethics at the University of

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1 Utah.

2 DR. WILFOND: Ben Wilfond,  
3 pediatrics and bioethics, University of  
4 Washington.

5 DR. FOST: Norm Fost, pediatrics  
6 and bioethics at the University of Wisconsin.

7 DR. PENA: Carlos Pena, Executive  
8 Secretary to the Pediatric Ethics  
9 Subcommittee.

10 DR. ROSENTHAL: Jeff Rosenthal,  
11 pediatric cardiology, Cleveland Clinic, and a  
12 member of the Pediatric Advisory Committee.

13 MS. VINING: Elaine Vining. I'm  
14 with the Pediatric Advisory Committee,  
15 consumer representative.

16 MS. CELENTO: Amy Celento with the  
17 Pediatric Advisory Committee, the patient  
18 representative.

19 DR. NELSON: Robert, Skip, Nelson,  
20 I'm the pediatric ethicist with the Office of  
21 Pediatric Therapeutics in the Office of the  
22 Commissioner, FDA.

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1 DR. ELVIN: Virginia Elvin. I work  
2 for the FDA on the Inborn Errors of Metabolism  
3 Team. I'm a Child Neurologist.

4 DR. FOST: Thank you. Our first --

5 DR. NELSON: Norm?

6 DR. FOST: Yes?

7 DR. NELSON: Just to mention, there  
8 are some other people from FDA here in case  
9 there is technical questions that they think  
10 might be helpful for the Committee to know. I  
11 can let you know now who's here, if that would  
12 be fine.

13 We have Celia Witten, who, I think,  
14 is Office Director of the Office of Cellular  
15 Products, and something else.

16 MS. WITTEN: Cellular Tissue and  
17 Gene Therapy.

18 DR. NELSON: Cellular Tissue and  
19 Gene Therapy. Mercedes Serabian, who is a  
20 toxicologist, and Karen Davis-Bruno, who is  
21 from CDER, as well, who is a toxicologist.  
22 They basically have interest in animal

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1 modeling, and preclinical, and the like, and  
2 then of course, Susan McCune, who is a  
3 neonatologist, who may be here of her own  
4 interest, who is with the Office of Counter-  
5 Terrorism, just not -- I'm unaware of any stem  
6 cell product that's in that domain, but just  
7 as a point of information.

8 DR. FOST: Thank you. Glad you're  
9 here. I think the issues today have some  
10 technical aspects that are further beyond the  
11 knowledge of many of us. So it will be very  
12 helpful to have technical advice.

13 Our opening agenda item today is  
14 the public hearing. We do not have anybody  
15 scheduled to speak. I'm sorry. Thank you.

16 DR. PENA: So good morning to  
17 members of the Pediatric Ethics Subcommittee,  
18 members of the public, and FDA staff. Welcome  
19 to the meeting. In general, I'd like to  
20 remind both the Subcommittee participants and  
21 meeting attendees of the need to exclude  
22 themselves from involvement in discussion of

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1 topics if their interest would be affected,  
2 and their exclusion will be noted for the  
3 record.

4 We have one open public comment  
5 period scheduled for 8:00 a.m., just shortly  
6 this morning. Please make sure that, when you  
7 speak, your microphones are turned on, so that  
8 the transcriber can pick up everything that  
9 you state, and turn them off when you are not  
10 speaking. I'd also request all meeting  
11 attendees to turn their cell phones and  
12 Blackberries to silent mode. Thank you.

13 DR. FOST: Thank you, Carlos. So  
14 our first item is an open hearing, and I  
15 believe we have nobody scheduled to speak. We  
16 do have the written statement from yesterday  
17 that I'm -- a short statement that I thought  
18 it might be helpful to read again,  
19 recapitulates one issue that we discussed  
20 yesterday, but it's also germane to today's  
21 discussion. So this is from Dr. Bernard  
22 Yablin.

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1           "Since I don't yet have medical  
2 clearance wheelchair needs or arrangements for  
3 remuneration, I would like to resubmit the  
4 following questions: One, in any pediatric  
5 study on asthma, how would it be possible to  
6 account for genomic variations in response to  
7 medications, e.g., antileukotrienes in each  
8 treatment arm; and two, in the periventricular  
9 injury study, would there be different time  
10 tables for imaging studies to hopefully  
11 determine the onset as soon as possible?

12           Any comments or reactions? We can  
13 perhaps incorporate the second comment as we  
14 go. So we'll start as before, with a  
15 presentation by Skip Nelson on some of the  
16 regulatory and conceptual issues, and then the  
17 hypothetical case for discussion. Skip?

18           DR. NELSON: Thank you, Norm.  
19 Well, before I get into the content of the  
20 presentation, let me just, for the benefit of  
21 those who weren't here yesterday, and also as  
22 a brief reminder, to just give a sort of quick

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1 thumbnail sketch, not of all the content, but  
2 at least of the issues that we've tackled.

3           So the approach to this meeting has  
4 been to use hypothetical cases, of which,  
5 yesterday, we had two - today we have the  
6 third - to explore the application of the  
7 regulatory category, 21 CFR 5052, to FDA  
8 regulated research. That particular category  
9 - you'll see some language later on the  
10 presents the essence of it - is the category  
11 that involves interventions that are greater  
12 than minimal risk, but offer the prospect of  
13 direct benefit, and then there's certain  
14 language in that regulation about the  
15 comparability of risk and benefit relative to  
16 the intervention, as well as relative to other  
17 alternatives.

18           And a lot of our discussion has  
19 been exploring the application of that. The  
20 themes that we touched on in the morning  
21 yesterday was the importance of scientific  
22 necessity in guiding whether or not you would

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1 do pediatric studies. We then talked  
2 primarily in the context of the timing of  
3 adolescent HIV vaccine studies with respect to  
4 adult studies about the prospect of direct  
5 benefit, at what point you might reach that  
6 threshold, and then in the afternoon, using a  
7 hypothetical case of the testing of a new  
8 inhaled corticosteroid in the context of a  
9 growth study, we then went into a much more  
10 complex discussion, if you will, of how one  
11 might approach the analysis of that kind of  
12 trial in the context of Subpart D.

13 This was a four-arm asthma trial  
14 where we touched on such issues as how one  
15 would think about the placebo arm, as well as  
16 the run-in and run-out placebo component of  
17 the study. We talked about component  
18 analysis. We talked about the inclusion  
19 benefit. In other words, indirect benefits  
20 that may come to having been in the research,  
21 and how that's folded into the analysis, and  
22 then we talked about issues of the

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1 risk/benefit assessment, and whether that  
2 should be done for the whole trial together,  
3 or whether you need to separate that out into  
4 an analysis of the individual arms of the  
5 trial, and then we also touched on choice of  
6 control groups.

7 So as you can see, yesterday  
8 afternoon, actually, even though we may have  
9 felt we're sort of moving around in different  
10 ways, I think touched on a number of complex  
11 issues that are very important for the  
12 application of Subpart D, particularly 5052,  
13 to pediatric research.

14 Well, today we go to a no less  
15 important topic, but in many ways a much  
16 simpler study design. We're going to be  
17 talking about early phase research. The  
18 hypothetical involves the use of a stem cell  
19 product, but we will be looking now at early  
20 phase clinical research in pediatrics, and  
21 exploring the prospect of direct benefit in  
22 that setting where, in fact, the hypothetical

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1 is a single arm study.

2 So it's a much different research  
3 design, but no less important relative to its  
4 issues. We alluded a little bit in our  
5 discussion yesterday to some things that may  
6 come up again today. There was occasional  
7 discussion of what was called Phase Zero  
8 Studies, Phase One Studies. There was --  
9 which were brought up by Ben, and I think  
10 Steve. Steve at one point talked about the  
11 prospect of direct benefit, and whether you  
12 could do that from animal studies. So I think  
13 there was a few points at which we brought up  
14 those issues, but today, we'll make them much  
15 more explicit, and hopefully explore them in  
16 more depth.

17 And I might say, this presentation  
18 I'm going to give you actually has been co-  
19 developed with Sara Goldkind, who is the  
20 ethicist with the Good Clinical Practice  
21 Program at FDA. She and I presented it in two  
22 different public venues. One, we presented it

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1 at the American Society for Bioethics and  
2 Humanities meeting that was held in  
3 Washington. I think that was either the  
4 meeting before this, or two meetings ago, but  
5 recently, we also presented this as a workshop  
6 in Boston at the PRIM&R Meeting, and so I know  
7 some of you have seen this. I think Steve was  
8 at the presentation at ASBH, and so this is a  
9 more, if you will, edited version of that  
10 presentation, but the concepts I'll be  
11 presenting have been developed, and have been  
12 presented previously by the two of us in a  
13 public forum.

14 Again, I should say that the fact  
15 that we did that means that it has nothing,  
16 necessarily, to imply about FDA policy. It  
17 just means the two of us decided to do that.  
18 So, which I appreciate the FDA for allowing us  
19 to do that kind of thing.

20 Now, the normal process of  
21 pediatric drug development - not so much  
22 normal, that may be an overstatement - but the

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1 sort of usual model we have in mind is that we  
2 sort of develop some pre-clinical animal  
3 modeling. We then look for the administration  
4 of that product in healthy human adults. We  
5 then move to adults with a disease, and then  
6 finally, we get to children with a disease.  
7 In many ways, you could view the discussion  
8 yesterday about the hypothetical HIV vaccine  
9 development trial as sort of moving through  
10 this model, where we administer that to  
11 healthy human adults who are willing to accept  
12 the risk of that administration, and then look  
13 for adults with disease, and then decide,  
14 based on the data that we're getting from that  
15 product development, that it's time to move  
16 into doing pediatric trials.

17 Well, the question that we're  
18 raising today explores different alternatives.

19 I mean, there may be situations where, in  
20 fact, administering a product would not be  
21 appropriate for a healthy human adult. There  
22 may be also situations where, in fact, there

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1 is no adult disease equivalent, and even  
2 though it may be appropriate to administer  
3 that product to healthy human adults for  
4 initial, if you will, dosing and toxicity  
5 data, assuming adequate and voluntary informed  
6 consent, that, in fact, there is no adult  
7 equivalent of the disease, and you would be  
8 then going directly into children with disease  
9 from that.

10           There may also be a situation where  
11 you need to go from preclinical animal  
12 modeling directly to children with the  
13 disease, and of course, if that is more than a  
14 minimal risk intervention, which the intent  
15 today is to discuss interventions that are  
16 more than minimal risk, you're not going to  
17 basically administer that to healthy children.

18           So the problematic that we're faced  
19 with is, what do you do? So looking at the  
20 ethical framework that's contained within the  
21 Subpart D regulations, basically, if the  
22 experimental intervention is more than a minor

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1 increase over minimal risk, you have one of  
2 two choices. Either the intervention must  
3 offer a prospect of direct benefit, which is  
4 the purpose of this discussion is to explore  
5 the issues surrounding that assessment under  
6 5052, or the IRB must refer the protocol for  
7 federal review under 5054. Otherwise, it's  
8 not approvable. And that's really meant to  
9 just be a logical assessment of the two  
10 alternatives that are available.

11 Now, the intent here is not to get  
12 us into a discussion of 5054, but more to  
13 explore what is the -- what are the  
14 constraints, if you will, as you apply  
15 prospect of direct benefit into this kind of a  
16 setting, where you don't have the ability to  
17 do studies in adults.

18 So the question is, first in  
19 children under 5052, and this just repeats  
20 5052, the language in a more truncated version  
21 from the full regulations. Basically, any  
22 clinical investigation presenting more than

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1 minimal risk to children by an intervention  
2 with the prospect of direct benefit may  
3 involve children as subjects only if risk is  
4 justified by the anticipated benefit to the  
5 subjects, and the relationship of anticipated  
6 benefit to risk is as favorable to the  
7 subjects as available alternative approaches.

8 That's simply restating the regulations, and  
9 how we assess risk and benefit from an ethical  
10 perspective within that context.

11 So absent a suitable adult human  
12 population, the challenge is to establish a  
13 sufficient prospect of direct benefit from  
14 animal studies alone to justify first in  
15 children clinical trial.

16 Now, again, I'm presenting some  
17 ideas for you to consider, some tools, if you  
18 will, to place on the table that you can  
19 choose to pick up or not, but here are some  
20 reflections about prospect of direct benefit.

21 So a benefit is direct if it accrues to the  
22 individual subject enrolled in a clinical

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1 trial. So the idea here is it's my benefit,  
2 not your benefit.

3 The second is that it results from  
4 the research interventions required to answer  
5 scientific questions posed by the trial, and  
6 not from other interventions included in the  
7 protocol but unrelated to the research  
8 question. So that gets a little bit into the  
9 discussion yesterday about a direct and  
10 indirect idea. The word benefit is often  
11 preceded by clinical, although that's not  
12 contained in the regulations, to indicate that  
13 direct benefit relates to the health status of  
14 the enrolled subject.

15 Now, a prospect of direct benefit  
16 is based on the structure of the intervention.

17 I mean, one -- yesterday, there were  
18 occasional discussions, I think Jeff brought  
19 it up, about intent, the intent of the  
20 research, et cetera. The point here is that  
21 intent is not meant to be simply a  
22 psychological claim, that I, as the

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1 investigator would not say, it's my intent to  
2 benefit, and therefore, that would be  
3 sufficient evidence, assuming that I'm  
4 accurately reporting the inner state of mind -  
5 - that my inner state of mind, that would not  
6 be sufficient evidence to say that, in fact,  
7 that intervention offers the prospect of  
8 direct benefit, so that it's based on the  
9 structure of the intervention.

10 For those philosophers in the  
11 audience, this is actually a sort of pre-  
12 Cartesian analysis of intent that's contained  
13 within the doctrine of double effect within  
14 Catholic moral theology, but we don't have to  
15 go there. The point is that it's about the  
16 structure of the act; it's not about some  
17 inner state of mind.

18 And so you need to look at things  
19 like dose and duration, method of  
20 administration. In other words, what are you  
21 actually doing. I mean, in an ICU setting, it  
22 would be patently false if I gave someone,

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1 say, 30 milligrams per kilogram of morphine to  
2 a narcotic-naive individual, and tried to  
3 claim I was simply relieving their pain. I  
4 mean, any ICU doc would say that that is false  
5 on the face of it, even if that was my intent,  
6 so that's what I'm trying to get at.

7 Now, the other point is that the  
8 evidence for prospect of direct benefit should  
9 be weaker than the evidence supporting  
10 efficacy. That's simply a claim about the  
11 circularity of the argument, because if, in  
12 fact, I demand that the evidence for prospect  
13 of direct benefit is the same as the evidence  
14 for efficacy, I can't do the research, because  
15 I'm demanding a level of proof about the  
16 research before I even do it. I mean, it's  
17 just -- so somewhere, the evidence in support  
18 of prospect of direct benefit would be weaker  
19 than the evidence for a claim of efficacy. We  
20 alluded to that a little bit in our discussion  
21 yesterday about HIV vaccines. Today, we would  
22 be exploring it in the context of what kind of

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1 information would one glean to support a first  
2 in children, where you're not using the adult,  
3 the human adult animal model, if I may, to  
4 justify that intervention.

5           So the justification of risk, you  
6 need empirical evidence of sufficient prospect  
7 of direct benefit to justify exposures to the  
8 risk. Now, this is a complex quantitative and  
9 qualitative judgment. There's data involved,  
10 but as people who look at risk perception,  
11 it's not purely a data-driven argument, and  
12 that's what makes it difficult. Often, these  
13 are risks that don't have a similar yardstick,  
14 if you will, to some extent, may be  
15 incommensurable. How do you actually make  
16 that assessment? It's complex. In many ways,  
17 this risk/benefit evaluation is similar to  
18 clinical practice. These are the kinds of  
19 judgments we make every day.

20           Now, the justification of risk by  
21 prospect of direct benefit can include,  
22 doesn't necessarily have to include, the

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1 importance of that direct benefit to the  
2 subject, the possibility of avoiding greater  
3 harm from the disease. This is not meant to  
4 be a complete list. I'm sure there's other  
5 things that could be put on this list, but  
6 these are a few thoughts. The risk of the  
7 experimental intervention can only be  
8 justified by benefits to be expected from that  
9 same intervention, which is a restatement of a  
10 previous point, and this justification is set  
11 in the context of the disease severity. I  
12 mean, what's the degree of disability, to what  
13 extent is it life-threatening, and what's the  
14 availability of alternative treatments?

15 And so the justification of the  
16 risk that one would be willing to accept with  
17 the prospect of direct benefit can include all  
18 of these various considerations. Now, when  
19 you look at FDA regulations, as well as back  
20 at The National Commission, here's a couple of  
21 quotes that suggest that this is an approach  
22 that can be found in other areas when you're

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1 looking at drugs that are intended to treat  
2 life-threatening and severely debilitating  
3 diseases.

4 So if you look at 21 CFR 312.84,  
5 which is the first quote, which is the  
6 regulations governing Investigational New  
7 Drugs, INDs, there's a statement that FDA's  
8 application of the statutory standards shall  
9 recognize the need for a medical risk benefit  
10 judgment in making the final decision on  
11 approvability.

12 Approvability is different from  
13 what we're talking about in terms of research,  
14 but I think it's an analogous situation when  
15 one might be evaluating the acceptability of  
16 the actual research itself. As part of this  
17 evaluation, FDA will consider the severity of  
18 the disease in the absence of satisfactory  
19 alternative therapy. So in fact, these  
20 considerations are part of the consideration  
21 around drug approval, and are part of the  
22 considerations about whether research ought to

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1 proceed under IND.

2           The National Commission, in 1978 -  
3 again, this is a similar quote to what I  
4 showed you yesterday, where -- by the National  
5 Commission on the research on -- the report on  
6 research involving children, says that the IRB  
7 should also make some of this risk/benefit  
8 assessment in a comparable way as that which  
9 is made in clinical practice. It should  
10 compare the risk and anticipated benefit of  
11 the study intervention with available  
12 alternative methods for achieving the same  
13 goal, and should also consider the risk and  
14 possible benefit of attempting no intervention  
15 whatsoever. So I mean, this is -- hopefully,  
16 I'm at least laying out the possibility that  
17 this sort of risk/benefit assessment in the  
18 context of the disease is, in fact, not a new  
19 idea.

20           So the proposal that I would put  
21 before you is what Sara and I now call sliding  
22 threshold, where the animal data necessary to

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1 establish a sufficient justification for the  
2 prospect of direct benefit would vary with the  
3 severity of the disease, and the adequacy of  
4 the alternative treatments.

5           And we tried to create what we see  
6 as a sort of hierarchy, if you will, of the  
7 kinds of data that one could bring to bear on  
8 that question. So the first would be, for  
9 example, structural change. I've made an  
10 intervention, I can show a change in  
11 structure, but absent any change in function,  
12 the view would be that would generally be  
13 insufficient for documenting prospect of  
14 direct benefit, or at least suggesting that  
15 there might be. The other might be a  
16 functional changed based on the mechanism of  
17 action, and there's various ways one can try  
18 to achieve that functional change. One is to  
19 identify a molecular target, and say -- and  
20 demonstrate you can hit it. Again, I'm  
21 talking animal models. You can hit it. The  
22 other might be a biomarker. You can show a

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1 change in an RNA, or a change in a protein,  
2 that would give you a sense that there is a  
3 prospect of direct benefit if you went into  
4 children.

5 The other might be a physiologic  
6 pathway. You can measure metabolic products,  
7 and show that you've made a change. One  
8 approach would also be transgenic technology.

9 It's possible that an animal model may lack  
10 the target, that we may be the ones that have  
11 that, and you may, with a transgenic  
12 technology, be able to take the human target,  
13 put it into the mouse, and then demonstrate  
14 that, in fact, if you give the mouse that  
15 product, you can hit that target.

16 And then finally, the gold  
17 standard, although there may be limited  
18 circumstances under which this approach is  
19 available to you, could be the existence of a  
20 clinical disease model, where, in fact, the  
21 animal disease mimics the human disease. I  
22 think there are circumstances where that's the

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1 case that have served as a justification of  
2 pediatric trials, and this could also be  
3 directed either towards a surrogate endpoint,  
4 or may, in fact, even allow you to test a  
5 clinical end point relative to survival.

6 So the idea here is to just give a  
7 sort of scale, if you will, of the kinds of  
8 evidence that could be cited, if you will, in  
9 support of prospect of direct benefit, not to  
10 say that, in any given instance, what evidence  
11 would be sufficient. That will vary depending  
12 upon the disease, and the alternatives that  
13 are available to you.

14 Now, the import here is that it's  
15 not so much the evidence that varies, but  
16 rather the threshold at which we have a  
17 sufficient basis for approving proposed  
18 research. This is a modification of Sara and  
19 I's presentation based on comments made in  
20 discussion at ASBH by a colleague who was part  
21 of that discussion, Tom Beechum, pointing out  
22 that we're not talking about the evidence that

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1 is varying, but really, it's at what point  
2 we've reached the threshold to argue, this  
3 ought to proceed under prospect of direct  
4 benefit.

5           And again, this threshold involves  
6 a number of different supporting arguments,  
7 the evidence in support of direct benefit,  
8 which is what I've been talking about, the  
9 severity of the condition, the presence or  
10 absence of alternative treatments, the  
11 importance of scientific knowledge, and the  
12 provision of informed consent, that all of  
13 that, seen as a justification, if you will, of  
14 proceeding, is part of this threshold,  
15 assuming that we have at least enough evidence  
16 to say that there is a prospect of direct  
17 benefit the first time we give that.

18           Now, a few comments, though, that  
19 are sort of cautionary notes, if you will,  
20 about dosing, and then about animal studies.  
21 The choice of dose is an important question.  
22 This is often what's discussed as different

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1 about pediatric Phase One oncology trials  
2 versus adult Phase One oncology trials, that  
3 they're choosing a different starting dose, et  
4 cetera. The difficulty is that often the  
5 maximum recommended starting dose, MRSD, is  
6 frequently based on the no observed adverse  
7 effect levels in tested animal species.

8 So you give them a certain  
9 escalating dose, you find the dose at which  
10 you don't see any adverse effect, and you  
11 choose to start there, assuming you make an  
12 appropriate conversion of this data to a human  
13 equivalent dose, and then you apply a safety  
14 factor to make sure you're not wrong.

15 The difficulty with this is that  
16 the assessment of the risk, if you will, and  
17 the potential for direct benefit of this safe  
18 starting dose, based on a no-observed adverse  
19 effect level, may not be equivalent to the  
20 dose that you may recommend that would give  
21 you the sufficient -- the greatest efficacy in  
22 animal studies, and so there may be a

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1 disconnect between the dose that you would  
2 start for safety, and the dose that you might  
3 start to optimize prospect of direct benefit  
4 in the context of the Risk Benefit Assessment.

5 So that's an issue that has to be on the  
6 table.

7           Whereas, in adults, you may decide  
8 simply to start low and work up, in  
9 pediatrics, given the ethical argument in  
10 favor of choosing a dose that optimizes the  
11 possibility of direct benefit for that child,  
12 that may be a different dose, maybe a higher  
13 dose, even though you're recognizing you may  
14 be increasing risk in doing that.

15           So that's one of the issues that we  
16 need to take into consideration. And then, I  
17 believe this is the final slide, we also need  
18 to keep in mind some limitations of animal  
19 studies. This particular list is based on an  
20 editorial I found about the limitations of  
21 animal studies, and what I found interesting  
22 about it is it was almost the exact same

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1 argument about all of the issues with human  
2 studies, and the need for registration.

3 You know, there's methodological  
4 biases in animal experimentation, lack of  
5 randomization in blinding, small sample sizes.

6 Animal models may not adequately mimic human  
7 pathophysiology to the extent that they may or  
8 may not predict human response. There's  
9 variability of animal modeling from one lab to  
10 another, in the sense that one may not be able  
11 to predict, from a preclinical animal model,  
12 what may happen in transitioning to the  
13 clinical setting. Animal data may diverge  
14 from human outcomes data collected in other  
15 settings, which may lead to difficulties  
16 assessing this prospect of direct benefit.  
17 The laboratory environment itself can lead to  
18 stressed animals, which may affect test  
19 results.

20 Some of you may be aware of the  
21 regulations governing care of animals. And  
22 when some of that tries to reduce that

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1 variability, but nevertheless, simple things  
2 like cage size and proximity of other animals,  
3 even if standardized, may affect some of those  
4 stress responses, again, depending upon what  
5 one is studying. And then, of course, the  
6 ethical requirement in the appropriate use of  
7 animals for the use of anesthesia to diminish  
8 suffering may alter physiologic state and  
9 affect end points.

10 And so, even if we feel that's an  
11 appropriate thing to do as far as the humane  
12 care of animals in human -- not human, in  
13 animal experimentation, we need to be  
14 cognizant that that care may impact on our  
15 assessment of end points, so there are issues  
16 that would need to be taken into consideration  
17 as we look towards this transition, if you  
18 will, from animal modeling into first in  
19 children studies.

20 So with that, I'm happy to  
21 entertain any questions of clarification about  
22 this presentation before we get into

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1 presenting the hypothetical for your  
2 discussion.

3 DR. FOST: Steve?

4 DR. JOFFE: Skip, can you go back  
5 to the slide that shows the sort of structure  
6 function clinical model?

7 DR. NELSON: Sure.

8 DR. JOFFE: So while you're getting  
9 there, just thinking about the oncology  
10 setting, which is what I know best, it's  
11 fairly routine, whether one is going first to  
12 adults, or in the rare case where one is  
13 forced to go first to children to base it on  
14 animal -- the clinical disease models, whether  
15 the end points are surrogate or clinical in  
16 animals, but it's hard for me to imagine going  
17 directly into kids based upon -- the structure  
18 you suggested wouldn't do it, but function, so  
19 something less than a clinical disease model.

20 Can you think, or anybody else  
21 think of any examples where one, maybe in  
22 another setting, a non-oncology setting, where

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1 one might go directly into children based upon  
2 --

3 DR. NELSON: Without a clinical  
4 disease model?

5 DR. JOFFE: Without a clinical  
6 disease model in animals. Are there any real  
7 examples of this?

8 DR. NELSON: Well, I think the  
9 hypothetical case you have before you today, I  
10 think, potentially raises that issue. I'm not  
11 sure -- you know, I guess it depends on how  
12 close you think the different animal models  
13 are to the clinical disease itself. So, you  
14 know, I think there are examples that come to  
15 mind. You know, the one today, I guess, it  
16 would be a point of debate whether the  
17 different animal models that have been  
18 proposed for hypoxic-ischemic encephalopathy  
19 are a clinical disease model where you feel  
20 it's predictive, if you will, of the human  
21 response.

22 So, Celia, sure. Probably Celia,

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1 if you could come up to a microphone so our  
2 transcriptionist -- and then just re-introduce  
3 yourself, perhaps.

4 DR. FOST: There's a chair right  
5 here.

6 DR. WITTEN: Celia Witten, Office  
7 Director, Office of Cell Tissue and Gene  
8 Therapy at the Center for Biologics. And just  
9 to give some kind of generic example, just to  
10 focus, you know, the vision of why this might  
11 -- why you might end up in this situation,  
12 aside from the hypothetical case, but you  
13 could think of some genetic diseases where  
14 people don't survive to adulthood, there's not  
15 an animal model of the disease, and using the  
16 terminology that Dr. Nelson provided, you  
17 might look at cell function in terms of  
18 genetic expression of a certain enzyme. So  
19 that would just be an example of a case where,  
20 you know, this would be the approach that one  
21 might take.

22 DR. NELSON: Thank you.

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1 DR. FOST: Other comments? Len?

2 DR. GLANTZ: So, Skip, you drew a  
3 distinction between the prospect of direct  
4 benefit and efficacy, but the regulations also  
5 talk about anticipated benefit, not just the  
6 prospect of benefit, which seems to be almost  
7 something else. So even when we use an  
8 efficacious drug, it's used because there's an  
9 anticipation of benefit, even though it may  
10 not benefit. And so we're talking about the  
11 level of certainty, I guess, or the argument  
12 that could be made.

13 So I'm just not sure -- I mean, you  
14 made it seem really quite bipolar that there's  
15 a prospect, but a prospect is more than hope,  
16 or more than theory, and it's somewhat less  
17 than considered efficacy, but there -- it  
18 seems to me there has to be at least some  
19 scientific basis to anticipate that the  
20 individual subject will benefit.

21 DR. NELSON: Yes, Leonard, I guess  
22 it's -- my intuition is that we are in

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1 agreement. I think part of the challenge is  
2 then how you flesh that out in any given  
3 instance, and clearly, around any argument  
4 based on data, there's usually boundaries of  
5 uncertainty that are placed, and I agree that  
6 part of the intent of arguing - there's the  
7 word intent - I hope I'm accurately reporting  
8 my psychological state of mind, but part of my  
9 intent in suggesting that it's not just about  
10 intent is to raise the question about data,  
11 but it doesn't answer the question about how  
12 much data. I mean, it's really about the act  
13 itself, and about the ability to judge the  
14 uncertainty of that relationship, and what's  
15 the data in support of it, et cetera, et  
16 cetera. I mean, that's part of why I raise  
17 that question around intent.

18 DR. GLANTZ: I mean, I was thinking  
19 about the Baby Fae case that involved  
20 xenotransplantation of baboon hearts, that if  
21 you asked the surgeon, did he anticipate, did  
22 he think there was a prospect of direct

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1 benefit, I think he would have said, yes.

2 That he didn't do it just for the heck of it.

3 And there's data that, you know, sometimes  
4 transplanting organs from someone to someone  
5 might be okay.

6 So he would argue - he did argue -  
7 that his goal was to treat this heart,  
8 although I don't know -- I mean, I don't know  
9 if that's his anticipated benefits. He's  
10 telling the parent that there's a prospect of  
11 direct benefit, or whether or not neutral  
12 observers would say that doesn't make any  
13 sense at all.

14 DR. NELSON: Well, I guess two  
15 comments. First of all, since I'm not aware  
16 of the data in support of arguing for the  
17 prospect of direct benefit based on an act,  
18 I'm not going to comment whether it was  
19 defensible or not, but I would agree with the  
20 distinction between the data that would have  
21 supported that intervention, which is one  
22 issue, and a separate issue, which is

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1 precisely -- you know, how one might  
2 communicate that, how that feeds into  
3 potentially over-expectations, optimism around  
4 that -- that's a whole other set of issues  
5 which I think are important, but my intent is  
6 to say, really, let's look at issues of data  
7 in support of that. And if that's the intent  
8 of your distinction, than I agree with that  
9 intent. But since I can't read your  
10 psychological state of mind, I only have to  
11 act on the evidence before me about your  
12 intent.

13 DR. GLANTZ: It's my post-Cartesian  
14 intent.

15 DR. NELSON: Thank you.

16 DR. FOST: Skip - Ben?

17 DR. WILFOND: Skip, I had two  
18 related questions regarding your slide about  
19 threshold for approval. And the -- first,  
20 there's a question of clarification. The  
21 impression I got from you with that is that  
22 you are saying, even if you had achieved a

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1 prospect of direct benefit, there would be  
2 these additional considerations for deciding  
3 whether, based upon that prospect of direct  
4 benefit, that we should go forward. These  
5 were on top of that, similar to the way the  
6 regulations are set up.

7 DR. NELSON: Ben, I guess I see it  
8 as similar to our discussion yesterday.

9 DR. WILFOND: Right.

10 DR. NELSON: I mean, in other  
11 words, there needs to be data that puts you  
12 into the ballpark, which -- and then, once  
13 you're in that ballpark, whether or not the  
14 data supports proceeding then gets into a more  
15 complex risk/benefit assessment, and to talk  
16 about the threshold. I mean, there is a  
17 relationship. I mean, if there's no data at  
18 all, than I think we're not in the ballpark,  
19 but then, you know, there is a relationship  
20 between which ballpark you want to play in,  
21 too. I mean, to continue that analogy. I'm  
22 not a baseball player, but you know, I mean, I

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1 think that's the intent is to say, you know,  
2 there are a range of other issues of what you  
3 might expect in terms of the evidence that you  
4 would require, if you will, for prospect of  
5 direct benefit in the absence of other  
6 alternatives or in the presence of a life-  
7 threatening disease may be very different than  
8 in the presence of other alternatives in a  
9 non-life-threatening disease. I mean, that's  
10 simply the claim that I'm making there.

11 DR. WILFOND: That makes sense to  
12 me. I just wanted you to clarify that. So  
13 but here's my second question regarding those  
14 threshold criteria, which I think are quite  
15 good. I'm thinking of examples of some of the  
16 initial gene transfer studies for cystic  
17 fibrosis where, for this to actually work, and  
18 actually benefitting patients, you'd actually  
19 have to give this repeatedly, repeated doses  
20 over a long time. So the initial studies were  
21 involving one dose or two doses. And so the  
22 interesting question is whether you would

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1 think of those as prospect of direct benefit,  
2 because even if there was a physiological  
3 response, it might be difficult to conceive of  
4 that as actually benefitting the person they  
5 sort of --

6 DR. NELSON: Were those studies  
7 done in adults?

8 DR. WILFOND: They were done in  
9 adults as well as in children.

10 DR. NELSON: And in children? I  
11 mean, I guess all I can say, Ben, is I'm not  
12 familiar with the evidence in support of that,  
13 so it's --

14 DR. WILFOND: I'm not actually  
15 speaking to the issue of the evidence. Well,  
16 it's more the concept that when you -- even if  
17 there's evidence to suggest this could work,  
18 if you're only giving, again, one dose, it's  
19 sort of like the PK study that, you know, the  
20 drug may work, but you're giving one does at  
21 one time, so no matter what happens with that,  
22 the question is whether you would consider

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1 that to be in the category of prospect of  
2 benefit.

3 DR. NELSON: Yes, Ben, I see that  
4 as simply a sort of further modification of  
5 the point I was making on this slide is that  
6 the choice of dose is important, and I'm not  
7 meaning to imply that it's simply one dose. I  
8 mean, one could perhaps broaden this to say  
9 the choice of dosing regimen is relevant to  
10 that assessment, as well.

11 So, yes, I think as a general idea,  
12 yes, that would be something that one would  
13 have to consider. But it may vary from -- I  
14 mean, there are some situations where maybe a  
15 one-dose might offer a prospect of direct  
16 benefit.

17 DR. FOST: Jeff?

18 DR. BOTKIN: My question is sort of  
19 related to Ben's second one, which is to say  
20 that, talking about thresholds here for  
21 prospect of direct benefit to move from animal  
22 models into first use of kids' approach. And

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1 if you're justifying that approach to kids on  
2 prospect of benefit, would you say that the  
3 study design for first use in the kids needs  
4 to be structured such that benefit can be  
5 measured?

6 DR. FOST: That was my -- let me  
7 amplify that, because that's my question, too,  
8 and it may clarify it. Excuse me back, Skip,  
9 but I'm just turning this way so I can talk  
10 into the mike.

11 DR. NELSON: That's fine.

12 DR. FOST: When Steve Joffe raised  
13 the Gelsinger case yesterday, it seemed to me  
14 analogous to the case we're discussing today  
15 in that you have a physiologic, a pathologic  
16 problem that affects infants, that affects  
17 older people, or at least, things like that  
18 can happen. One of the advantages of using  
19 Jesse, the older person, was not just consent,  
20 it was that you could measure very subtle  
21 changes, that is, for a couple of reasons.  
22 First, he can talk to you, he can -- I mean,

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1 mood changes, slight changes in intellectual  
2 ability, motor functions, whatever his  
3 symptoms were.

4 Second, you had a natural history.

5 He'd been here for 18 or 20 years, and so if  
6 he now improved, you can say it was probably  
7 due to the treatment, whereas, in the infant,  
8 you could have, with OTC deficiency, you could  
9 have a spectacular effect, and not know it. I  
10 mean, you might be able to measure some  
11 biochemical effect, but whether the infant was  
12 smarter than he otherwise would have been, or  
13 more comfortable, or less jittery, it's just  
14 much harder to measure.

15 So I think that's relevant to the  
16 model we're going to talk about later, and we  
17 don't need to get into it now, but I think the  
18 conceptual issue is, I think, another thing to  
19 add to your list of relevant variables,  
20 severity of disease is measure -- the ability  
21 to measure the result in some way other than  
22 just the biochemical, or that it measure a

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1 functional result.

2 DR. NELSON: Yes, Norm, I --

3 DR. FOST: Is that your point?

4 DR. NELSON: Right. Norm, my only  
5 point there would be, back to this slide, that  
6 to some extent, one could view that  
7 development strategy as within this model,  
8 where there is at least the availability of  
9 adults with a disease equivalent for doing  
10 that study. I think the challenge is when, in  
11 fact, that doesn't exist. So, you know, but  
12 whether or not that exists in the hypothetical  
13 I think could be seen as a point of  
14 discussion. Is there a context you could  
15 generate adult data that would be relevant to  
16 a pediatric trial?

17 DR. FOST: Yes, I guess even if  
18 there's no adult model, you still have to ask,  
19 if we give this thing to the infant, how are  
20 we going to know whether it worked or not in a  
21 functional way?

22 DR. NELSON: Right, absolutely. I

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1 think, back to the principle of scientific  
2 necessity, we discussed yesterday, if you  
3 can't get any useful information, it's  
4 obviously silly to do the trial.

5 DR. FOST: I just wanted to modify  
6 Ben's point, also, and get your response to  
7 it. The issue Ben is raising is not about  
8 what is the right dose, or do you need two  
9 doses or eight doses, but it comes up in  
10 clinical trials for chronic diseases all the  
11 time. So let's say asthma.

12 You've got a new drug. Let's say  
13 the trial is not problematic in any particular  
14 way, but they're just measuring over four  
15 weeks, or eight weeks, a change in FEV.  
16 Great, you changed the kid's FEV for a month.

17 Is that going to change his life? No. So is  
18 that a benefit? We're -- IRB is increasingly  
19 wrestling with that. Is that a direct  
20 benefit? I don't think so, being better for a  
21 month, other than the remote chance that you  
22 saved some catastrophic asthma attack, but

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1 that's not usually what they're claiming. And  
2 the same thing comes up with CF trials, not  
3 just the gene therapy trials. We just had a  
4 big to-do with Mike Rock this year.

5 He wanted to do a study that  
6 involved quite a lot of intrusion into kids  
7 admitting to the hospital for two weeks to a  
8 clinical research unit to -- it was a new  
9 pancreatic enzyme thing. And my argument was,  
10 let's say it's spectacular, and it works, so  
11 for two weeks, the kid absorbs fats better.  
12 Is that a benefit? I don't think so. And,  
13 you know, a substantial burden here, not  
14 medical burden, but two weeks in the hospital,  
15 missing school and all of that.

16 So it may -- an intervention may  
17 hit a home run in a scientific sense of doing  
18 what it does, but I don't know if you can call  
19 that direct benefit to a kid, just because he  
20 has some laboratory change. So that's another  
21 way of -- I think that's the point you were  
22 making about just is this benefit really --

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1 that is, in the case we're going to discuss,  
2 may be something interesting biochemically or  
3 cellularly happens, but that may make no  
4 difference in the life of the kid.

5 DR. NELSON: With all due respect,  
6 Norm, when we talked about that, there was  
7 some disagreement around the assessment of  
8 prospect of direct benefit around -- whether  
9 change in the life of the child needs to be  
10 the standard or not. So -- but that's to be  
11 discussed.

12 DR. FOST: Other questions or  
13 comments about the concepts here --

14 DR. NELSON: I guess my only  
15 question is at what point -- you know, one  
16 virtue of cases is you can actually have  
17 something to chew on. So I'm just happy to  
18 let the questions -- but if it goes into  
19 discussion, I think I'd rather get the case on  
20 the table and sit down, but it's up to you.

21 DR. FOST: Jeff?

22 DR. BOTKIN: Maybe just one more

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1 comment on this issue of evidence on the  
2 receiving end, and I guess it just seems to me  
3 that this -- I like this sliding threshold  
4 idea, and it seems to me this is focused on  
5 when it is you make that transition from  
6 animals to humans, and what constitutes  
7 adequate evidence. But then you have the  
8 evidence on the receiving end as well, and is  
9 it adequate, say, with an animal model, if  
10 you've got a clinical disease model in an  
11 animal, but yet once it's applied to humans,  
12 you'll only be able to ascertain structural  
13 changes. In other words, where do the cells  
14 go? Do they end up where they're supposed to  
15 go, and that's all you can tell, but you might  
16 not be able to tell anything further about  
17 whether they're functioning, or whether  
18 they're impacting the clinical disease of the  
19 child.

20 So that, I don't know, just  
21 pointing out that that sliding threshold seems  
22 to work on both sides of the equation here,

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1 and might it be sufficient, in some  
2 circumstances, simply to determine that  
3 there's been structural change based on your  
4 intervention, but not actual benefit, from a  
5 clinical perspective, to the child.

6 At any rate, I'm kind of thinking  
7 out loud about that.

8 DR. FOST: Okay, well, if there are  
9 no other questions on the concepts, maybe move  
10 ahead to the case.

11 DR. NELSON: Now again, this is a  
12 hypothetical case description, which uses  
13 published information to construct a generic  
14 description of a typical clinical  
15 investigation that is not unique or specific  
16 to any particular product. Its intent is to  
17 allow us to explore some of the issues in the  
18 application of prospect of direct benefit to  
19 pediatric research now using a different  
20 hypothetical case than the two that we were  
21 exploring yesterday to sort of draw out  
22 different issues.

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1           The background is that a hypoxic-  
2           ischemic injury is a common cause of neonatal  
3           brain injury in pre-term and term infants  
4           leading to significant neurological deficits  
5           such as learning disabilities, cerebral palsy,  
6           or mental retardation. Injury to  
7           oligodendrocyte precursor cells to the cells  
8           that create myelin may contribute to the  
9           pathogenesis of hypoxic-ischemic injury by  
10          disrupting the maturation of myeline forming  
11          oligodendrocytes. Now, the preclinical  
12          experience is documented in the literature,  
13          some of which you had distributed for you in  
14          your background packet. Human neurostem cells  
15          have demonstrated the capacity to engraft,  
16          proliferate, migrate and differentiate into  
17          different neuro phenotypes in vitro, meaning  
18          in the dish, and in vivo, using neonatal mouse  
19          models.

20                 The study hypothesis, these and  
21                 other observations have led to the hypothesis  
22                 that inserted human neurostem cells may reduce

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1 or reverse the neurological deficit secondary  
2 to neonatal brain injury after a hypoxic-  
3 ischemic event. There are several  
4 experimental animal models of neonatal  
5 hypoxic-ischemic injury that are discussed in  
6 the literature. You were provided with some  
7 of that background literature in your packet.

8 Perinatal rodent models have been developed  
9 as an experimental platform of hypoxic-  
10 ischemic injury for pre-clinical testing of  
11 potential therapeutic interventions. However,  
12 they do not reproduce the many distinct  
13 physiologic features unique to the premature  
14 human infant.

15 Other models are thus being  
16 developed, such as the pre-term fetal sheep,  
17 and non-human primate models such as the pre-  
18 term baboon and Rhesus monkey. Several  
19 investigators are currently exploring the role  
20 of human neurostem cells in reducing or  
21 reversing hypoxic-ischemic injury in these  
22 different models in anticipation of pediatric

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1 clinical trials.

2 Of necessity, the human neurostem  
3 cells would need to be surgically inserted  
4 while a child was under general anesthesia,  
5 rendering the experimental intervention  
6 greater than minimal risk regardless of the  
7 risks of stem cell insertion itself. In  
8 addition, the child may need immunosuppressive  
9 medication to assure engraftment.

10 Question one, please discuss the  
11 ethical issues in selecting an appropriate  
12 subject population for the initial clinical  
13 development plan of these products. Issues  
14 you may want to consider include differences  
15 in the natural history of the disease between  
16 adults and pediatric subjects which may  
17 influence the timing of human neurostem cell  
18 insertion, whether dosing safety and/or  
19 efficacy should first be established in  
20 suitable adult subjects prior to enrolling  
21 children, if any, and differences between  
22 pediatric and adult subjects with hypoxic-

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1 ischemic brain injury, for example,  
2 possibility of direct benefit, usefulness of  
3 safety information, assessment of physiologic  
4 response, long-term effects, some of the  
5 issues, I think, that Jeff was eluding to; how  
6 would you make your assessment?

7           Question two, please discuss the  
8 ethical issues in designing a first in  
9 children clinical trial of these human  
10 neurostem cell products. Issues you may want  
11 to consider include the need to establish a  
12 sufficient prospect of direct benefit to  
13 justify the risk of the experimental  
14 intervention, the range of animal models  
15 available for pre-clinical studies, the  
16 different types of physiologic changes in  
17 response to the experimental product,  
18 structural functional disease reversible,  
19 alluding to the sliding threshold that I  
20 presented, the severity of the disease, and  
21 the availability of alternative treatments,  
22 sort of asking you to get into that sort of

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1 risk/benefit discussion.

2 Now, I might say the intent here is  
3 to discuss the ethical issues. I realize  
4 there's a lot of technical issues that could  
5 be put on the table, but that's not the  
6 intent, nor is this the right group to address  
7 those kind of technical issues. So I'm hoping  
8 that the case will get us into a nice  
9 discussion of these early phase trials, and  
10 the complexity of these early phase trials,  
11 and I'm happy to answer any questions of  
12 clarification, if you will, around the case  
13 and around the questions, so that you can be  
14 on target as you start your discussion.

15 DR. FOST: Okay, thank you.  
16 Questions for Skip about the premise, the  
17 case? Steve?

18 DR. JOFFE: Skip, you raised the  
19 possibility and the questions, and I guess  
20 we'll get there about looking at dosing,  
21 safety efficacy in suitable adult subjects  
22 before children, and I guess, based on the

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1 description of the case, it's not clear to me  
2 what the adult analogue might be. Are you  
3 arguing that there are -- that adult hypoxic-  
4 ischemic injury might be, you know, an analogy  
5 that -- for this disease that should be  
6 explored first, because it strikes me  
7 initially that that is likely to be a very  
8 different context, a very different sort of  
9 substrate and developmental biology going on.

10 DR. NELSON: The intent in asking  
11 the question was precisely to ask it, and not  
12 to suggest the answer. One of the reasons I  
13 asked Virginia to be here was a pediatric  
14 neurologist. They also, in training in  
15 neurology, have to look at adults, if I  
16 recall, as part of their training, so that, to  
17 the extent that one wants to explore that  
18 question, one could, but the intent was to  
19 say, you know, in some sense, before one  
20 decides to go from the animal to the child,  
21 one could at least ask the question whether  
22 there is an appropriate adult setting within

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1 which you can gain meaningful information. It  
2 was not to suggest the answer to that  
3 question.

4 DR. ELVIN: I don't have an answer  
5 to that. I come with more questions than  
6 answers. It is a fascinating topic for  
7 discussion. One of the areas of concern that  
8 I have in this whole topic is that I don't  
9 believe that we have a good enough level of  
10 understanding of the molecular mechanisms of  
11 the differentiation of stem cells, vis-a-vis,  
12 different time periods in which the brain is  
13 developing, and how would you study that?

14 Animal models, we have that. We  
15 know that some of those cells can  
16 differentiate even into tumors. That's  
17 dangerous, we know that. I had a sibling with  
18 Parkinson's disease a couple of years ago, and  
19 I was researching this for him, and I told  
20 him, I said, you can't do this. It might  
21 just differentiate into a tumor. So now,  
22 talking about the human brain and

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1 periventricular white matter disease, I  
2 certainly have lots of clinical experience  
3 working with that. It's very, very common,  
4 and there's a whole gradation of injury. My  
5 thought is, I have no idea if this is really  
6 possible to do, but what I would think, okay,  
7 kids, just to take an example, pre-term kids,  
8 because of the immaturity of their  
9 vasculature, and problems with auto-  
10 regulation, et cetera, are vulnerable to  
11 intraventricular hemorrhages. If it's bad  
12 enough, they end up with a shunt at a certain  
13 point in time. So then I start to wonder,  
14 well, if you have to put the shunt in, could  
15 you take a sample of live brain tissue, and in  
16 culture, look and study the cellular  
17 mechanisms so that you could then take the  
18 stem cells that you're going to isolate with  
19 the right markers and see, under the proper  
20 growth factors, whether you're directing that  
21 cell in the right direction so that,  
22 eventually, it could be reinserted back into

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1 that brain at the appropriate developmental  
2 time in order to help that brain recover, if  
3 that makes any sense. You could do that  
4 with adults, too. People have to have  
5 surgeries. So I mean, I don't know what a  
6 neurosurgeon would say to what I'm saying.  
7 Maybe they would balk at this, but it seems to  
8 me it's not that farfetched, and that I don't  
9 think -- we're not where we need to be. I  
10 mean, we don't understand -- it's like an  
11 orchestra, you know, all the different cells,  
12 the music changes as the brain develops.

13 So I'm wondering if we shouldn't  
14 study along those lines before we consider  
15 just going into a pediatric study. And I  
16 think there may be ways to do that.

17 DR. FOST: Skip?

18 DR. NELSON: Let me just make one  
19 comment. This case is very much what I would  
20 call leaning forward, to quote a former, I  
21 guess, Secretary of Defense, leaning forward  
22 view of ethics. In other words, there are a

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1 lot of issues such as were raised  
2 scientifically about where we are in the state  
3 of that development. I think part of the  
4 intent here is to get us to sort of lean  
5 forward, and explore what the ethical issues  
6 might be as we look into the future around  
7 this sort of product development.

8 DR. FOST: Alex, and then Ben.

9 DR. KON: So I had a question,  
10 maybe Virginia, you can answer it, or maybe  
11 Skip, if you'd put on your neonatologist hat,  
12 you know, dust it off a little bit. What I'm  
13 wondering is, since I think some of what  
14 we're going to be talking about is  
15 justification based on the severity of  
16 illness, and a lack of other alternate  
17 therapies for these children, there certainly  
18 is a very broad range in the outcome of  
19 children with hypoxic-ischemic injury in the  
20 neonatal period, and what I'm wondering is how  
21 predictable is it, or how well can you look at  
22 a child and say, this is a child who's going

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1 to end up with a little bit of CP, not so  
2 badly off, normal neuro-development, but this  
3 is a child who's going to end up  
4 neurologically devastated with very little  
5 that many might consider to be meaningful  
6 life, because I think that may become an issue  
7 for us. So I'm just sort of wondering, how  
8 well can you differentiate that.

9 DR. ELVIN: It can be challenging  
10 in in the middle of the road cases. Those are  
11 full of surprises. In the devastating cases,  
12 it's not difficult to say it's devastating.  
13 It's obvious, but in the middle of the road  
14 cases, you can see high variability. I saw a  
15 child once in Harlem Hospital who, the reason  
16 I was consulted was because of a lazy eye.  
17 That was the quote unquote reason for the  
18 consult.

19 So she was about eight years old,  
20 and as I was examining her, I noticed that her  
21 left side was a little bit smaller than the  
22 other side. She had a visual field cut. She

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1 had a massive, massive stroke. Unbelievable.

2 Here she was doing well in school, and I  
3 noticed how she was reading to compensate for  
4 the field cut. She'd just turn her head, and  
5 you would never know. I mean, her parents  
6 didn't know. No one knew. She was a sickle  
7 cell kid, and that's how she'd stroked out.

8 No one knew, now grant you, she may  
9 not have had the best follow-up medical care,  
10 but so sometimes people's compensation for  
11 brain injury can be quite remarkable. So it  
12 is always difficult. We ball park it as best  
13 we can for parents. You know, you have a  
14 Grade 4 hemorrhage, Grade 3, Grade 4  
15 hemorrhage, you're going to have a 70 percent  
16 likelihood of deficit. I usually say, you're  
17 going to have some deficit. It's a question  
18 of how finely you want to measure it. It's  
19 going to be there; it's a question of what  
20 tools you're using to measure it, because it  
21 will be there.

22 There's always a price to pay for

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1 brain injury. If you lose function in one  
2 part of your brain, you know, your average lay  
3 person, what they understand is that the brain  
4 is going to make up for it in another part of  
5 the brain, that will be fine. But there's a  
6 price to pay. So if you -- if you have to use  
7 up some of your spatial organization part of  
8 your brain in order to help with some other  
9 language association cortex, you're going to  
10 lose some of your spatial function. So  
11 there's always -- there's a price that you pay  
12 for that compensation. It's something that a  
13 lot of people don't realize.

14 So, you know, it is difficult,  
15 especially in the middle of the road cases.

16 DR. GLANTZ: My question is really  
17 a follow-up from Alex's questions and it's  
18 really to address two additional areas of  
19 uncertainty. One would be the question of the  
20 timing. In other words, would you need to do  
21 this? I mean, Alex's question was based upon  
22 having to make a prediction so you know who to

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1 select for the intervention because whether  
2 you need to do it early on versus later on.

3 The second question is, if you  
4 could do it later on, then the question would  
5 be, well, might there be a differential impact  
6 on people who are more severely effected  
7 versus more mildly effected because it may be  
8 the severely effected individuals won't have a  
9 response but somebody in the more mild range  
10 would. I realize these are all purely  
11 speculative things, but they just strike me as  
12 being very fundamental to even imagining how  
13 to go forward.

14 DR. NELSON: Actually, you gave  
15 much of the answer I was going to give. Is  
16 if, what you're driving at, Alex, is the  
17 importance of trying to be able to predict the  
18 severity of the disease to sort of get into,  
19 if you will, analyzing kind of where you are  
20 in this sliding threshold, it's not only the  
21 predictability early on, but it's the  
22 challenge that in many diseases as that

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1 disease progresses, you may end up with  
2 changes that render you less responsive to the  
3 therapeutic intervention and so the timing is  
4 then crucial.

5           And this is not unique to this  
6 particular hypothetical case. There's plenty  
7 of situations where the adults with a disease,  
8 if it's a degenerative disease it results in  
9 fibrosis, may, in fact, have no possibility of  
10 direct benefit from that intervention, whereas  
11 an earlier intervention may. So that's part  
12 of the challenge, I think, in this  
13 hypothetical case, but also part of the  
14 challenge in selecting this.

15           Yes, if it's -- you want to select  
16 perhaps children with a severe enough disease  
17 to justify the intervention but on the other  
18 hand, if you wait till you're certain, you  
19 have recognize you may have waited to the  
20 point where that very population may or may  
21 not have the response that you even hoped to  
22 achieve. So if that's what you're getting at,

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1 then I think you've identified a problem.

2 Now, I'm not sure how much more we  
3 can say about that problem other than to say  
4 that's an important consideration. But I  
5 mean, there may be other issues that could be  
6 --

7 DR. FOST: Len and then Jeff.

8 DR. GLANTZ: I have really two  
9 technical questions. One is given what you've  
10 said about, you know, you could tell that  
11 there will be neurological damage, but how  
12 much, that you have thought of, you know, the  
13 horrible cases, which are easier to determine.

14 In a study like this, do you think that one  
15 could determine that the intervention led to  
16 an improvement? This has to do with the  
17 anticipated benefit question. Do you think,  
18 you know, by examining the child before and  
19 after you could say, "Well", since there's a  
20 variability, it would be possible to do that?

21

22 DR. ELVIN: I see what you're

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1 saying. I think that it would be critical to  
2 have a view of long-term neuro-developmental  
3 outcome that you would follow and that is  
4 doable. The idea of seeing sudden change in  
5 their tone, reflexes, you know, you're just  
6 not going to see those things. It's going to  
7 take time but it's possible to measure.  
8 Whether spectroscopy could be a tool for that,  
9 I don't know. You know, there's a lot of  
10 questions about how you could measure this but  
11 neuro-developmental outcome can and would need  
12 to be measured with a view to the long-term in  
13 these cases.

14 DR. GLANTZ: But isn't the long-  
15 term variable, even without an intervention,  
16 that you can't predict -- I'm asking this  
17 question. When you look at this child's MRI  
18 and you look at their --

19 DR. ELVIN: You could compare them  
20 to people who didn't get that intervention  
21 with a similar injury. I mean, that's  
22 probably the best you can do. I mean, it's

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1 true that there's variation among individuals  
2 but I think you know, you have to have a  
3 certain number of patients that one could look  
4 at to get a feeling for that. But that's not  
5 -- I don't see that as something that cannot  
6 be done.

7 DR. GLANTZ: So you think it's  
8 predictable enough? And again, I'm really  
9 asking a different question of what outcome  
10 would be based on --

11 DR. ELVIN: There's a range, just  
12 like in any disease process. There's always a  
13 range of outcome but that doesn't mean you  
14 can't look and measure and see a shift in the  
15 curve and that's what you need. It doesn't  
16 have to even be a big shift in the curve, but  
17 it's like renal failure, if you can see a  
18 shift in the protein area, now you've got  
19 something. It might not be everything you  
20 want but in a disease like Fabry's disease,  
21 that might be the medicine that will at least  
22 lessen the progression of the disease. So

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1 there's -- yes.

2 So I think that that's what you're  
3 looking for, and I think it's doable.

4 DR. FOST: Jeff here wants to  
5 follow up on this and then --

6 DR. WITTEN: Can I just add, may I  
7 add a comment?

8 DR. ELVIN: Please.

9 DR. WITTEN: I think just to add to  
10 what you were saying, you have to look at the  
11 difference in what we're going to learn from  
12 an early phase study and a late phase study,  
13 just in general in our products -- in these  
14 kind of products and you're not going to prove  
15 that it worked or that it -- from an early  
16 phase study, not matter what you know up front  
17 in terms of the evidence for prospect of  
18 direct benefit, that early phase study is not  
19 going to be able to show direct benefit. It's  
20 not going to show it for this. It's not going  
21 to show it for our adult study. So I think  
22 the question that was raised earlier about

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1 making sure that you have some assessment  
2 tools and as was just said, these assessment  
3 tools in this kind of setting should be  
4 looking at long-term issues as well, is one  
5 thing, but to say that you do that  
6 intervention and then you know whether it  
7 worked it's no more true here than in anything  
8 else that we do.

9 DR. FOST: Jeff Rosenthal and then  
10 Jeff Botkin.

11 DR. ROSENTHAL: So just real  
12 quickly, I mean, I guess one issue is, do we  
13 have the ability to identify comparable  
14 lesions at this point with our diagnostic  
15 capacity and the other is, is there sufficient  
16 variability in the outcomes, given what we  
17 think are comparable lesions so that -- or is  
18 the variability so great that the numbers of  
19 subjects needed to be studied over the long  
20 haul would just be sort of, you know, huge in  
21 order to account for the degree of variability  
22 in trying to identify a meaningful outcome, a

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1 meaningful shift in the curve to use your  
2 term?

3 So I guess --

4 DR. ELVIN: I'm not sure I  
5 understand. What do you mean by comparable?

6 DR. ROSENTHAL: Well, you know, I  
7 guess it gets back to this issue of, you know,  
8 if you see two MRIs and they look the same, is  
9 it the same or do we have the diagnostic  
10 specificity at this point to even say that  
11 lesions are comparable, because, I mean,  
12 ultimately with this study, I guess we're  
13 going to be looking at -- we would ultimately  
14 be using historical controls and trying to  
15 identify whether the developmental outcomes in  
16 the long run are better following our -- you  
17 know our intervention than they would have  
18 been if the child had not received it.

19 So I'm trying to decide, you know,  
20 do we even have a -- do we have a constant  
21 baseline that we can point to?

22 DR. ELVIN: I think that's a little

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1 bit of a moving target. And I hate people who  
2 say, yes and no, but I'm having to say yes and  
3 no. But, you know, people's nerve -- excuse  
4 me, neuro-status can be evaluated from the  
5 time you evaluate them, that can be done in  
6 the short term as well as the long term. All  
7 I'm saying is that you would need to take  
8 long-term view and yes, you could compare them  
9 to people with relatively same injuries,  
10 knowing that there's variability of outcome.

11 I don't -- I think that is doable,  
12 but you know, I -- it raises another question  
13 for me in my mind. I'm just sort of taking a  
14 step back from this whole issue of studying  
15 this in a pediatric population. I'm saying,  
16 okay, what about the adults I know who had an  
17 intra-ventricular hemorrhage? He's got a  
18 shunt and this person has got some deficits.  
19 Going to have to have a shunt revision. What  
20 about testing live cells that would be sampled  
21 from them in culture and you know, working --  
22 there are adult cases out there. I'm

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1 wondering whether we couldn't work with that  
2 first. I'm not so sure we couldn't. I'm not  
3 -- we're just not there yet in terms of the  
4 molecular mechanisms to do this in kids.

5 I know I'm talking not enough about  
6 ethics and too much about the science, but we  
7 have to -- you know, the two things ultimately  
8 are inseparable. You know, the science and  
9 the ethics are just inseparable. We have to  
10 think about, do we really have a good enough  
11 grounding in our understanding of what these  
12 mechanisms are to justify doing this? I don't  
13 think we're there yet.

14 DR. FOST: Jeff Botkin and then  
15 Skip.

16 DR. BOTKIN: Yes, Len asked my  
17 first question but, so, just to take from the  
18 answers for that, in this particular context,  
19 sounds like an end of one experiment wouldn't  
20 be helpful from a clinical perspective. There  
21 might be other circumstances say with severe  
22 storage diseases that are uniformly

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1 progressive that you might be able to see a  
2 clinical response in one child based on an  
3 intervention but with this sort of neurologic  
4 process, you wouldn't be able to determine a  
5 clinical improvement based on one child or a  
6 small number and you'd need a controlled  
7 experiment. So you'd really have to have a  
8 comparison group to see differences. So  
9 that's a different prospect.

10 But so I want to take a step back  
11 from that and say, okay, so we're not looking  
12 at clinical response here as our outcome  
13 measure. With this hypothetical case, how  
14 would you determine other outcome measures?  
15 Background studies using animals, of course,  
16 you've got brain slices, you can tell where  
17 those cells went. If you were to insert stem  
18 cells into a baby's brain, how would you  
19 determine whether those cells were retained  
20 within the brain and then secondly, whether,  
21 using Skip and Sarah's threshold, whether  
22 there was functional change based on those

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1 insertions, so you weren't looking at clinical  
2 response but you want to figure -- you've got  
3 to measure something. What would you measure  
4 to determine where those cells went and  
5 whether they were working in any meaningful  
6 way.

7 MALE PARTICIPANT: Monthly  
8 biopsies.

9 DR. FOST: Skip?

10 DR. NELSON: I'd like to just offer  
11 a brief reminder to what we're up to. It's  
12 not our goal here to decide how necessarily to  
13 do stem cell product development on hypoxic  
14 scheme encephalopathy from a scientific  
15 perspective. All right, so what I'm  
16 interested in is a layout of the issues, and  
17 not necessarily to come to any kind of  
18 conclusion. And so some of the issues I've  
19 heard are that are problematic or variability.  
20 You need to measure response. I think your  
21 point about applying a threshold even to the  
22 evidence based after the fact and the like.

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1                   One could speculate, for example,  
2                   that I mean, I attended the -- there was a  
3                   meeting that SEBR put on about embryonic stem  
4                   cells.    These, notice, these are not human  
5                   embryonic stem cells, just to be clear.    But  
6                   that was an issue of the discussion of safety  
7                   and there was a very interesting presentation  
8                   there by a radiologist who just wowed me with  
9                   his graphics but who basically talked about  
10                  things like putting little tiny magnetic  
11                  particles in the cells and doing scans and see  
12                  where they are and that sort of thing.

13                  I don't think the purpose here is  
14                  for us to try to draw any kind of conclusions.

15                  The idea of at least getting enough facts on  
16                  the table is so we can then lay out some of  
17                  the ethical issues around how we may approach  
18                  a proposed future trial.    And I realize a  
19                  little bit of that is -- I mean, I don't  
20                  intend this to be science fiction, I mean, but  
21                  so we need some facts on the case to do that,  
22                  but I just want to caution us.    The intent

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1 here is not to decide whether you can or can't  
2 study this but to lay out what are the ethical  
3 issues around trying to imagine a path  
4 forward, not the scientific issues.

5 DR. FOST: Jeff, yes, and then I  
6 had a comment.

7 DR. BOTKIN: But I think the crux  
8 of the issue we're talking about is the  
9 threshold that needs to be achieved in order  
10 to make that transition from animal studies to  
11 human studies. So I guess the point I'm  
12 trying to make is that threshold has to  
13 include some assessment of what the outcome  
14 measure is you're using. And if you don't  
15 have a good outcome measure, then you probably  
16 haven't achieved the threshold to start  
17 putting needles in babies' brains.

18 DR. FOST: I would make a comment,  
19 then Steve. I mean, the ethical issue is  
20 simple. You don't do a research study if you  
21 can't measure the results. So there's no  
22 disagreement on that. And what's being

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1 questioned here is how -- so it's always about  
2 the case. It's -- I mean, that principle is  
3 too simple to require repeating. So the issue  
4 is in any given case, can the results --  
5 there are several issues but one is can the  
6 effect of this intervention be measured and  
7 we're having -- it sounds like everybody is  
8 having trouble understanding either at a  
9 cellular level, a molecular level, a  
10 radiologic level, a clinical level, how would  
11 you determine in a study like this whether you  
12 had any effect at all, whether on a molecular  
13 or cellular basis or clinically?

14 DR. NELSON: And I agree, Norm, but  
15 if there's general agreement, for example,  
16 that a structural change is insufficient, that  
17 in my mind is fine. Whether or not -- you  
18 know, what the nature of the functional  
19 change, you know, I mean, it's -- we are  
20 elaborating the sort of notion of appropriate  
21 scientific design and that sort of thing. All  
22 I'm saying is having elaborated that approach,

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1 we don't need to drive to a conclusion on it,  
2 because in fact, we don't have the data nor  
3 the expertise to do that.

4 DR. FOST: Steve and then Len.

5 DR. JOFFE: So let me move a little  
6 bit from the specific to the general. So I'm  
7 not sure that there is general agreement on --  
8 at least I'm not ready to, sort of, join the  
9 general agreement about what is necessary for  
10 our threshold in terms of what you can measure  
11 in the kid. So just to -- Skip, this is not  
12 to work out the sort of appropriate design for  
13 the study but just to make sure we're all  
14 talking about the same thing. So I would  
15 imagine that if an investigator were to  
16 propose the first "in children" study of these  
17 human neural stem cells, the primary  
18 objectives of that protocol would first be  
19 safety and secondly, be some marker of quote  
20 "engraftment" of the neural stem cells and  
21 those would probably be the primary  
22 objectives. And the secondary

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1 objectives would be measuring neural  
2 anatomical change both in the short term and  
3 the long term and following neural development  
4 over time with probably a very up front  
5 recognition that actually being able to assess  
6 long-term neural developmental impact, whether  
7 anatomically or functionally, that there'd be  
8 a high chance of not being able to make --  
9 draw any inferences whatsoever because small  
10 numbers, uncontrolled, et cetera. So what  
11 we'd be left with is some degree of confidence  
12 that we could measure the safety and  
13 engraftment endpoints and a very low degree of  
14 confidence that we could measure anything else  
15 with any ability to draw inferences.

16 And so the question would be, would  
17 it be sufficient to proceed with such a study  
18 on the basis of the ability to measure those  
19 endpoints but not other endpoints. I think as  
20 I read your threshold, Skip, the threshold was  
21 not what do you need to be able to measure in  
22 the first in human studies, but rather what do

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1 you need to be able to measure in your animal  
2 or preclinical models in order to sort of make  
3 that first leap into first in humans.

4           So that's -- as I think about it,  
5 even if the investigators conceded, "We're not  
6 going to be able to measure any direct or  
7 surrogate marker for clinical benefit in these  
8 children, all we can measure is markers of  
9 engraftment and safety", that wouldn't change  
10 things for me. It wouldn't change my  
11 assessment of the prospect of direct benefit  
12 of that study. It would be a shame. It would  
13 be nice to be able to at least develop some  
14 information that might inform further studies  
15 but it wouldn't change the assessment of the  
16 risks and benefits for the infants who were  
17 potential participants in the study.

18           It would be a study purely of  
19 safety in engraftment would be a valuable  
20 scientific study, assuming that those end  
21 points could be measured and it may be that  
22 even on the basis of those things, we might

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1 conclude, I'm not suggesting that we will, but  
2 we might conclude that there's a prospect of  
3 direct benefit for those children even if we  
4 couldn't measure clinical or proxy outcomes  
5 for clinical benefit.

6 DR. FOST: Just to clarify those  
7 issues, Steve, I mean, how would safety be  
8 measured even in this study?

9 DR. JOFFE: You mentioned,  
10 Virginia, that tumor formation is a potential  
11 risk. So, you know, serial scans to look for  
12 tumor formation. Movement disorders, I recall  
13 in some of the early trials or in the trial of  
14 fetal neural stem cells or fetal neural cells  
15 for Parkinson's disease, that there was a  
16 terrible complication in those who got the  
17 fetal cells of just uncontrollable movement  
18 disorders. So those are the sorts of  
19 functional anatomical changes that one would  
20 think about.

21 I mean, those would clearly be, you  
22 know, adverse safety outcomes.

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1 DR. FOST: But again, you might,  
2 given the variability and clinical outcome of  
3 this disorder, you might need substantial  
4 numbers to see -- tumors, you wouldn't need  
5 that.

6 DR. JOFFE: You're certainly not  
7 going to pick up -- if the sort of definitive  
8 control 1,000 baby hypothetical study would  
9 show that there was subtle neural  
10 developmental impairments associated with  
11 this, that there wasn't any sort of overt,  
12 easily measurable toxicity but in large  
13 studies, you could see you know, clinically  
14 and statistically significant impairments, you  
15 would never pick that up in the first in human  
16 studies. That would require going to, you  
17 know, much larger studies further down the  
18 line. So you have to accept that all you can  
19 pick up in the initial studies is common,  
20 serious, relatively obvious kinds of  
21 toxicities.

22 DR. ELVIN: I want to mention also

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1 that part of the safety issues would revolve  
2 around the mechanisms by which the stem cells  
3 would be delivered. You know, the more  
4 invasive you get, the more risk you have of  
5 infection and bleeding and those can be  
6 relatively small to relatively serious  
7 complications. So none of this is without  
8 risk, whether it's the abnormal  
9 differentiation where the stem cell doesn't do  
10 what we wanted it to do three months after it  
11 started doing what we wanted it to do. It  
12 starts doing something else or just the  
13 procedure itself.

14 DR. FOST: Len?

15 DR. GLANTZ: Yes, I think that the  
16 reason why these technical questions become  
17 important goes to the issue of the prospect of  
18 direct benefit as Steve has noted. So I would  
19 disagree with Steve, that if you could only  
20 measure neural anatomical changes, I would say  
21 there's no prospect of direct benefit.

22 I think in order for there to be

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1 direct benefit to the subject, it has to in  
2 some way benefit the subject and not benefit  
3 the subject's cells. And that becomes the  
4 measurement issue, that if we can't measure  
5 improvement or at least lack of deterioration  
6 that might be expected in a way, if all we're  
7 doing is looking at neural anatomical markers,  
8 then I think there's no prospect of direct  
9 benefit. And if you can't measure it, you  
10 can't know that there's direct benefit. I'll  
11 put that out.

12 DR. FOST: Skip.

13 DR. NELSON: I think there's a way  
14 that one could perhaps agree with both of you  
15 and let me see if I can articulate that. As  
16 one makes a decision to start a clinical trial  
17 in this environment for intervention, or any  
18 intervention at all that is greater than  
19 minimal risk, one needs to attend to issues of  
20 data that are in support of it, as well as  
21 design that offers prospect of direct benefit.  
22 So I think that, you know, serves Steve's

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1 point as I interpret it is it as you are  
2 considering the trial and then starting, you  
3 have to have some sense that you're offering a  
4 prospect of direct benefit to that first child  
5 based on what's gone on before, now, and  
6 that's -- you know, in this environment,  
7 likely pre-clinical animal modeling.

8 I agree, though, that you should  
9 have some sense that you're going to benefit  
10 the person and not the cell. I mean, I'm not  
11 -- you know, and so that you're making that  
12 sort of assessment based on that pre-clinical  
13 animal modeling. Now, the issue of what you  
14 then are able to measure, I think is important  
15 and I was actually going to ask Steve this  
16 when I heard his argument, how, as an  
17 oncologist, he would approach this because  
18 often they're in this setting, is not so much  
19 related to that trial and whether or not  
20 there's prospect of direct benefit because  
21 you've got to decide that to start in the  
22 first child. But, well, what information do

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1 you need to go forward? I mean, if you can't  
2 measure anything, even let's say a biomarker  
3 change, I mean, even if you think you're  
4 benefitting the whole person, you need  
5 something to decide that the trial supports  
6 the next step and what would that be? I mean,  
7 thatt could be a biomarker change.

8 I mean, you know, again, where the  
9 evidence there may fit, may well fit this  
10 sliding threshold as well, even though you've  
11 now got some human data. So the question  
12 you're raising about measurability could well  
13 be viewed not necessarily to justify the  
14 inference of prospect of direct benefit to  
15 start the trial, but certainly if you can't  
16 measure anything that tells you what to do  
17 next, that would be a problem.

18 You know, how are you going to use  
19 that data even if it's one or two or three or  
20 four, however many in that first trial to  
21 decide to do it again.

22 So that's where I would see a

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1 potential, you know -- right.

2 DR. FOST: I have a response, too.  
3 Steve.

4 DR. JOFFE: So let me give you --  
5 I'm not -- my comment is not about the  
6 measurement issue in terms of what you do  
7 going forward, but let me give you an example  
8 again from the oncology context that may help  
9 to lay this out. So Phase One oncology  
10 trials, whether done in adults or children,  
11 again, set out to measure safety, to establish  
12 a dose for taking forward to Phase Two, and to  
13 look at pharmacokinetics and then a secondary  
14 end point will look for anecdotes and that's  
15 the most that they are of response.

16 Typically, although most  
17 individuals who participate in Phase One  
18 trials have measurable disease. It is  
19 typically not an eligibility requirement. So  
20 somebody who has at the present time no  
21 measurable disease but has an extremely high  
22 likelihood that their cancer will return, will

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1 typically be viewed by clinicians,  
2 investigators, it will meet eligibility  
3 criteria and people will consider offering  
4 Phase One trial enrollment to those  
5 individuals.

6 And then those individuals, let's  
7 say we predict that the person has a 95  
8 percent chance that the tumor will return, but  
9 that leaves a five percent chance that it  
10 won't just by natural history without any  
11 intervention. We -- they consider enrollment  
12 in the Phase One trial. They get the drug and  
13 there's no way of knowing whether they  
14 received any -- that individual received any  
15 drug benefit. There's no way of measuring  
16 whether they received any direct benefit from  
17 the study.

18 If their tumor does not return, it  
19 may be because that was the natural history of  
20 what their tumor was going to do anyway. It  
21 may be that the drug helped and the drug  
22 contributed to their -- the non-return of

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1 their tumor. And the fact that you can't  
2 measure anything in that individual, I don't  
3 think changes the calculus about whether or  
4 not that study enrollment offers them a  
5 prospect of direct benefit. So even if we had  
6 a Phase One trial where everybody was in this  
7 group of 95 percent likelihood that the cancer  
8 would return, five percent chance that it  
9 wouldn't, and so there was no possibility not  
10 only in the individual subject but across the  
11 group of subjects of measuring -- assessing  
12 the prospect of direct -- assessing the  
13 clinical benefit of the drug, I think we could  
14 still -- I think it would still be plausible  
15 to conclude that entry into that study offered  
16 a prospect of direct benefit to the  
17 participants.

18 DR. FOST: I wanted to say  
19 something similar. Let's just start with  
20 adult situation and extend it to kids. Adults  
21 who have desperate situations, ALS, no  
22 effective treatment, they're deteriorating,

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1 commonly will -- you know, some of them will  
2 want to try anything. Early days of the AIDS  
3 epidemic, when every case was fatal, and the  
4 AIDS activist group sat in David Kessler's  
5 office wanting fast-tracking. You know, we  
6 all want this AZT stuff. We don't want to be  
7 part of a randomized placebo controlled trial.

8 So if you take the hypothesis that somebody  
9 is desperately ill and has nothing to lose,  
10 that is there's -- they'll take anything. So  
11 a doctor taking care of such a person under  
12 rubric of innovative therapy, don't call it  
13 research, might appropriately offer him or her  
14 anything, I mean, not ridiculous things but  
15 things that have even a remote possible,  
16 plausible thing, even though they might not be  
17 able to learn a lot from it.

18 All right, let's not call it  
19 research. It's just innovative therapy, I'm  
20 going to do it in this person and I'll never  
21 know whether it really helped him or her or  
22 not, but I think it's ethically appropriate to

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1 do it with appropriate standards of consent.

2           So change that now to somebody who  
3 has that situation and it happens in clinical  
4 medicine and we don't prohibit it from  
5 happening and I don't think we condemn it on  
6 the face of it. Suppose a person says, "Well,  
7 I want to do it really carefully though, and  
8 so I'll measure whatever I can, whether  
9 through imaging and through clinical follow-up  
10 and maybe after I do five or ten of these I'll  
11 learn something."

12           Well, if that's all -- you know, at  
13 least I'll report it, at least I'll publish it  
14 so people will know what happened in this  
15 case, at least if something terrible happened  
16 from a toxicity standpoint, we'll know about  
17 it. So it seems to me the same arguments  
18 could be applied to the pediatric setting. If  
19 you had a high predictive probability that a  
20 child had severe enough brain damage that he  
21 or she was almost certainly going to have a  
22 horrendous outcome, you know, something barely

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1 above a vegetative state, just to take a worst  
2 case example, it wouldn't be inappropriate, I  
3 don't think, for parents and a physician to  
4 say, "Let's try this wacky idea. It's not  
5 completely wacky. A lot of people think it's  
6 quite sensible. Even though we can't -- we  
7 won't know in my child's case whether it ever  
8 helped or not, but it's worth trying". And if  
9 that makes sense, then let's do it five times  
10 or ten times and report it and see where we  
11 are. So that's one justification for offering  
12 the therapy.

13 DR. WILFOND: So I have a question  
14 for you about that. I mean I liked your  
15 scenario. The question is whether you would  
16 want to describe that as offering a prospect  
17 of direct benefit or just the fact that  
18 parents are -- or adults are willing to do  
19 this because maybe this will be helpful at  
20 some point down the line. It sounds like it's  
21 more of the social benefit rather than the  
22 direct benefit that's motivating them.

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1 DR. FOST: I would say it's a  
2 prospect. I mean, the probability of it may  
3 be extremely, extremely low. You may never  
4 know whether it happened or not. You're doing  
5 it, that's obviously the intent, although Skip  
6 says that's not all there is to it.

7 DR. WILFOND: Let me clarify what  
8 I'm trying to say. In other words, first of  
9 all I think what you're describing is  
10 ethically appropriate and the question really  
11 I'm trying to push on is whether it's  
12 necessary to label that as prospect of direct  
13 benefit because that seems to me that this  
14 notion of prospect of direct benefit is  
15 stretched, when we talk about that but yet the  
16 study itself still could be plausible.

17 DR. FOST: We'll, let others  
18 comment and then I'll come back. Amy, yes.

19 MS. CELENTO: Well, I guess as I  
20 sit here and say what's my perspective as a  
21 parent, I'm kind of hearing this in what you  
22 just said, Norm, in terms of innovative

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1 research, maybe someone doesn't have much of a  
2 prospect of having a life. I just see this as  
3 20 years from now. We won't be discussing  
4 this issue, it will just be happening because  
5 someone will have done it to say, "Let's try  
6 it, let's see what happens". The child isn't  
7 going to have much of a life, do you want to  
8 do this", and some parents will say, you know,  
9 "I want to take the risk for the betterment of  
10 society hopefully for some future benefit for  
11 other parents", so I think that it's a  
12 slippery slope. I guess we have sliding  
13 threshold for approval and we have slippery  
14 slope in term of as society evolves, as  
15 virtual reality becomes the norm for kids who  
16 are growing up today. In one sense, people  
17 may say, again, "I'll try something for the  
18 betterment of society. I'll do this for the  
19 future. I'll take the risk".

20 But on the other side, the flip  
21 side, you have the people who are going to  
22 say, "I'm used to getting what I want in any

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1 form or fashion and do you know what, I want  
2 you to do everything you can to make my kid as  
3 close to perfect as possible". So I guess I  
4 have more of a longer term view of, you know,  
5 I think what's being discussed here today is  
6 critical but I just see the evolution sort of  
7 potentially getting out of control at one  
8 point, but it's almost inevitable.

9 DR. FOST: So you're troubled by  
10 this happening to a point till you think we  
11 shouldn't all these sorts of things to happen?

12 MS. CELENTO: No, I mean, I don't  
13 think it should be disallowed. I guess I'm  
14 just saying I think that the future of what  
15 will come of this, again, will be probably  
16 some amazing insights and research that will  
17 benefit human society, the evolution of  
18 mankind but I just think that there's a risk  
19 of you will have some people in sort of the  
20 back laboratory saying, "You know, let's try  
21 this, let's push the envelope", and in one  
22 sense you can have people doing it, hopefully

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1 for the -- I guess the benefit of their  
2 children and their family but you could also  
3 have the flip side of people just saying, "But  
4 I live in America, I can get what I want. I  
5 want what I want. I want you to do everything  
6 possible to improve the situation here".

7 DR. FOST: Let's just go around -

**NEAL R. GROSS**

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