regard to the use of the 407 or 54 panel as precedent. So a hypothetical would be a case came or a protocol came to the panel. The panel ruled that it was approvable under something less than 407 or 54 and then that protocol went to a multi-center status. So then can the ruling of or the opinion of the panel be taken as precedent, that they've approved this before under such and so, so we're free then to, as an IRB, approve it under that, or do you see what I mean? What is the status of the precedent of these rulings to be applied?

Certainly, we apply it in the reverse where we say like the UCLA case I've actually used myself with the HIV is that no, it was not approved. They said it had to have a 407 approval so we can't do it here. We can't approve it here. Does it work in the reverse?

DR. FOST: As a hypothetical fact situation that has never yet presented itself

to a 50.54 panel?

Well, no, I'm just saying that's the situation you've just outlined as a hypothetical because that's not come up before but if what you're saying is if a panel met and said this protocol could be approvable under 50.52, and it's a multi-center study where everybody else is doing the same protocol, then I certainly don't see it as problematic if the local IRB seeing it subsequent to that chose not to refer it. I'm not going to speculate if another IRB decided to refer it about what FDA would do because that's never arisen and I probably shouldn't speculate that unless I talk with a number of people both behind me and elsewhere.

PARTICIPANT: And then the second point was on the ontological conflict of principle and I think it's a bit simplistic to say that either you tell the truth or you protect the innocent. So deontologist, particularly of the Kantian ilk are not

required to answer questions. So there's no conflict in that case. You simply don't answer. Do you see my point?

DR. FOST: Yes, but I think we're getting into some estero at this point.

But there are those that would argue that telling the truth ought to be greater but my only point is that what brings them into conflict is the facts.

You need to then resolve that conflict based on the facts. They're not in conflict in another fact situation.

Steve?

DR. JOFFE: So I've been accumulating a number of points as people have been going around the table, so let me sort of briefly touch on some of them. So the first thing to say is, just quickly in response to Len's being disturbed and I'm sorry you're feeling disturbed and I hope by the end of the day you'll be --

(Laughter.)

DR. JOFFE: I just want to say again, that the judgment that this -- and again, Skip's repeated point that we don't have the facts before us is worth saying again, but the judgment that under certain fact conditions this might be judged on offer of prospect of direct benefit does not imply that it is approvable either by a local IRB or at all, because there are additional considerations that have to be met and so I don't think anybody around the table has come to the judgment that this would be approvable because it offers a prospect of direct benefit. Again, that hinges on waiting for the facts.

A second thing is one of the original questions you asked, Norm, is what counts as a benefit and I think what counts as a benefit is something that either lengthens the quantity or improves the quality of a child or an individual's life. It does not -- from that it does not follow that one has to

be able to measure improved quantity or quality of life, either in the population of participants in the particular study or in any individual participant in order to be able to make a valid claim that that intervention offers a prospect of direct benefit.

The third point is basically just to -- this was a while back now, but just to endorse from my own perspective the way that Jeff framed his approach, his general approach to a study like this which fits well with the way that I approached it. I also want to point out that there are other studies that have been done in the recent past that we could have been talking about at this panel before they had been done, where we could have been having arguments about whether they offered a prospect of direct benefit which in fact, looking back did, in fact, offer direct benefits to participants and even direct benefits that were measurable in those -- or that occurred in those studies. So let me

just give you a couple of examples.

One, when infants or fetuses during pregnancy are diagnosed with valvular obstructions on the left side of the heart that are associated with development of hypoplastic left heart syndrome and Jeff Rosenthal will correct me if I say anything incorrectly here, one can predict that the child will develop hypoplastic left heart which is a very, very serious congenital heart condition and investigators proposed a study to do a fetal intervention where a catheter was inserted through a needle through the mother's -- the pregnant woman's abdominal wall, uterus into the chest cavity or the abdominal cavity of the infant, a catheter threaded up into the left ventricle of the heart, a balloon placed in that restricted valve opening and the balloon inflated to dilate this valve in a 20 something week fetus or maybe even earlier than that in pregnancy.

And that was done in a small number

of children and the data would suggest that those children have less cardiac disability than they would have had absent the intervention. I don't know if that's a fair description of what's been -- I'll give Jeff a moment to just respond to that.

DR. ROSENTHAL: You've got -- that's pretty good. This procedure has been done in I believe over 100 fetuses now and it's probably not fair to say -- to make a general statement that the fetuses do better. I think that by going through this intervention on 100 fetuses, the -- I'll call them investigators, have identified subsets that seem to do better and others which seem to do worse. So -- but you're right on.

DR. JOFFE: Okay, the other example I want to cite which is maybe even a little closer to our particular case is so the track record of gene transfer in terms of translating into benefit for recipients of gene transfers is not so great at this point

but there are isolated examples. So one probably the first measurable success with gene transfer was common gamma change severe combined immuno deficiency which is a lethal or absent bone marrow transplant which is the only sort of previously proven effective for these children is a lethal condition and infants die very young of opportunistic infections because of their congenital immuno deficiency. And investigators in France used ex-vivo gene transfer. I believe they took cord blood cells, transfected them with gene transfer, were able to get the normal common gamma chain into those cells and then transplant them back into the infants and were able to develop normal immune function or a much better immune function than they would have had otherwise in a significant number of these children.

Now, this was also the study you may be familiar with because two or three of the children developed leukemias that were a

result of the sort of aberrant insertion of the gene factor into the cells. So there was clearly a down side to that. On the other hand, there were clearly some children who benefitted and if we had been having this discussion two years prior to that protocol, at a point where it was fairly hypothetical, we could have been arguing about whether there was a prospect of direct benefit from that protocol, but in fact, I think looking back, there was evidence of direct benefit.

The final point I want to make and then I'll stop is just to this other issue of desperate parents. We are often talking pediatric clinical decision making about best interests for young children who can't express their own views and you know, we ought to do what is in the best interest of the child, but then it's been pointed out that it sometimes is hard to figure out what is the one thing that is in their best interest and whose perspective on their best interest counts and

maybe there's a number of things that are compatible with their best interests and just how much discretion do parents have, whether they're desperate parents or not desperate parents.

And so an alternative view is beginning to take shape which is around this notion of clear harm that has been explored in the context of when a state should intervene to prevent a parent from doing something to their child. Rebecca Dresser has explored this in other contexts, and the question there is -- or the perspective there is parents ought to have discretion to do the things that they perceive to be appropriate for their children but there are boundaries on that discretion. Those boundaries are around the notion that they should not be able to do things that present a likelihood of clear harm to the child.

And I think one of our functions as regulators, as advisory committee members, as

IRB members, as investigators and as clinicians is to identify those things that impose clear harm on a child and not make those available or not offer them as options and so that may be a way of framing the amount of discretion that parents, whether they are desperate or not, ought to get and that our job may not be to suggest what is the thing that we can come up with that is in the best interests of the child but what are the things that impose clear harm in the child that, therefore, ought to be off the table for parents who are decision makers, whether they're desperate or not.

DR. FOST: And is the technology we're describing you're talking about today realizing we don't have a specific protocol, an example of that do you think?

DR. JOFFE: In deference to Skip, I'm not going to speculate.

DR. FOST: Can I ask a quick, back to the cardiology example, I'm not quite sure

if this is for Steve or Jeff, the -- when this has been done, has this been done as an investigational protocol or is this being done more as an innovative clinical intervention?

DR. ROSENTHAL: My understanding is that it's being done as an innovative clinical intervention that a group of clinicians is making a recommendation but I think the IRB has been involved and I'm not sure all the nuances of that. It's at a different institution than mine.

DR. JOFFE: I can speak to that, at least I don't know if it's been done any place else in the country under a different mechanism. I can at least speak to the way the first phase of it was done. Whether it's been translated into a different mechanism later I'm not sure, but the very first is an article the first author is Toretsky, Wayne Toretsky, is published in Circulation I think it 2004. And so they describe their approval mechanism in that article and it was under an

alternative, "innovative" therapies protocol, or innovative therapies pathway that involved a level of IRB review outside of the sort of defined regulatory function of IRBs and involved sort of local departmental clinical oversight.

So it was done as a prospective innovation with more oversight than one would expect for just the usual sort of clinical off the cuff kind of thing but was not a -- at least initially, I think it may have been translated later into one but was not at least initially a formal IRB reviewed protocol in the sense that we understand that from a regulatory point of view.

DR. ROSENTHAL: Was it because they weren't planning on counting this or what was the justification for not doing that?

DR. JOFFE: You'd have to ask them.

DR. FOST: Other comments? Well, one last thing, Skip, is whether we addressed your questions -- Alex, but my sense is that

we've talked about your questions en passant and I don't know that we've had specific answers to them, so let me just hear from Alex and then you whether you think we've given you the kind of feedback that you were looking for.

DR. KON: Okay, so I'll try and stay brief because I know that we're trying to move a little bit, but I guess I want to come back to something that you said, Theresa, which was just sort of this concept if a tree falls in the forest and there's no one there to hear it, does it make a sound, and I have an undergraduate degree in philosophy so, I'm no philosopher but I'll, you know, do my undergraduate attempt. So I think that the question in those terms is really much more if there's a tree in the forest somewhere, and there's no one around, then it falls, it did actually fall and I think the answer is, well, yes, it did.

MS. O'LONERGAN: No, it's not if it

fell.

DR. KON: Well, but I think that that's really the question because I think it comes back to what Steve was talking about which is that a child -- whether or not the child benefits is somewhat irrelevant whether or not we're able to measure whether or not that child benefits because the benefit to the child is really the benefit to the child.

And our ability to directly measure that, I think it's an important thing to think about but I don't think that our inability to actually definitively say, yes, this child benefitted actually has bearing as to whether or not the child himself or herself benefitted.

So I would be more inclined to say that even if we can't directly measure the benefit that that doesn't mean that there is no benefit. But I think -- coming back to this concept of, you know, what we really try to do is have gestalt and try and fit the regs

to meet our gestalt, I was actually personally very impressed by something that Len said which was this concept of -- there you go, which was this concept of you know, if the words have no meaning, then what's sort of the point.

And so I decided, well, in that vein, maybe I'm going to go back and actually really look at the wording because, you know, part of me feels that well, if it's just semantics, it's just semantics. But part of me also feels that we really do need to stay true to it and in reading through again, you know, I've been sort of hung up on this concept of prospect of direct benefit but maybe I think what's even more important is this concept of anticipated benefit and I think that that term, anticipated becomes very meaningful because I think when we're talking about this and I, myself have made the argument sort this -- sort of looking back as sort of a reasonable person standard, that

reasonable persons might say that the possibility of benefit for my child outweighs all of the myriad risks I think is fair but when we start asking is that an anticipated benefit, I'm hard pressed to say that I anticipate a benefit but I think that there's a possibility for a benefit and so I think that that becomes very important, because I don't think that we can really say that there's an anticipated benefit here.

And then I think I come down to I think where Ben was saying that really this would require a higher level of review and I hate to get hung up in the semantics but I do think it becomes important because when we lose the semantics, then we're really in the situation where IRBs are just saying, "Well, this feels right to me so let's go ahead and do it and fit it in", and I'm not a big fan of that. So I think that that's where I'm thinking.

DR. FOST: Skip, Steve and then

Terry.

DR. NELSON: Well, I guess, Norm, two comments, and I don't know French but I assume en passant means you've answered the questions in passing?

All right, I figured that out. The context was helpful. I think the answer to that is, yes. I mean, I think in many ways perhaps en passant was more effective because it allowed what I would consider a richer and more free-ranging discussion of the various issues that would have to go into thinking about how one would transition from preclinical testing into pediatric first in child trial and I think the important point there is independent of product, because this is not unique to this setting. The hypothetical was chosen to stimulate discussion and I think in that it's been successful. And you know, you can -- whether or not you want to go around and hear additional comment, you know, I think it's

fine to hear more but I do feel that we've -- I will confess, I'm beginning to hear some repetition as well, so you know, where you decide that -- you know, saying to again is more important versus going home and when does going home become more important than saying it again, that's your choice.

DR. FOST: That's our next topic.

DR. NELSON: But I will -- let me just make one comment to Leonard's comment. Words do have meaning and are important and I think just speaking from a personal perspective, when I'm asked a question of ethics in the context of answering it, in this setting, either in a public setting or even in a private setting as part of my responsibilities as the pediatric ethicist, I think one needs to attend to the interpretation of those words and the sort of history of that interpretation and the meaning of that interpretation and in many ways it's sort of similar to a Judge interpreting case

law, to just sort of make it up because you think it feels right is in fact, not what's done. And it really needs to be framed in terms of the strengths of the arguments and how those words have been understood and how they've been applied in the past.

And so I very much attend to, if you will, the sort of history of the interpretation of these concepts dating back to the National Commission potentially before and then up through even this discussion to inform that interpretation and I wouldn't want anybody to leave -- you know, in many ways it's sort of like doing public bioethics. It's more than simply coming up with what I think is the right answer as opposed to framing it within a history of interpretation which tries to place it in a much more public setting. I don't intend to open up the issue of case law and judicial interpretation and that sort of thing but I will point out that Gadamer actually used case law and judicial

interpretation as an example of hermeneutics within his writing. Philosophical comment, couldn't resist.

DR. GLANTZ: If I could just comment on that, I agree with you entirely and that's why I'm saying that they didn't use -- you also look at the words when you interpret the words or what the words they didn't use. So the words possibility aren't there. The words that you can do it if you have a willing parent and a willing investigator aren't there. That the words prospect and anticipated are words that have meaning and that the people who wrote it, and the fundamental documents upon which the regulations were based, if you go back and you look at that, you see that there's something that people had in mind. And so the notion that we can intuit it and then fit the words in, it depends on which direction you come from.

Here's what we're going to do, you

know, the Frankfurter approach. I'll tell you what I want to do and then give me a reason for doing it is one way of doing it. The other way of doing it is looking at what you're suggesting and trying to fit it into that.

DR. FOST: Yes, go ahead, Steve.

DR. JOFFE: Two very brief comments. One, if you look up the definition of the word --I mean, this is not all about definitions as found in dictionaries but the definition of the word "prospect" as I looked it up about a half hour ago, one of the alternative definitions is possibilities, so the fact that prospect was chosen over possibility doesn't necessarily rule out possibility.

The second is just again to say about anticipated benefit, that that appropriately comes in when judging the benefits against the risks and so absolutely, when you think about anticipated benefits, but

at the stage of when we start to weigh benefit against risk.

DR. FOST: There was -- responding to Len, I wasn't -- first of all, I was just quoting Frankfurter because here's somebody who claimed to be guided by the Constitution as written in his theoretical writings but later after retirement said that's not exactly the way it worked, and second this seems to me a very -- consistent with what almost everybody that I know that have read about this incognitive psychology says that's just the way it happens, that is, how could it be otherwise? You have nine Justices, all of whom know the law. They know what the Constitution says and four of them say, I think it says this and five of them say I think it says this, so they're not just looking at the document. They're making up their mind on some other basis and then trying to squeeze the document into their point of view and I think that's what IRBs do all the

time, too. So the squeezing is important.

DR. GLANTZ: And again, I would just say that there are good judges and there are bad judges and that one of the things that marks a good judge, is a judge who decides cases which you know he philosophically is opposed to and that is -- and that's to me is the sign of a good judge. You know, if they just left it to their own discretion, that they would decide otherwise, but that's a discussion for --

DR. FOST: Ben?

DR. WILFOND: I was just thinking back to Steve's examples of the gene transfer and the hypoplastic heart. It occurs to me that one of the differences between those two examples, are the denominators. In other words, the overall experience in general with using balloons to do things to hearts is a fairly robust area, so to make this -- although there is things to go for, you can -- a new context, you can see where the

plausibility comes it, whereas you know, prior to that first experience, there had been a 10-year history of over 400 gene transfer trials that hadn't worked and so I think there's an accumulating sense that we shouldn't get our hopes up.

DR. FOST: Other comments. If not, I'll try to summarize here and again, please -- this is mainly to help us direct those of us who have to write some sort of summary of this. So it sounds to me like on the topic that we discussed today that like yesterday, we had a range of views on what counts as benefit. And that while the -- there seems to be agreement that direct medical benefit has to be something about the quantity or quality of life of the child or patient into whom the intervention goes, that what's at dispute here is how probable does that have to be? Can the -- under some circumstances of desperate situations, lack of alternatives and so on, might even a very, very tiny possibility of

that count as benefit or at least the prospect of benefit?

And then also some disagreement about whether surrogate measures would count as benefit, engraftment, evidence that the concept work, would that be sufficient to count as a prospect of benefit even though you couldn't measure whether it changed the child's quantity or quality of life.

Second, everyone agreed that it's important to be able to measure the effects of these kinds of interventions in some way, whether through surrogate measures, laboratory measures, imaging and so on or clinical measures. Obviously it's impossible to judge whether they've ever accomplished anything if we can't do that, but again there was a division of opinion about whether uncertainty about how to measure it at the front end would be a show-stopper in saying that we shouldn't go ahead if there was some animal evidence that the concept was okay.

There was some view, I don't know if it was everybody, but there seemed to be a majority at least who thought that technologies as innovative and complex as these ought to have the highest level of review for scientific merit and on the ethics of it and that using something like the 50.54 process would be desirable. And whether you want to call it squeezing or not it sounded like this kind of study could be justified in the 50.54 process regardless of whether you thought there was a prospect of benefit. But I think nearly everybody said if you're going to do it, it ought to have the very highest standards of scientific and ethical review and consent with all that that implies.

There were some who thought that -- and we didn't talk about this in great depth because the science of it, I think is a little unclear, but that if there were an adult model for stem cell therapy for example, for hypoxic brain injury, it would be desirable to at

least measure the proof of concept there first but we didn't discuss that in as much depth as we did yesterday, the children first, the adult first model. I think we were mainly operating under the assumption that there was no adult model.

Is this a reasonable summary? Before we leave, I want to, on behalf of everybody, thank Carlos for his extraordinary help in organizing this and in helping us get out work done and in guiding me on running the meeting. He's been very helpful, and thanks to Skip for obviously all the thought that went into organizing this conceptually and organizationally and for inviting us. It's been a very interesting discussion and appreciate the chance to be here.

With that, if there are no other closing comments, Skip, did you want to make some closing comments?

DR. NELSON: Simply just to thank everyone. I think my goal was to present some

challenging hypothetical cases. I was hoping for a diversity of opinion, a unanimity of opinion in my mind would have meant that I provided much too simplistic cases for you to chew on. I'm pleased that there is a diversity and I think that there was a very nice presentation of the various issues that would need to be addressed.

You know, there's a lot of brain power around this room and I certainly appreciate everybody taking the time to engage with the material and then to spend the time here to share your thoughts about that material and I don't know when, where and how but I mean, I would look forward to if we have an opportunity to do this again.

DR. FOST: Thank you very much. The meeting is adjourned.

(Whereupon, at 11:56 a.m. the above-entitled matter concluded.)