

1 this happening to a point till you think we
2 shouldn't all these sorts of things to happen?

3 MS. CELENTO: No, I mean, I don't
4 think it should be disallowed. I guess I'm
5 just saying I think that the future of what
6 will come of this, again, will be probably
7 some amazing insights and research that will
8 benefit human society, the evolution of
9 mankind but I just think that there's a risk
10 of you will have some people in sort of the
11 back laboratory saying, "You know, let's try
12 this, let's push the envelope", and in one
13 sense you can have people doing it, hopefully
14 for the -- I guess the benefit of their
15 children and their family but you could also
16 have the flip side of people just saying, "But
17 I live in America, I can get what I want. I
18 want what I want. I want you to do everything
19 possible to improve the situation here".

20 DR. FOST: Let's just go around --
21 we're going to -- let's go around the whole
22 table. Start with Len and go around.

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1 DR. GLANTZ: Yes, I think if we use
2 your formulation of prospect as you laid it
3 forth, then the word ends up having no meaning
4 at all. Laetrile has a prospect of direct
5 benefit and, you know, it means that, you
6 know, maybe somebody thinks that something
7 might happen, I think. And that the word
8 "prospect" and the anticipation of benefit
9 means more than, "Gee, let's try something and
10 maybe we'll do it".

11 The second point is that in the
12 oncology studies, we often see in the benefit
13 section to the patient that, "You know, it may
14 shrink your tumor", and we always take that
15 out of the benefit section because there's no
16 evidence that that will actually matter to
17 anybody. That there were all sorts of people
18 whose tumors shrank and they die as quickly
19 and suffer as much. So it may be scientific
20 benefit but it's not benefit to the
21 individual.

22 The third thing, Norm, in listening

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1 to you talk about it is that we're dealing
2 with a desperate parent issue here and that
3 has to do with your kid is desperately ill and
4 this goes back to the Baby Fae case, so is it
5 okay to cut a heart out and put in a baboon
6 heart even though it's never worked and
7 there's been no evidence of gene transplants
8 of any long-term benefit. Is it okay to do
9 that and she says, "Sure", because you say,
10 you know, "Well, your baby is going to die
11 without it".

12 And it seems that when one is
13 dealing with desperate situations that it's
14 even that much more important not to rely upon
15 the parental consent to make this ethical.
16 You said it yesterday yourself, Norm, that the
17 fact that somebody will consent to something
18 doesn't make it ethical. And I think when
19 you're dealing with a desperate parent
20 scenario, you have to be particularly careful
21 not to say, "Well, you can do it," because if
22 we can find a parent who will say that you can

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1 do it, then people who are involved in ethics
2 need to discuss whether it's okay to ask.

3 DR. FOST: Steve?

4 DR. JOFFE: So this is good because
5 it gets us to focusing on what we mean by
6 prospect of direct benefit which I know we've
7 talked about yesterday and today but I think
8 it probably bears some more discussion. So I
9 have a number of points to make about it but I
10 think I'll just take them one at a time.

11 But before saying that, I think
12 perhaps Len and I ought to be separated so
13 that nothing, you know, bad happens over here,
14 because I think the disagreements will
15 continue. Notice he's sitting back. So one
16 of the points about prospect of direct benefit
17 that our discussion has brought out is the
18 idea -- so the word "prospect" sort of brings
19 out that you're sort of standing on some
20 hilltop someplace with a view of you know,
21 view out of the countryside, view of the
22 future and I suspect that there's no one

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1 single place from which one -- some -- one
2 ideal observation spot from which one must,
3 sort of, stand and survey the field and decide
4 whether or not there is a prospect of direct
5 benefit. And what I mean by that is that we -
6 - let's say we're on an IRB, for example,
7 reviewing a protocol that comes through may
8 have one point of view. And a patient or a
9 parent, as Norm's case eludes to, may look
10 with -- may have a different point of view and
11 may make different judgments about risk and
12 benefit than a bunch of professionals sitting
13 in a room making judgments about benefit and
14 weighing risks and benefits against each other
15 may make and that is not to say that anybody
16 is right or wrong and it may be that some
17 judgments, sort of stepping back, are
18 unreasonable, perhaps. But I'm not sure that
19 we ought to discount the perspective of the
20 very sick patient, the parent of a very sick
21 child so quickly.

22 And we ought to take seriously the

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1 risks and benefits when you're in the middle
2 of a very difficult situation, maybe weighed
3 differently against each other and for a
4 professional standing back and thinking about
5 them in a less personal kind of a way.

6 DR. FOST: Alex.

7 DR. KON: So, I wanted to follow up
8 actually on what Steve said, which is this
9 issue of, sort of, you know, different
10 perspective. So on the one hand of, sort of,
11 the far extreme I would think of, for example,
12 a patient who has a 100 percent chance of
13 dying within the next month and we have some
14 patients like that, and I think for a patient
15 like that you could reasonably say we would
16 allow this child or these -- we would allow
17 parents to agree to some highly experimental
18 intervention even with the most remote chance
19 that it could benefit this child because the
20 chance that this child is going to survive is
21 zero and even if there's only a one in a
22 thousand chance that with this very highly

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1 experimental intervention, this child might
2 survive, that many reasonable people would
3 say, "Well, one in a thousand chance is better
4 than zero and even though it's very unlikely,
5 I still consider that to be a possible direct
6 benefit to my child and so I'd like to move
7 forward with it".

8 And then when we start talking and
9 this was sort of why I was asking some of
10 these questions earlier about how certain can
11 we be and how early, because then the question
12 of well, now we're not talking about the child
13 who is going to be dead but we're talking
14 about a child who's going to be neurologically
15 devastated and what's the quality of that
16 child's life. And certainly different people
17 would view that very differently and for some
18 people they would view that as a meaningful
19 life and other people would say that that's a
20 life that's really not worth living.

21 And if the parents and family are
22 in the category of saying, "Well, that's

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1 really not a life that's worth living and
2 we're 100 percent certain that our child is
3 going to be in this category of completely
4 neurologically devastated with no meaningful
5 neurological activity, and now we have this
6 experimental protocol that has the most remote
7 chance of being success -- of benefitting him
8 directly, but it's the only chance out there
9 then getting back to what Ben said, I'm not
10 sure that we're really talking about
11 necessarily a societal benefit. I think we
12 can really look at that as a -- as a chance, I
13 guess, of direct benefit and then I think this
14 comes back to what you were talking about,
15 Len, is this question of where do you go from
16 a chance to prospect, and I would say in some
17 ways that really needs to be modulated by
18 what's the predicted outcome without any
19 intervention based on standard of care and so
20 I think that that's a real sliding scale.

21 MS. O'LONERGAN: I'm going to bring
22 it back to Len's point about desperate parents

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1 and I think are we benefitting -- are we
2 thinking that we're benefitting the child
3 because if we're benefitting the child, we're
4 going to make the child live longer, live
5 better, have an easier time while he's here
6 and what I'm hearing is that we feel sorry for
7 parents and I think that this is appropriate
8 that we feel sorry for them and understand
9 their pain, but if we're talking about direct
10 benefit, we're talking about direct benefit
11 for the baby not for the parents, and to
12 prolong a child's life where there's a one in
13 a million chance, this borders on believing in
14 magic almost, that the chances are so remote
15 that putting the child through these
16 additional procedures is not benefitting the
17 child.

18 So even if there were a one in a
19 thousand chance of benefitting the child, at
20 what cost? Is there increased pain? Is there
21 increased intrusion into the child? So we
22 can't just say a one in a thousand chance is

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1 worth it. At what cost is it and how does
2 that play into direct benefit?

3 DR. FOST: Jeff, do you want to
4 weigh in on this? I think we should go around
5 completely on this issue.

6 DR. BOTKIN: Well, I wanted to
7 touch on Len's little bit earlier comment, not
8 so much the parental issue and also a little
9 bit of what Steve said a bit ago about
10 oncology trials and I would just make the
11 point that you've described what is done in
12 some occasions and analogous sorts of
13 circumstances, but that of course, in and of
14 itself isn't a justification and I would have
15 some concerns about that approach. So I
16 wouldn't necessarily say we want to use that
17 as a parallel issue but in getting back to
18 Len's comment, I guess, treating cells versus
19 treating patients, and I, at least, am
20 comfortable with what are surrogate markers
21 for potential benefit or prospect of benefit.
22 In other words, if you see these cells

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1 engraft in the brain, but yet you don't have
2 the ability to measure whether the child
3 benefits clinically, I'm still okay with that
4 because that is at least a plausible stepping
5 stone. The child still may benefit but you
6 just may not be able to measure that.

7 But if you can measure something
8 that is in a causal chain of events towards
9 realistic benefit, then that may be adequate
10 for early phase studies and enabling you to go
11 forward understanding that there's going to be
12 stepping stones towards an effective
13 intervention.

14 Where I would draw the line is to
15 say that if you're simply doing a PK study or
16 a maximum tolerated dose study, where the
17 intervention is not going -- and what you're
18 measuring and what you're doing really does
19 not have any prospects of realistic benefit
20 for this child, then I don't think you can
21 justify that study on prospect of benefit.
22 That the intervention has to be meaningful and

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1 you have to have some at least surrogate
2 marker that might assess benefit.

3 DR. FOST: Yes, Terry?

4 MS. O'LONERGAN: So the idea that
5 it's in the causal pathway of direct benefit
6 is well and good, but not for this child. So
7 if we can't measure, if all we can do is show
8 engraftment, and we can't even come close to
9 showing benefit. This child is just a step in
10 a scientific investigation and not -- and it's
11 a societal benefit certainly, but I would
12 dispute that it was a benefit for -- a
13 possible benefit for the child.

14 DR. BOTKIN: Well, I guess I would
15 say that you don't know whether it's a benefit
16 or not, but -- because you can't measure it,
17 not because it isn't there.

18 DR. FOST: Ben?

19 DR. WILFOND: I have a suspicion
20 that part of why we're stretching -- in some
21 cases stretching what we mean by prospect of
22 direct benefit is because of a sense that

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1 there might be good reasons that the study
2 would be justified, but I'd be much more
3 comfortable having a much more narrow view of
4 prospect of direct benefit but stipulate that
5 we could still do certain studies in which
6 there was no prospect of direct benefit. I
7 think even for those desperate parents, I
8 would much rather say to them, "Look, this in
9 no way will help your child. This will in no
10 way will help -- do not expect this at all",
11 and we can say it till we're blue in the face,
12 they'll still hope for it. But let's be as
13 absolutely clear as we can, and have the IRBs
14 be as clear as they can about why they're
15 approving this because we think this is a
16 necessary study. This is the only way to do
17 it. This is the only -- and we that we have
18 good evidence for it. But not pretend that,
19 well, maybe it might help.

20 DR. BOTKIN: So is that 407?

21 DR. WILFOND: I think it would be
22 407, but my point though is I think we could

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1 then -- I think it's possible we could go
2 forward in that setting but not because it's -
3 - we're going to pretend there's a benefit.

4 DR. FOST: A couple responses to
5 the comments that have been made, if this --
6 if we weren't talking about an unapproved
7 moiety here, that is if it were at a
8 previously approved thing, a substance, and a
9 physician wanted to use it off label, that is
10 for completely unindicated use, he or she
11 would be allowed to do that subject only to
12 rules of malpractice and licensing and so on.

13 So it's a peculiar restraint when
14 the entity is not yet labeled that the
15 physician and the parent don't have the
16 freedom to do that. And the question here is
17 whether they should have the freedom to do
18 that even for a remote chance of benefit in a
19 desperate situation. The fact that the parent
20 is also desperate, of course, is true of all
21 of pediatrics. I mean, we always have that
22 problem. So there has to be some -- it's not

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1 sufficient that the parent says do this wacky
2 thing. Somebody else, you need a licensed
3 physician. In this case, you would want an
4 IRB -- I mean, you'd want to really have a
5 really, really good process but you know,
6 we've gotten to this point, where it's being
7 discussed at an FDA meeting with FDA experts,
8 so it's not magic. It's not Laetrile. It's
9 something that has some plausibility to it, so
10 it's not at the crazy end of things to do.

11 And if the rules prohibit it,
12 because prospect of direct benefit has to mean
13 something much more than most likely to happen
14 here, then maybe there's something wrong with
15 the rules. That is the rules are guidelines
16 and they're a good starting point, but they're
17 wrong in all sorts of ways. You know, the
18 rules say if you're dead, it's not human
19 subjects research and it doesn't need IRB
20 review. That's crazy. Of course, you don't
21 want -- you want stuff reviewed occurring with
22 brain-dead patients.

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1 So there's all sorts of ways in
2 which the rules need some adjustment and maybe
3 this is one of them. Maybe earlier -- so
4 earlier -- this is a long debate, from the
5 AIDS epidemic and from the ALS population and
6 so on that many people think the FDA is just
7 much too restrictive in granting early access
8 to things that may be very remote and
9 theoretical at the front end but some things
10 turn out that were remote and theoretical
11 turned out to be good. So we now know that
12 laetrile is bad, but laetrile -- not
13 everything -- not every homeopathic or
14 naturific remedy is a bad idea. You know,
15 many of them, some of the turn out to be
16 really good ideas and so using laetrile wasn't
17 a wacky idea at the front end but if somebody
18 was going to use it at the front end, we would
19 want them to do it really carefully and
20 measure results and so on even though the
21 prospect to benefit. So I don't know that
22 anything that's been said so far would

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1 preclude a parent and a physician with very
2 high levels of review and so on from trying
3 this.

4 I'm very much sensitive to Amy's
5 concern that there's too much of this in
6 medicine, there's too much wacky stuff that
7 gets tried and then it becomes standard of
8 care and then gets done to tens of thousands
9 of people and decades go by before we found
10 out it was not only useless but harmful. But
11 harmful doesn't have a lot of meaning in a kid
12 who has almost no prospect of really any sort
13 of meaningful life, assuming you have very
14 good prognosis.

15 I'm going to keep going around
16 because I think it's a rich topic. Jeff?

17 DR. ROSENTHAL: Well, my only
18 reflection on this part of the discussion is
19 just that I think we've identified a
20 vulnerable population which hasn't previously
21 been called such and that's parents who are
22 desperate. And I do think it's great that the

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1 FDA has brought this group together to have
2 these discussions because I think parents need
3 some smarter heads to help to inform their
4 decisions in these circumstances because of
5 this drive to do whatever can be done for
6 their children.

7 DR. FOST: Elaine?

8 MS. VINING: I think it's just a
9 fascinating discussion and I think I concur
10 with a lot of the things that people say and
11 sometimes they seem to be at odds, but one of
12 the things that I keep going back to as a
13 parent is I think if I were in a situation
14 where I had a child that had a very low
15 prospect of any kind of benefit from the
16 research, I think I'm not alone that there is
17 altruism in trying to get my child into a
18 research situation where if it may have
19 benefit to the child in terms of he's in pain
20 or discomfort through this process, that may
21 be a direct benefit to my own child but to the
22 greater good of other children who may suffer

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1 from this illness or condition, I think there
2 are a vast number of parents that might -- may
3 very well agree to put their child into some
4 sort of a situation or a research program.

5 I think at that point, though, the
6 burden falls on IRBs or others to make sure
7 that there isn't coercion through over-eager
8 scientists through some sort of financial
9 incentives that would encourage a desperate
10 parent who has a long prospect of you know,
11 potentially financial issues that have plagued
12 them during the child's illness.

13 So that those factors are taken out
14 of the mix so that the child isn't going to be
15 -- the desperate situation doesn't go beyond
16 the child and into some sort of a financial
17 situation that the parent is now struggling
18 with as well. So complicated, I don't know on
19 a case-by-case basis, I supposed.

20 DR. FOST: Amy?

21 MS. CELENTO: Well, that's a very
22 good point about the financial situation and

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1 you know, that certainly could play into in
2 the picture but I guess I want to go back to
3 what Alex said and then what Ben said, you
4 know, there could be a remote shot, you know,
5 the snowball's chance that something could
6 work and that really could give a parent hope
7 and could give the scientists, doctors, hope
8 and say, let's do it, let's try it, everyone
9 is willing to take that risk and then there's
10 the side that Ben presented that, you know,
11 everybody could say, this will probably do
12 nothing but do you want to do it anyway? Do
13 you want to take that risk, and I think that's
14 where you build on trying these things and
15 saying, "Hey, we're learning as we go". I
16 think that's how scientific advances occur.
17 What I was saying is that as you go further
18 down the road, and you have these minor
19 advances and you start to tweak it and maybe
20 you do find you have success, my concern is
21 just really more along the lines of you do get
22 collusion, you do get people actually that

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1 have unlimited funds, doctors that are looking
2 to make breakthroughs that maybe are not in
3 the best interest of a child and the next
4 thing you know, you know, you have the folks
5 that are announcing, you know, "We can make
6 your child intelligent. We can do this, we
7 can do that".

8 So that's really my concern. It's
9 certainly not don't ever do this. I think as
10 long as the risks are laid on the table and
11 everyone says this may not work, but do you
12 want to do it anyway to have knowledge that
13 could help somebody else, you know, parents
14 need to be able to make that decision, I
15 think, assisted by doctors.

16 DR. FOST: Skip, do you want to
17 weigh in on this?

18 DR. NELSON: Well, let me just give
19 a couple of observations sort of from a
20 regulatory perspective if you will. I think
21 this has been a great discussion. I think
22 people have laid out a lot of the issues that

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1 are involved in these kind of early phase
2 research and I hear a lot of agreement and a
3 lot of then modification of further points, et
4 cetera. So I mean I --

5 Let me just sort of two points; one
6 of the challenges I think and this is a
7 challenge for an IRB. It's also a challenge
8 for I think I use challenge and that's a
9 position of responsibility, if you will, for
10 FDA. So anyways I think about it is sort of
11 concentric circles. There may not be much
12 distance between those circles depending upon
13 the issue but basically, the question is the
14 reasonableness of going forward with a given
15 protocol. There's layers of decision making
16 that exist.

17 We've talked some about the
18 parental layer of decision making of a child
19 that's competent of assent. There would be
20 the child level of decision making but those
21 sort of exist. Prior question is whether the
22 IRB thinks that's a reasonable option to

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1 present to the parent. I mean, that's part of
2 the responsibility of the IRB, but then at an
3 FDA level, there is the responsibility of
4 deciding whether it's even appropriate to let
5 an IRB consider whether it's appropriate to
6 let that protocol be presented to parents who
7 have to consider whether it's appropriate to
8 present that to their child.

9 So it's a concentric circle and at
10 those different levels, we need to address, if
11 you will, the responsibility that comes with
12 that and there may be circumstances where in
13 the context of the severity of the disease and
14 the presence of alternatives, the distance, if
15 you will, between those circles may be quite
16 narrow meaning the pass-through, if you will,
17 of that protocol to the point of the child
18 being enrolled on it, would have a different
19 threshold, if you will, than in other settings
20 and that's precisely what we're talking about.

21 So I think, you know, that is our
22 responsibility. I will say that these kinds

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1 of considerations are folded into the decision
2 making process. It's unusual in my
3 experience. I'm told it's rare. There may be
4 instances where for existing products,
5 requests for treatment IND or compassionate
6 use IND, sort of off-protocol use of existing
7 investigational products is allowed by FDA, so
8 a lot of it is because of these very same
9 considerations. I, myself, have advised, when
10 asked by individuals whether they -- you
11 know, about going for IND on innovative
12 approaches to even say you have -- if you have
13 access to that product, you could decide to do
14 it as a non-research innovative treatment.
15 That's your choice as a clinician. Or if you
16 wanted to go the IND route, if you don't have
17 access, or even if you have access, you'd
18 prefer to do that way, that's also an
19 alternative but picking that latter
20 alternative, I think, then raises the
21 responsibility of others in making sure that
22 what's then presented to the IRB and presented

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1 downstream to the parents is not, if I may --
2 is not simply wacky, but is justifiably wacky.

3
4 I mean, you know, so the devil is
5 in the details. And, you know, I -- my view
6 is we've had a nice rich discussion of a lot
7 of the issues that have to go into that. So I
8 mean, I don't hear people disagreeing. In
9 many ways, what we're doing is sort of
10 modifying the points that are people making to
11 sort of enrich the conversation.

12 DR. ELVIN: I would make, I guess,
13 two comments, one in regard to the desperate
14 parent. Your heart always goes out to the
15 desperate parent but I guess the comment that
16 I would make in regard to the desperate parent
17 is that their ability to hear what you're
18 saying varies considerably. And so you have
19 to be very careful when you pick that parent
20 that they're willing to take a risk and you
21 can't say, "I can't promise you no outcome."
22 You have to say, "It may even be worse",

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1 because what about that brain tumor that shows
2 up a year later? And if you think they were
3 cooperative then, you might be facing
4 something very different when they had a
5 neurologic -- the predictable neurologic
6 devastation and now you're introduced an
7 additional devastation.

8 So those are the -- you can't just
9 say, "It might not get better", you have to be
10 -- you have to go further than that. And then
11 the other comment has to do with how studies
12 are done and research is done. Just from my
13 own experience and I went on a DSI inspection
14 recently of an investigator of a drug to treat
15 rare inborn error of metabolism which involves
16 a neurologic, severe neurologic compromise.
17 And so this person -- there were so many 483
18 violations, you could sink a ship.

19 People were consented who couldn't
20 speak English with English speaking forms.
21 There was multiple adverse events that for
22 decades went unreported and then we met with

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1 the IRBs and everybody and every -- "Oh, we
2 had them on our radar screen". I think, you
3 know, this is -- without naming, getting
4 specific, this IRB said, "Well, we have 1,000
5 investigators and they're overwhelmed. Their
6 ability to monitor sometimes is not so great
7 so they would do superficial inspections", and
8 this person continued to do what they were
9 doing. We didn't even know if this -- if
10 these patients are getting chemical grade
11 versus pharmaceutical grade substance.

12 There was one patient who's getting
13 -- one sample of the type of thing that
14 happened -- can happen out there in the
15 field. There was a person who came from a
16 nursing home, neurologically going down the
17 tubes, received the experimental drug, left
18 eight weeks later, went back to the nursing
19 home which was several hundred miles away.
20 The person had things like dystonia, drooling,
21 and those are causes of suffering which are
22 treatable, not curable, but neurologists can

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1 do things to help like Botox injections for
2 contractures, dystonia, et cetera.

3 This particular investigator was
4 saying when the parents in desperation were e-
5 mailing him about should they get a
6 neurologist locally that they could have, no
7 particular need for a neurologist. The brain
8 will take six to 24 months to recover. I
9 didn't see any recovery happening in the
10 patient like this. This was -- I mean, this
11 was very upsetting to see what I saw in these
12 charts.

13 But so there's the other caution is
14 you'd like to think that people would not
15 advertise their product inappropriately or
16 what they're offering but this guy made it
17 sound like fast and easy, no problem, minimal
18 side effects. So we -- you know, we have to
19 realize that there are people out there who
20 are kind of blinded by their own belief in
21 what their product is going to offer and that
22 coupled with the desperate parent is a formula

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1 for disaster.

2 DR. FOST: Thank you. We're going
3 to go around again. Let me ask people to
4 frame their comments, I mean, you can say
5 obviously, whatever you want to say but I'm
6 trying to think of my duty to see if there's
7 something close to consensus in any of these
8 things. So far there have been two themes of
9 the discussion this morning, it seems to me.

10 One, a very restrictive view on
11 this hypothetical proposal, that is if you
12 can't measure the outcomes, what's the point
13 of doing it? And most of us are having a lot
14 of trouble trying to figure out how you're
15 going to measure it, either at a cellular
16 level and certainly at a functional level.
17 And so there's a reluctance to do something
18 that has substantial risk when the benefit or
19 even an objective response is difficult to
20 measurement.

21 So the first round of discussion
22 was pretty cautionary. Then for the last 45

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1 minutes, we've been hearing a counter-argument
2 that even though that's true, there may be a
3 rationale under a rubric of compassionate use
4 or innovative therapy done carefully to allow
5 something like this to happen in desperate --
6 in suitably desperate cases with very strong
7 caveats about brutally consent. Consent
8 monitoring, I would add to that to make sure
9 nobody is doing this under false pretenses and
10 so on. So these are oppositional views.

11 So as we go around again, we're
12 about 10 minutes or 15 minutes from a break
13 and we can continue after the break but if
14 people can begin to reconcile these two views
15 or say something about where you stand on it,
16 that would be helpful. So we'll start with
17 Len.

18 DR. GLANTZ: Let me just comment
19 briefly on Virginia's, about the desperate
20 patient and the over-enthusiastic researcher,
21 that's why there are IRBs. Is that there has
22 to be something that stands between those

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1 folks. There are a couple of points I want to
2 make.

3 One is that we are continuously
4 mixing up the therapeutic relationship and the
5 research relationship. That the law at the
6 moment is that doctors can do whatever they
7 want to with patients. That if you have a
8 willing doctor and a willing patient, that's
9 okay.

10 That, by the way, may also be a
11 rule that should be adjusted but that's
12 another story for another day. The standard,
13 the regulatory standard, is not a willing
14 patient and a willing doctor. The regulatory
15 standard is the anticipation of direct benefit
16 to the subject. So that we should not use, it
17 seems to me, the unregulated circumstance of
18 the doctor/patient relationship to try to
19 inform the regulated circumstance of creating
20 a research protocol and that the research
21 protocol is not about a treating doctor and
22 the patient to be treated. It's about the

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1 creation of a protocol in which people would
2 be treated the same way over time and the main
3 purpose is to derive information. The main
4 purpose is not to treat, okay. So I think
5 it's really very important.

6 The second thing I want to say is
7 that when I hear about the 100 percent risk of
8 death or the 100 percent risk of very, very
9 serious neurological defects, I think that
10 that's a very concerning notion because what I
11 really think people are saying and you can
12 comment on this, is that they think you can't
13 hurt them. It's not so much that you know,
14 anything might help them but really what's the
15 down side? They're like so desperate that
16 pretty much whatever you do, that's sort of
17 the Baby Fae argument.

18 Jeff's point about the causal trend
19 that -- and this goes to Ben and I think Ben
20 made like really an essential point that I
21 would raise my hand to follow, and that is
22 don't torture the language because you want to

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1 get to an end result. What you may need to do
2 is change the language but that the thought
3 that it may be true that a neural anatomical
4 change may be an indicator that down the road
5 there might be benefit but it is not in and of
6 itself an anticipated benefit, so that as an
7 ethics advisory group. Well, you can say well
8 maybe we should have another category. But
9 that looks like a 407 or whatever it is here,
10 a 55 or 54 at this point, but it's hard to see
11 how that is a benefit to the subject. But the
12 prospect of direct benefit and the anticipated
13 benefit is not the same as a willing parent
14 and a willing researcher. That's not the
15 standard.

16 I also want to just say something
17 about -- and Amy said something about parents
18 will have hope. And without in any way, you
19 know, denying the importance of that, that I
20 would say that that's not a reason for doing
21 serious interventions on children. That
22 that's not -- to me without trying to sound

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1 cruel, that I wouldn't treat the parents'
2 desperation by doing something to the child
3 which you know, would not seem to be
4 beneficial to the child and my guess is that
5 you would agree with that.

6 But I'm saying that the creation of
7 hope is not in and of itself a justification
8 for intervention.

9 DR. FOST: Steve?

10 DR. JOFFE: So let me agree with
11 Len before I disagree with him. The agreement
12 --

13 DR. GLANTZ: We're getting closer.
14 You're learning.

15 DR. JOFFE: It's remote. The
16 agreement is any time one hears or one says
17 that patient, a child and adult, potential
18 research subjects has nothing to lose, I think
19 we have to be careful of that sort of -- I
20 think we shouldn't think like that and any
21 investigator who says that ought to be
22 presumptively disqualified from doing what

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1 they want to do. So that was my point of
2 agreement.

3 The point of disagreement is around
4 the concept of anticipated benefit. What
5 actually -- and you said that's the regulatory
6 standard, but the word "anticipated" doesn't
7 appear in the regulation.

8 DR. GLANTZ: Yes, it does actually.

9 DR. JOFFE: So, well, I'm looking
10 at 50.52 and it says -- so yes, but fair
11 enough, it does not appear in the heading of
12 50.52.

13 DR. GLANTZ: Right, the heading,
14 technically is not the regulation.

15 DR. JOFFE: Let me work through
16 this. So clinical -- so the first -- so the
17 point is that prospect of direct benefit, I
18 think we all agree, is a threshold concept and
19 there's some disagreement about where that
20 threshold ought to be. It may be that it's a
21 very low threshold or it may be that it's a
22 higher threshold and that's part of what I

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1 think our discussion has been about. And I've
2 been arguing that one can claim a prospect of
3 direct benefit with a rather low threshold of
4 probability for that. I don't believe that
5 that exposes us to doing unethical or
6 excessively risky research in children because
7 we still have to meet the other criteria and
8 this is where the notion of anticipated
9 benefit comes in. So let's just talk about
10 this notion of a low threshold.

11 So if we use the phrase, "remote
12 prospect of benefit", I don't think we see
13 remote modifying prospect as an oxymoron. So
14 I think prospect includes the possibility that
15 that prospect is very low or remote. Where we
16 have to judge what the anticipated benefit is
17 when we start to judge it in relation to risk,
18 which is not -- that comes next.

19 First we establish that there is or
20 is not a prospect of direct benefit and
21 secondly, we have to think, how does that
22 prospect of direct benefit in terms of its

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1 magnitude and its likelihood relate to the
2 risk? So 50.52(a) is to say that the risk is
3 justified by the anticipated benefit to the
4 subject.

5 So here in judging risk versus
6 benefit we have to say just how great is that
7 anticipated benefit and we have to have an
8 honest discussion, is it very unlikely, is the
9 magnitude of any benefits we might expect very
10 limited or is it much more likely and much
11 more substantial magnitude of benefit? And
12 how does that relation of anticipated benefit
13 to risk, this is 50.52(b) compared to
14 available -- to that of available
15 alternatives. And there again, we have to
16 start making judgments about the magnitude of
17 this prospect, both in terms of the meaning of
18 the benefit if it occurs and the likelihood
19 that such a benefit will occur.

20 So to me, the structure of the
21 regulation asks us to make -- to -- allows us
22 to claim prospect of direct benefit when the

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1 threshold or the likelihood of that prospect
2 is very low but then in judging how it relates
3 to risk and how that compares to the context
4 of the alternatives, there we have to start to
5 make judgments about is it sufficient to
6 justify the risk?

7 So just to take this case, for
8 example, I would -- let's assume that a non-
9 human primate model or sheep model that the
10 sort of experts in the field believe that that
11 was a good pre-clinical model for the disease
12 and the analogous experiment was done in
13 animals with strikingly positive results in
14 the appropriate animal model.

15 And then the question came, are we
16 ready to take this to babies and we don't
17 believe that there's an adult analogue so one
18 has to go to first in children experiments.
19 So there we would say -- I would be willing to
20 say there is a prospect of direct benefit to
21 that first child who enters the study. And
22 the difficulty for me and the part where we

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1 get protective is where we just that
2 relationship of that prospect to risk because
3 I think that the risks would be substantial,
4 both the risks of the delivery procedure and
5 also the risk of what the stem cells are going
6 to do once they get in there. And it may be
7 that at least under 50.52, we couldn't approve
8 that first in human study, not because there
9 wasn't a prospect of direct benefit but
10 because whatever prospect of direct benefit
11 was there was not sufficient to justify the
12 risks. And so that's how I would reason
13 through the regulatory requirements, and I
14 think that it's a -- the regulatory
15 requirements are appropriately structured to
16 get us to reason in this way and we might come
17 out to the same conclusion but I just wanted
18 to sort of lay out how I would think through
19 the requirements to get to that conclusion.

20 DR. FOST: Putting the regs aside
21 for just 60 seconds, how would you weigh in
22 the third factor of the desperateness of the

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1 situation? That is given -- that is doing
2 nothing is kind of result in a very bad
3 outcome? Wouldn't that allow a much worse
4 risk/benefit ratio than other situations?

5 DR. JOFFE: Well, I mean, that goes
6 back to, I think, a point that Skip has made
7 which is that the FDA, the investigators, IRBs
8 need to make a decision about whether this is
9 something that one could reasonably offer to
10 families, parents, children in this situation
11 and the desperation of families is part of
12 judging whether the relationship is at least
13 as favorable as that of alternatives, and we
14 might conclude that it is or we might conclude
15 that it is not --

16 DR. FOST: And if you were in --

17 DR. JOFFE: However, one would also
18 want to take into account, the desperation in
19 thinking about Step C, 50.52(c) which is this
20 notion of adequate provisions for soliciting
21 assent and parental permission, in the sense
22 that one would -- and it is a point that you

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1 made, Norm, is that one would want unusually
2 robust consent, permission, et cetera,
3 procedures if one were going to go forward
4 with this research.

5 DR. FOST: So if you were on an
6 IRB, how would you come out in this case? I
7 realize you might want more information, the
8 animal studies and so on?

9 DR. JOFFE: So it's very hard to
10 say how I'd come out in the case given the
11 information that we have but it would -- I
12 think it would be likely that I would want to
13 say, well, I'm not confident in saying that
14 that the risks are justified by the benefits
15 and therefore -- but yet it may be a very
16 important study and therefore, I think about a
17 50.54 referral, but it wouldn't be because I
18 didn't think there was a prospect of direct
19 benefit. I would just say that that prospect
20 is not sufficient or may not be sufficient to
21 justify the risks.

22 DR. GLANTZ: Norm, can I just ask

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1 Steve a brief question?

2 DR. FOST: Sure.

3 DR. GLANTZ: In Jeff's notion of
4 neural anatomical change, would that be a
5 direct benefit?

6 DR. JOFFE: So, distinguish here
7 between measured benefit and unmeasured but
8 potentially real benefits. So if we could
9 sort of go down the whole developmental
10 pathway and at the end of, you know, the whole
11 trajectory of studies conclude that you could
12 develop -- that you could get measurable
13 neural anatomical change, but that would
14 translate definitively into no measurable
15 benefit for children over time as you've
16 developed the intervention through the years,
17 then that answer in retrospect would be, no,
18 that was not sufficient for benefit. The fact
19 that all you could measure is neural
20 anatomical change at this point, is not itself
21 proof of benefit or necessarily evidence of
22 benefit to the child, but it doesn't preclude

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1 unmeasured benefit.

2 DR. GLANTZ: But is it -- I'm going
3 to anticipate a benefit. Would that be enough
4 if that were the outcome measure?

5 DR. FOST: If the scientist told me
6 that we are likely to get neural anatomical
7 change and we are certainly not going to get
8 any improvement in quality or quantity of
9 life, I would say no, but the problem is we
10 don't know at this point whether we're going
11 to get improvement of -- in quantity or
12 quality of life and it's certainly, assuming
13 appropriate animal models and good responses
14 in those animal models, it certainly is not
15 implausible.

16 DR. FOST: Let's take one mor
17 comment and then break and then we can
18 certainly pick up again. Alex?

19 DR. KON: So I wanted to get back
20 to this idea of sort of if they're so bad you
21 can't hurt them. And I don't think that
22 that's really the concept but the concept is

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1 more they -- certainly there's a possibility
2 of harm but that the alternative of quote
3 "doing nothing" is so dire that even for a
4 very small chance we might accept a relatively
5 high rate of risk.

6 And I think some of the way -- and
7 it becomes very difficult when we're talking
8 about this study because it's unclear to me
9 what exact patient population we're talking
10 about, how bad off are they, what is their --
11 how well do we understand what their outcome
12 is going to be if they're not part of the
13 study, so when I'm thinking through it, for
14 example, I think about if we're talking about
15 children that are so devastated that many
16 parents might choose to withdraw life
17 prolonging measures, stop artificial nutrition
18 and hydration, and allow these children to
19 die, then if that's the population that we're
20 talking about and now we're saying well, there
21 is this protocol that offers a very slim
22 chance of any meaningful benefit but there is

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1 a very slim chance and if on the one hand,
2 we're saying, "Well, this child is going to be
3 so devastated that we're going to withdraw
4 artificial nutrition and hydration, but there
5 is this very small chance that this might
6 help", then we get back to this question of
7 we're really in a different category than the
8 doctor/patient relationship but the question
9 becomes, well, you know, might we use this
10 under sort of a compassionate use and we may
11 say, yes.

12 And I find it interesting that Ben
13 and I are on different sides of this table
14 because normally I'm on the side saying things
15 should go through a 407 panel and Ben, you're
16 on the side of saying, let's keep it local.
17 And I find it interesting because now we're on
18 the exact opposite side and I guess it comes
19 down to me. I'm less worried about how much
20 prospect there really needs to be when we're
21 talking about prospect of direct benefit and
22 it's more important to me when we're looking

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1 at how do we weigh the potential risks and the
2 potential benefits to this child and if we
3 conclude that the potential benefits to a
4 specific child out -- may outweigh the
5 potential risks to that child, then to me
6 that's sufficient to meet the prospect of
7 direct benefit clause and so I actually
8 believe it would be approvable under that
9 category and not require a federal panel.

10 But so I think getting hung up on
11 sort of what do we mean by prospect versus
12 chance, et cetera, is less important than
13 weighing the potential risks and benefits for
14 individuals that would fall into the study
15 protocol and I don't think that it would be a
16 problem to do this in a systematic way that
17 would qualify -- that would require IRB review
18 understanding that this might be done outside
19 of the research setting in a much less robust
20 way.

21 DR. FOST: I think we should take a
22 break. After the break, you'll be able to say

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1 something to us about travel and
2 reimbursement.

3 MALE PARTICIPANT: During the
4 break.

5 DR. FOST: During the break, okay,
6 thank you. So we'll take a -- some of us need
7 to sign out so let's take a 20-minute break,
8 be back here at 25 before the hour.

9 (Whereupon, the above-entitled
10 matter went off the record at 10:16 a.m. and
11 resumed at 10:39 a.m.)

12 DR. FOST: So we are waiting for
13 Leonard and Elaine. So we are scheduled at
14 least until 1:00 o'clock. There is no FDA
15 regulation that says we have to go to 1:00.

16 DR. NELSON: Actually, Norm -- no.

17

18 DR. FOST: The Advisory Committee
19 of which this is a subcommittee is interested
20 in getting some sort of summary, and there
21 will be minutes generated from this meeting
22 that will endeavor to do that but towards that

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1 end, to help us in the drafting of those, it
2 would be helpful if in the time remaining if
3 people could sort of summarize their views, at
4 least on the topic of today. I think we had
5 some summary consensus yesterday, which we
6 stated and which we'll be able to reconstruct
7 but on the issues that we're talking about
8 today, if we can continue, I think, going
9 around the table, we can, I think start with
10 Terry where we left off but come back to the
11 others, so in this round of discussion, if
12 people could sort of frame their remarks or
13 end them at least with some sort of summary
14 statement and to help you frame it, we have on
15 the one hand concerns about moving from animal
16 studies to children for an intervention in
17 which measurement is difficult, both objective
18 measurement, and that is molecular or cellular
19 measurement, and clinical measurement.

20 So we had mainly cautionary
21 concerns about that but on the other hand,
22 we're beginning now to hear people who think

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1 that under some rubric of compassion or care
2 or the treatment IND emergency IND, for
3 desperately ill children with appropriate
4 safeguards of accurate prognosis, careful IRB
5 review, high standards for consent, consent
6 monitoring and so on, it might be appropriate,
7 even given all the uncertainties we have about
8 measurement. So if you could comment on where
9 you stand on -- or at least your views on
10 those two sides of the divide as some people
11 have already done.

12 Second, an issue of which it would
13 be helpful, I think, to get, if we can see
14 what people's sort of final views are on what
15 counts as benefit, whether it's simply
16 cellular or objective measure of proof of
17 concept essentially, counts as a reasonable
18 enough surrogate for benefit or if it has to
19 be something clinical, and even if the
20 clinical thing can't be measured because the
21 variability of the disease, is at least the
22 possibility that it might benefit even though

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1 we might never know it? Is there just enough
2 here in the sort of concept of what's being
3 proposed here to constitute prospect of
4 benefit. That would be helpful. So if people
5 could -- you could comment on any aspect of
6 the discussion that we've had. Yes.

7 DR. WITTEN: I'm sorry, I didn't
8 mean to interrupt. I just thought I would
9 give the little regulatory perspective on some
10 of these terms if that would be helpful.

11 DR. FOST: In just one minute. So
12 I don't want to inhibit people who have free-
13 floating ideas, but if you could, at the end
14 of your comments say something that could work
15 its way into some allowing Carlos and I to at
16 least summarize the meeting, that would be
17 very helpful. If you want to add, this would
18 be a good time.

19 DR. WITTEN: Yes, thank you, Celia
20 Whitten, Office Director, Office of Cell
21 Tissue and Gene Therapy at the Center for
22 Biologics. Just to talk about a couple of

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1 these terms, since they've been, you know,
2 floating around in this meeting and may be
3 interpreted more expansively than what we
4 would -- how we would use them at FDA, I'll
5 just mention that treatment IND generally is
6 for a study where the sponsor is working
7 towards their marketing application. They've
8 perhaps enrolled all their patients and
9 they're gathering data, that would be one
10 example.

11 Or sometimes if you have a patient
12 who doesn't fit in a protocol for an existing
13 experimental therapy, we may have a single
14 patient IND for that patient and/or if there's
15 a number of patients who don't fit into the
16 protocol, there may be a treatment IND to
17 allow therapy and under an investigational
18 setting for those patients in the treatment
19 IND.

20 And then there's emergency -- you
21 know emergency IND. I think generally, how --
22 I'm not sure whether there's actually a formal

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1 FDA definition. There probably is but how
2 it's generally interpreted would be, you know,
3 fairly -- I think fairly more confidence
4 that you actually have a prospect of benefit
5 than some of the kinds of products that we've
6 been discussing or studies we've been
7 discussing here today. So most of these kind
8 of things that are really highly experimental
9 might not be considered under emergency IND.
10 So I just wanted to clarify those three
11 settings which aren't really, you know, what
12 the committee has been discussing.

13 DR. FOST: And one last issue in
14 which to frame your comments, we've had some
15 discussion about whether these kind of
16 judgments we are talking about here could be
17 made by a local IRB with appropriate FDA
18 authorization or whether a 407 or 50.54 panel
19 would be needed for the kind of intervention
20 that we're talking about today, that would be
21 helpful.

22 So we'll go around completely again

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1 and wander our way back to Alex, but if we
2 could start with Terry, that would be good.

3 MS. O'LONERGAN: Okay, as one of
4 the philosophers on the panel, I'm going to
5 wax philosophical for a moment. It's my duty.

6 So I think that it doesn't -- this case
7 doesn't meet what I would consider the
8 threshold for prospect of direct benefit, and
9 in the philosophical vein, I would think it
10 analogous to the question that if a tree falls
11 in the forest and there's no auditory system
12 to hear it, does it make a sound. And I think
13 the fact that we can't measure -- there's no
14 way to measure whether or not there was direct
15 benefit to the child, I think that it fails on
16 that score.

17 However, I think that it's probably
18 scientifically and ethically justifiable to
19 conduct the study, but I don't think that we
20 can dress it up and call it prospect of direct
21 benefit. So I think that the justifiable
22 arguments from a philosophical perspective may

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1 be found in arguments for obligations to
2 future generations. I think that there's any
3 number of arguments that can be stated in that
4 vein.

5 I think that altruistic behavior
6 and altruistic coping mechanisms, if you will,
7 on the part of parents are justifiable
8 reasons, perhaps, but I think we need to call
9 it what it is. It's a potential societal
10 benefit and not a direct benefit to the child.

11 DR. FOST: And would therefore need
12 a 50.54 review because it's more than minimal
13 risk.

14 MS. O'LONERGAN: Yes, I believe it
15 would. I believe it would.

16 DR. FOST: But if you were part of
17 such a review process, you could imagine
18 approving of such a thing it sounds like.

19 MS. O'LONERGAN: Yes, I think I
20 would.

21 DR. FOST: Okay.

22 DR. BOTKIN: A couple of comments;

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1 mostly in disagreement with what Terry just
2 said.

3 MS. O'LONERGAN: With the tree
4 part, too?

5 DR. BOTKIN: Oh, the tree part I
6 liked, that was good.

7 MS. O'LONERGAN: I was going to go
8 with you can put it in a tutu, but you can't
9 make it dance.

10 DR. BOTKIN: That's a little too
11 philosophical for me. So I think there's two
12 levels we want to think about here at least
13 and part of the question is when do you make
14 that jump from the animal research into first
15 human trials. And I think in this particular
16 context, I would want a pretty high threshold,
17 in other words, pretty far down on Skip and
18 Sarah's model here to have a pretty good
19 animal model and evidence that there was
20 clinical improvement in the animals, based on
21 the intervention before moving to human model.

22

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1 I, at least, would not be satisfied
2 in an animal model with saying just because
3 you had engraftment in the right places or you
4 had some evidence of neuronal function within
5 the animal brain, that that was sufficient to
6 move on to humans. Because of the luxuries of
7 animal models, I think you can hope to provide
8 evidence of clinical benefit before making
9 that transition.

10 So once you make that transition,
11 what kind of an experiment are you going to
12 design for those kids. And it think by
13 necessity, you're going to want to have a
14 fairly small scope experiment. You're not
15 going to want to initiate your first human
16 experiments with the 40 kids in order to have
17 a controlled intervention group and try to
18 determine a definitive clinical response to
19 the intervention. You're going to want some
20 safety evaluations first on a small number of
21 children.

22 And I think that that's likely to

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1 preclude your ability to show in a definitive
2 way whether those kids have responded
3 clinically or not in this kind of disease
4 context at least. So does that mean you can't
5 do -- you can't take that step? In other
6 words, are you forced into a situation to say,
7 "Well if you can't do it on 40 kids, you can't
8 do it at all and I think that that would be a
9 mistake to take that interpretation but by
10 doing it on two or three kids and having a
11 series of specific aims for that project,
12 you've got a justifiable protocol.

13 Your first specific aim is going to
14 look at safety issues. The second specific
15 aim is likely to look at some of the surrogate
16 markers, did the cells go anywhere, did they
17 engraft, and that's not a benefit in and of
18 itself but it's necessary if not sufficient
19 for benefit.

20 In other words, if you find in
21 those three kids that the cells never
22 engrafted, then you don't need to go any

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1 further than those three kids. You don't need
2 to expose other kids to the intervention
3 because you've perhaps decided that it's not
4 working in the human model, and therefore, the
5 risk to additional kids is not justified. You
6 still may have a third specific aim as
7 evaluating the clinical response of those
8 kids.

9 In other words, you're going to
10 look at whether the kids change in their tone
11 or neurologic function in some way but that's
12 not going to be the primary outcome of the
13 study and you understand that the study in
14 three kids isn't going to give you a
15 definitive answer on whether there's been
16 clinical response to the intervention. So
17 from my perspective, that's a justifiable
18 approach, even though you don't have an
19 experiment that will provide definitive
20 answers on the clinical evaluation. And
21 you're relying to a certain extent on one
22 safety, but two, surrogate markers. And

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1 again, it's not that you consider the
2 engraftment a benefit in and of itself, of
3 course, it's not, but it's a prerequisite to
4 benefit and those kids, in fact, may be
5 benefitting. It's just that you can't tell.

6 So I think that remains within
7 prospect of benefit and again, I would draw
8 that distinction between experimental design
9 that is sufficiently providing enough, say,
10 cells in this circumstance to plausibly have a
11 benefit as opposed to something like a PK
12 study or something that would under no
13 circumstances be likely to provide benefit.

14 And finally, I would say with
15 respect to sort of the parent role, I think
16 kids are vulnerable, and they're vulnerable
17 for a variety of reasons, in the past, due to
18 more careless attitudes about the welfare of
19 kids, but I think they can be vulnerable to
20 excessive enthusiasm by investigators and
21 parents as well. And I think the regs are
22 designed appropriately and I pretty much like

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1 how the regs are designed to protect kids from
2 excessive enthusiasm.

3 And so I think parent enthusiasm is
4 relevant to the informed consent process,
5 certainly, but I wouldn't use parent
6 desperation as significant criterion to move
7 from one threshold point to another about when
8 it's okay to initiate experimental
9 interventions and last point, perhaps obvious
10 here but some of the talk about kids who have
11 nothing to lose would tend to suggest that
12 maybe we're looking or thinking about our risk
13 criteria in a relative sense rather than
14 absolute sense as we've talked a little about.

15
16 And I don't think it's appropriate
17 to say because these kids are in such
18 desperate circumstances that brain cell
19 therapy is minimal risk for example. Nobody's
20 said that, but I think we may be at risk for
21 thinking in those types of terms and I think
22 we want to move away from the sense that it's

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1 a small risk because these kids are in such
2 desperate situations because I think that
3 would be a systematic abuse of the terminology
4 that would put kids in a more vulnerable
5 situation.

6 DR. FOST: So Jeff, you think the
7 prospect of benefit is enough to not require a
8 5054 review?

9 DR. BOTKIN: I would say that --
10 I've a mixed answer to that, and one would be
11 I think based on fitting within the regulatory
12 criteria, I think it would be enough for local
13 review, based on the innovative nature of the
14 intervention, the expertise necessary from a
15 variety of perspectives to answer the critical
16 questions, I think there aren't very many
17 local IRBs that should take on an evaluation
18 of this protocol.

19 So I would be more interested in
20 federal level review based on the complexity
21 of the issues, rather than the fact that I
22 don't think it fits within established

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1 criteria.

2 DR. NELSON: Norm, can I just make
3 one point? I'll only point out in the
4 hypothetical case there is, in fact, no
5 clinical protocol in that case, so it's -- I
6 could understand under certain fact situations
7 for presenters in the future, we might think
8 it fits 50.52 and in other fact situations, we
9 might think it fits 50.54 but there are no
10 facts on the table that would address that,
11 nor is there any proposed clinical trial in
12 the hypothetical example, just as a reminder.

13 DR. WILFOND: Well, I appreciate
14 that reminder, because it allows me to dodge
15 the question about whether it belongs in the -
16 -

17 DR. NELSON: If there were a
18 protocol.

19 DR. WILFOND: But as Skip said,
20 then you have to specify what that protocol
21 was.

22 DR. NELSON: And the problem is,

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1 there is no protocol that we've even outlined.

2 So to say if there is a protocol, is I think,
3 much too speculative.

4 DR. WILFOND: But the title is
5 about clinical trials. That's the title of
6 the hypothetical.

7 DR. NELSON: Read the case, there's
8 no protocol in there. That's my only point.
9 It says in anticipation, what's the -- you
10 know, I mean, we've outlined all the issues
11 that would be involved in framing that
12 protocol. I'm just saying there is no
13 protocol that we've framed in light of those
14 issues, and so to then said whether it should
15 or shouldn't be under a certain category is in
16 my mind, asking a question of which there's no
17 evidence on which one can base it because
18 there's no protocol that's been outlined.

19 DR. WILFOND: Are you uneasy about
20 this group expressing opinions on that topic?

21 DR. NELSON: I don't think knowing
22 whether it should or shouldn't go to 50.54

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1 provides me any information in the absence of
2 knowing what that protocol is, I think. And
3 everybody is going to design it differently in
4 their mind and, therefore, answer the question
5 differently. And so I don't see that as
6 terribly useful, yes.

7 DR. WILFOND: Okay, so thank you.
8 So, you know, it's interesting, Jeff, because
9 I agree with Terry's comments, and I think all
10 of your comments are compatible with what
11 Terry said. With the exception of the single
12 statement, I think this falls in the prospect
13 of direct benefit.

14 I think that if we're -- and to get
15 back to Norm's initial question about this
16 apparent dichotomy between our reluctance to
17 even go forward at all because there's not
18 enough scientific evidence and yet on the
19 other hand, seeming to be wanting to provide
20 this as a compassion use thing, I think the
21 way we can reconcile those to is to avoid this
22 language of prospect of direct benefit and

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1 say, "Look, let's decide when scientifically
2 and clinically, we're at the right time to
3 make the move from animals to children." It's
4 going to depend upon a lot of different
5 circumstances. Let's be very careful and
6 let's be very cautious about that. But when
7 we make that move, we can make that not only
8 because of a prospect of direct benefit but
9 because we believe that the next step in the
10 scientific inquiry based upon a broad range of
11 considerations about the importance of
12 disease, the -- all the contextual things that
13 Skip made in the very beginning about
14 severity, alternatives, all those things fit
15 into that decision, but then that decision
16 could still be described as this will be of
17 social and scientific value, not direct value
18 to that particular family.

19 I actually think that -- again, as
20 I said before, that simplifies -- it doesn't
21 avoid the problems of the consent challenges
22 of desperate families but at least gives us

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1 one more tool to use when we try to
2 communicate with them where we can, you know,
3 stand on our heads and say, "This will not
4 help you". They'll still think it will help
5 no matter what we say to them, but we can just
6 try as explicitly as possible to avoid that
7 problem and you know, probably some of the
8 families will say if you ask some of them,
9 "I'm doing this for altruistic reasons," but
10 there will be others who will still say,
11 "Well, I think this will help my child". I'm
12 not going to get in trouble by those families
13 who still do it out of those beliefs, as long
14 as we, ourselves, are clear that we are doing
15 this because we think scientifically, this is
16 an important and valuable study and to
17 conclude all this, I also do agree with this
18 general notion that regardless of whether it's
19 54 or 52 or whether -- is the idea of there
20 being some value to a broad based, possibly,
21 you know, federal panel to discuss this is a
22 valuable thing because of the issue of the

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1 novelty, the uniqueness, and that would be the
2 reasons to do it rather than whether we want
3 to call it or don't call prospect of direct
4 benefit.

5 DR. BOTKIN: Norm, can I pressure
6 Ben for a second?

7 DR. FOST: Sure.

8 DR. BOTKIN: Let's imagine you had
9 the animal model and the research that showed
10 that some aliquot of stem cells injected into
11 the brain of anoxic ischemic animals showed a
12 statistically significant improvement in
13 neurologic function. You're going to
14 translate that same therapy up to initial
15 human -- that same intervention up to initial
16 human studies using what you think is a
17 parallel dose in humans. It's been
18 demonstrated to be beneficial in the animal
19 model.

20 You're now going to try it in
21 humans for the first time. Why wouldn't the
22 fit under a prospect of benefit?

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1 DR. WILFOND: I think the reason --
2 again, we had some of this -- I think it's
3 slightly more plausible because it's at least
4 remotely possible that it could benefit as
5 compared to, you know, the design where it's a
6 single study or something, single dose where
7 there's no way it could benefit. So you're at
8 least saying we have reasons where it possibly
9 could. I would still say even in those
10 circumstances, the likelihood of benefit is
11 probably going to be so low based upon all of
12 our prior experiences with these types of
13 things, that we're just going to be in a much
14 better place, you know, in terms of our
15 genuine appraisal of the likelihood it's
16 happening to justify it based upon this being
17 scientifically valid and not sort of pretend
18 this is -- it's not just one in a thousand,
19 it's way lower than that and just use that to
20 justify it.

21 DR. FOST: I -- Felix Frankfurter,
22 the Supreme Court Justice who was one of the

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1 strict constructionist, if ever there was one,
2 in his memoirs said, "First I make up my mind,
3 then I send out the clerks to look for a
4 precedent". So, and I think that's the way
5 IRBs and other people think about these
6 things. Also, I think that's the way most
7 ethicists think. I mean, they have some
8 intuitive view and then they look for fancy
9 arguments to try to steam-roll their
10 opponents.

11 So I think anything can be squeezed
12 into the regulations. I think this can be
13 squeezed into the prospect of direct benefit
14 even though I agree with Ben and I think
15 probably everybody else. It's extremely
16 remote. So I think the central question is
17 whether it's ethically appropriate to do it
18 and for reasons that I said earlier, I think
19 if it were -- there were very good animal
20 studies showing that this concept made some
21 sense, if there were very good scientific
22 review and I presume this would be an NIH-

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1 funded study, so there probably would be, I
2 think and very high standards of consent and
3 so on and so on, I think it could be justified
4 under prospect of benefit and squeezed into it
5 and approved locally.

6 That said, I also agree that I
7 think there ought to be more national -- a
8 much more intense ethical scrutiny of the
9 project and as Skip correctly says, we don't
10 know what the project is, so -- but whenever
11 it comes a long, a lot will, as always, depend
12 on the facts, what the animal studies show and
13 what the monitoring system is and how outcomes
14 are being assessed and so on.

15 So I think the 407 -- the NIH
16 process is one way to at least make sure -- to
17 increase the chance that it's scientifically
18 sound, but I think the 407, 50.54 process is
19 another very good way to make sure there's
20 really strict ethical review of it. I don't
21 think a -- so I think even though it could be
22 approved locally, I don't think it should be

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1 because I think it would be a very complicated
2 set of issues, very controversial and arguably
3 could go forward, but ought to be reviewed in
4 some -- by some more expert group such as
5 this.

6 Now, how would you get from here to
7 there if you're already saying it has a
8 prospect of benefit? It doesn't a call for a
9 54 review, so that's a question about the
10 50.54 process, you know, could it be used as a
11 consultation process for -- okay, I'd be
12 interested in your thoughts about that because
13 I think there are examples like this which
14 don't strictly require a 50.54 panel but in
15 which it would be very useful, a properly-
16 assembled group.

17 So in summary, I can imagine a
18 protocol like this with an appropriate set of
19 facts being approvable. I think the reason
20 for approving it is that there at least be
21 some chance, however remote, in a desperate
22 situation. The part that I worry about the

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1 most that hasn't been discussed here yet is
2 that once this gets into a research mode, the
3 conflict of interest of the investigator to
4 keep the kid alive in an intensive care
5 setting, that is you get complications, you
6 get brain inflammation from all this. He
7 winds up on a ventilator, and I worry about
8 pressures on parents from investigators to,
9 you know, see how long we can make him live,
10 to see -- to get the maximum chance for
11 engraftment and all that.

12 I think that happens a lot in
13 clinical trials with critically ill, so that's
14 the part that worry me about the child's
15 interests the most, not that something was
16 being injected.

17 If what was injected into his head
18 was going badly, and we could withhold and
19 withdraw treatment soon after so that -- I'm
20 not so worried about the child suffering from
21 the immediate injection as I am from a
22 prolonged period of suffering, and if the

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1 parents and a true attending physician, not an
2 investigator, were in charge of all that, I
3 would hope that it would be handled in a way
4 that was directed at the child, but once you
5 add clinical investigation to all that, that
6 ugly risk arises.

7 DR. JOFFE: Norm, can I just very
8 quickly respond to one point, one
9 clarification of something you said which is
10 that this still could go to 50.54 review even
11 if it were determined to fall under the
12 prospect of direct benefit because it didn't
13 satisfy A, B, or potentially C even if we
14 considered it to have a prospect of direct
15 benefit.

16 DR. FOST: Remind us what A, B, and
17 C are.

18 DR. JOFFE: I think C is unlikely
19 to be the issue, but we might decide that
20 there's a prospect of direct benefit but for
21 example, A, the risk is not justified by the
22 anticipated benefit to the subjects, and if

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1 that were the determination of the local IRB,
2 then I think the next step would be to refer
3 it.

4 DR. FOST: So once again, proving
5 my point, if you have a view about the ethics
6 of something, you can squeeze it into the regs
7 and get it where you want it to go. Jeff?

8 DR. ROSENTHAL: Well, in the
9 absence of a protocol, I'm inclined to just
10 let the philosophers discuss the points. I'm
11 finding myself agreeing with what everyone is
12 saying as they're saying it, and I don't
13 really think I have much to add. I'm
14 impressed by the discussion.

15 DR. FOST: Thank you. Elaine.

16 MS. VINING: I think I find myself
17 in a similar spot to Jeff. But I did want to
18 just kind of concur with what Ben had said as
19 far as making sure that if I understand you
20 correctly, making sure that there is a sense
21 that if there isn't a direct benefit, you've
22 got to make it very clear in these -- as

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1 you're moving forward to whatever protocol it
2 is, and I know that we don't have a specific
3 protocol that we're talking about, but it
4 seems to me that we do have some -- to some
5 degree we can predict what the snapshot of a
6 vulnerable parent will be for any child that
7 has been even struggling with, you know, days
8 or weeks or months or years of a child's
9 illness, when there is little prospect of any
10 kind of resolve to the illness and they are
11 presented with some ability to, possibly even
12 if it's a very longshot, come up with some way
13 of addressing their child's illness.

14 And whether it is -- the
15 determination is made that they're going to
16 enroll the child in a protocol for altruistic
17 reasons with maybe there's a glimmer of hope
18 that they have some prospect of helping their
19 child. I think that that is a very real
20 consideration in whatever kind of studies are
21 designed and the enrollment that takes place.

22

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1 Parents -- I believe that most
2 parents are going to do whatever they possibly
3 can to help their child or help other
4 children. So I think you're going to have
5 people that will enroll children, whether for
6 the glimmer of hope that it will help their
7 child or some other children.

8 Having said that, I think my faith
9 in what I thought the IRB process was or would
10 be was a little bit shaken with what Virginia
11 said, as far as the follow-through and some of
12 the requirements that may not be met. So I
13 would concur with others who say perhaps we
14 really do need to move this up to the national
15 review for any kind of studies that have not
16 direct benefit to the child but would
17 potentially have scientific -- some scientific
18 and clinical necessities or possible outcomes.

19 So I think you have to raise that up past the
20 local to the national review.

21 DR. FOST: Amy.

22 MS. CELENTO: So that was a very

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1 nice summary. I agree with most of what you
2 said and I guess that, you know, my final
3 comment is the hundred shades of gray in any
4 of this and again, looking at, you know, the
5 progression 10 years, 15 years and when people
6 start -- where do you draw the line when
7 someone is ill or is in a situation where
8 there could be, hopefully, a big improvement
9 in their life versus, you know, this is that
10 they came with. This is the hand they were
11 dealt. They were born in this situation and
12 you know, you can't just push the envelop
13 because the science is there. So mine is more
14 of a long-term concern. I don't know if that
15 makes sense, but --

16 DR. FOST: Yes, I'm glad you
17 reminded me of that because it's another
18 comment I wanted to make. There's been talk
19 about whether this should be a small study or
20 a big study. I think there seems to be
21 agreement that it would be unwarranted to do a
22 big study and it would have to probably be

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1 huge, given the variability. So we're talking
2 about a small study, essentially a Phase One
3 study, a proof of concept study, and I think
4 it ought to be -- have a moratorium to avoid
5 this -- that is, you know, three to five
6 patients and then see what happens.

7 Some of them will have died,
8 unfortunately. There might be autopsy
9 information on those. We might actually have
10 tissue benefits, but there ought to be -- to
11 avoid the concern that Amy is raising, which
12 I'm sympathetic to, that this doesn't just go
13 on and on for a decade, and we still don't
14 know really whether it's working or not would
15 not be good. So there ought to be some very
16 time-limited goal of the proof of concept or
17 Phase One study. Skip?

18 DR. NELSON: Well, there's many
19 points of the conversation that I could
20 comment on from my own perspective, but I'm
21 going to limit it, I guess, to three general
22 observations. The first is, I think, the

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1 broader context of product development which,
2 I think, Norm, your last comment goes to is
3 that we need to keep the overall perspective.

4 I think Jeff's observations relate to that of
5 how one moves from early phase to later phase
6 sorts of trials when you try to get a product
7 basically to the point where it can be
8 approved and then licensed for a particular
9 use.

10 And that issue is, you know,
11 universal across all product lines. So I
12 think that's a perspective that needs to be
13 maintained. My two comments, I'm going to
14 start with one philosophical one. People may
15 not know that I do have a PhD. It happens to
16 be in religious ethics so I have the right to
17 wax philosophical. The second is going to be
18 the procedural one the FDA had about their
19 relationship between national review and
20 federal review and 50.54 to sort of clarify to
21 people some of those procedural issues and
22 again, both of these remarks are meant in

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1 general and don't have any specific
2 application to this hypothetical.

3 The first philosophical one is the
4 interesting relationship between facts and
5 ethical principles. The philosophers that I
6 have been influenced by, Habermas, one, would
7 argue that in fact there is no conflict
8 between ethical principles. What creates the
9 conflict is the fact situation which brings
10 them into conflict.

11 I think a classic example is if
12 you're a deontologist, your problem in
13 struggling with the conflict between the
14 ethical principle of tell the truth or protect
15 the innocent, and a good Kantian thinks they
16 should always tell the truth and therefore,
17 would, in fact, reveal the hiding innocent
18 person to that murderer at the door who comes
19 in and asks, "Where are they?" So it's that
20 fact situation that is what brings those two
21 ethical principles into conflict. It's not
22 the principles themselves.

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1 So that's partly why I think I've
2 been pleased with, in many ways, the richness
3 of this discussion and its ability to have
4 brought forth all of the various
5 considerations in their complexity around how
6 one might think of approaching a first in
7 child trial regardless of the product. And
8 you know, the facts were there to sort of get
9 us into that conversation. I think it did
10 that in a useful way, but there's insufficient
11 facts, in my mind, to begin to opine, if you
12 will, on the merits of why a protocol design
13 ought to look like.

14 It's just not there, and we
15 actually don't have the right people around
16 the table to provide the kind of expertise we
17 would need to answer that in this specific
18 hypothetical. So I'm -- you know, and I root
19 that to the sort of philosophical point I'm
20 making, is you know, so I would argue, Norm,
21 that in fact, the conflict that you've
22 identified is really not a conflict.

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1 Depending on the facts, it may be a conflict
2 or it may not be a conflict.

3 And the difficulty is, we could all
4 sort of fill out the facts in our own way and
5 then -- but we don't have a uniform, sort of
6 set of facts on which to sort of then
7 adjudicate that conflict in this particular
8 instance.

9 So that might be a segue into the
10 procedural, and so I'll step away from the
11 philosophy and just talk about the procedural.

12 The 50.54, to provide a little bit of
13 background, I mean, this subcommittee and in
14 particular the Pediatric Advisory Committee is
15 the committee that's chartered to review IRB
16 referrals under 21 CFR 50.54 and/or 45 CFR
17 46.407. The language there is the same. The
18 reason of the and/or depends upon the
19 relationship of HHS funding and FDA regulation
20 or both, so that's mainly a procedural
21 distinction.

22 When those panels have been

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1 convened, of which there's been three, it's
2 been this ethics subcommittee, some of whom --
3 some of the members who are here have served
4 on some of those past panels, but then it's
5 always supplemented with appropriate content
6 experts in scientific areas as we're
7 struggling with the specifics of a given
8 protocol, as well as individuals represent the
9 parent and patient point of view. The key
10 there is that it's initiated by an IRB
11 referral of a protocol.

12 To date the protocols, I think as I
13 mentioned yesterday, that have been referred,
14 have been referred because of healthy
15 children, i.e., children without a condition
16 being enrolled as the control group in non-
17 beneficial research only investigations that
18 have involved interventions that are -- have
19 been felt to be more than minimal risk, in
20 other words, but limited to a minor increase
21 over minimum risk. That happens to be the
22 three referrals.

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1 So there have been no protocols
2 that fit this kind of category referred to
3 date. Now, part of the difficulty is, in my
4 own mind, separating out the question of
5 whether broad public and ethical discussion of
6 certain issues are merited in innovative
7 settings or innovative products, separating
8 that from the procedural issue of an IRB
9 referral, and one of the difficulties is, as
10 much as one might argue that such a public
11 discussion is worthwhile and the FDA, I think
12 one of the strengths of the FDA is its
13 advisory committee process and centers and
14 divisions make decisions all the time to take
15 these kinds of questions about early product
16 development or about innovative products to
17 their advisory committees to get advice. That
18 happens all the time, that's fairly standard.

19 The difficulty separating out that
20 question from the procedural issue of can such
21 a panel -- let's imagine if we met today, we
22 had a whole bunch of experts around a

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1 particular topic and we all decided, yes, you
2 could go forward, the difficulty is that that
3 may not be with enough specificity in terms of
4 the protocol and the protocol design to where
5 one could use that discussion to necessarily
6 guide a decision around a given protocol that
7 could come down the line later, because if you
8 imagine it, what we, as a 50.54 panel are
9 obligated then to do in a sense, is to make
10 the very same decisions and to assess the
11 decisions that an IRB needs to make relative
12 to the approvability of that research. If you
13 look at 50.54, that's what it says, that it
14 could be approvable under either 50.51, `2, `3
15 or could go forward under 54 and the only way
16 you can do that is to really have all of the
17 information and so one of the challenges, I'll
18 just leave it at this, in thinking about how
19 one could advance, if you will, the ethical
20 and scientific discussion in different product
21 areas, is the more general ethical and
22 scientific virtue, if you will, of public

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1 discussion versus the sort of protocol
2 specific work that would go on, given an IRB
3 50.54 referral.

4 And then one final comment is the
5 other important question which would be
6 handled potentially in different ways is also
7 how one then folds in the issue of
8 confidential and commercial information
9 relative to that review. The three referrals
10 that have taken place to this committee
11 although involving FDA regulated products were
12 all being done by academic and not commercial
13 investigators. There's never been a referral
14 for a sponsor protocol where the issue of
15 confidential commercial information in that
16 setting has been a question.

17 And so I think you know, there are
18 -- all I'm saying is these are -- I'm not
19 giving you conclusions. I'm just saying these
20 -- this is the terrain. These are the issues
21 that would have to be addressed in that
22 setting. And I'm happy to answer clarifying

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1 questions, but I don't think we're going to
2 solve those issues, just to let you know that
3 today. I wouldn't have that expectation.

4 DR. WILFOND: Skip, I just want to
5 ask one clarifying question. That was
6 actually very helpful. What's your view about
7 if something has gone to a 54 panel, how when
8 a similar or somewhat similar trial comes up
9 in the future, how should the IRBs -- should
10 they look to what that panel did? Should they
11 count that in some way or not. What's your
12 thoughts about that?

13 DR. NELSON: Another IRB with a
14 similar kind of protocol?

15 DR. WILFOND: Yes.

16 DR. NELSON: Ben, that's a tough
17 question because I think it depends on how you
18 rank the ethical requirement for public
19 discussion and how an IRB would fold that into
20 their discussion versus whether or not they
21 can actually fit that into their local
22 requirements. So from a -- if, in fact, the

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1 panel has only said that such a protocol could
2 go forward under 50.54, I think the IRB would
3 be obligated to refer it. Part of the
4 difficulty I have is that I think IRBs by and
5 large, I'm not -- I think Norm had eluded to
6 this, look and decide if a protocol ought to
7 be done and then look to ways to fit it into
8 the other three categories.

9 The difficulty in doing that after
10 a panel has met -- I might say that's never
11 come up so this is a hypothetical situation.
12 If I'm doing that after a panel has met, if we
13 all decided for that protocol it should have
14 gone -- it can only go forward under 50.54.
15 Their ability to fit and justify it under the
16 other categories is undermined.

17 DR. WILFOND: Can I just respond to
18 that because I could also imagine that
19 paradoxically going the other way. In other
20 words, imagine I was the IRB initially and I
21 was uncomfortable stretching prospect of
22 direct benefit because -- particularly because

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1 I thought really it was stretching to the
2 limit, there was some sort of more public
3 discussion, it went to the 54 panel. The
4 public discussion occurred and there was a
5 consensus, this was ethically appropriate. I
6 might subsequently be a little more inclined
7 to then stretch my definition because now I
8 have a sense that my -- you know, sort of
9 gestalt judgment is on track because it's
10 going to this other committee, so therefore,
11 I'd be a little more willing to stretch it.

12 DR. NELSON: Well, if you're
13 pointing out that if, in fact, there was an
14 agreement by such a committee, again,
15 hypothetical, that a certain protocol could be
16 viewed as offering prospect or direct benefit
17 under 50.52 --

18 DR. WILFOND: Just that they
19 thought ethically, it was reasonable to go
20 forward.

21 DR. NELSON: Under 50.54.

22 DR. WILFOND: Yes.

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1 DR. NELSON: The point is I think
2 if they -- you know, Ben, we're speculating.
3 The point is I think the difficulty is for a
4 local IRB to take something that ought to be
5 in 50.54 was discussed under 50.54 and to say
6 we're going to fit it under 50.52, just
7 because a panel said it could go forward under
8 50.54, is, in fact, not in accordance with our
9 existing regulations.

10 DR. FOST: I think the following,
11 though does happen, has happened. There's an
12 intervention, let's call it X, which an IRB A
13 thinks is more than minimal risk, more than a
14 minor increment over minimal, no prospect of
15 benefit in the study and therefore, they send
16 it to 407 review.

17 Other IRB's concurrently are not
18 far away in time around the country, are
19 approving Intervention X or Technique X
20 because they conclude it's not more than
21 minimal risk. That is I think we have things
22 -- I think we have a lot of variability in

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1 what some IRBs think require 407 review and
2 which don't.

3 There are very few IRB -- 407
4 referrals, you said three under the current
5 system, but there were a dozen or so more or
6 less all together before that under a
7 different structure. And some of them
8 involved interventions that were being
9 approved locally by IRBs without 407 review.
10 That is there's very little guidelines here as
11 to what the precedent weight of a 407 review
12 is, whether it requires -- there's no
13 requirement for consistency.

14 DR. NELSON: Well, I was with you
15 all the way up to that last phrase, Norm, that
16 there's no requirement for consistency. There
17 is a requirement for the consistent
18 application of federal regulations. So that
19 as well, is a point of debate in terms of the
20 kinds of warnings that investigations lead up
21 to. My only point is, yes, there is
22 variability and some of that variability may

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1 be justified and some of it is likely
2 unjustified. There is need for better
3 guidance and part of that is the reason why
4 we're here.

5 DR. FOST: I want to get FDA people
6 to get their views in on these general issues
7 we've been discussing and then we can still
8 have more discussion. Virginia, did you want
9 to comment on sort of the general themes we've
10 been talking about?

11 DR. ELVIN: I don't have too much
12 to add other than what's been said. I don't -
13 - you know, I don't think we have a sufficient
14 pre-clinical animal data to do this study in
15 humans. This may sound strange but I think
16 that I would start with adults before going in
17 to pediatrics and hypoxic injury.

18 I do believe that there would be
19 eventually a way to do this in the pediatric
20 population. I also believe that there would
21 be a way to measure a functional benefit but
22 not so much in the short term. You'd have to

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1 look at the short term and long term. I'm
2 seeing that as something that's in the future.

3 The risk/benefit threshold right now has not
4 arrived in terms of the science.

5 Just a comment about IRBs, I had an
6 eye-opening experience on this inspection and
7 I'm beginning to realize that you know, IRBs
8 are all over the country and they do very
9 different things with research projects and
10 their ability to monitor things. I have the
11 sense that that varies greatly, too, and so --
12 and that's an important factor when you're
13 trying to launch a research protocol.

14 DR. FOST: Thank you. Okay, be
15 more specific.

16 DR. GLANTZ: There are a number of
17 things about this discussion that I find
18 surprising and actually some of it that I find
19 disturbing. One has to do with the lack of
20 any notion of burden of proof or what the
21 starting point is. And the fact that
22 scientists are using possibilities to justify

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1 intrusions into the brains of children is like
2 surprising to me. That there is no important
3 decision that anybody in law would make that
4 would be based on a possibility, even whether
5 or not I would pay for your, you know, dented
6 fender, would require a preponderance of the
7 evidence that I did it, and I did it
8 negligently, not that is was possible that
9 maybe I dented your fender.

10 So one has to do with really the
11 very low level of proof that seems to satisfy
12 the people. The second has to do with at
13 least the sense of some people that the words
14 have no meaning and I find that troubling,
15 too. This is, you know, different IRBs
16 interpret 407 differently and part of the
17 reason for that is that there's actually no
18 enforcement and there's an unusual set of
19 regulations that the enforcement has been
20 largely procedural, how many IRB members were
21 there, was it a convened meeting and that sort
22 of stuff, instead of saying, you know, this is

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1 not what we mean by direct benefit. This is
2 not -- you know, there's nothing about that.
3 And it's because you know, most regulations
4 involve industries that litigate things and
5 none of this ever gets litigated.

6 So that the argument that words
7 could mean anything that you want them to
8 mean, means if that's true that it's
9 standardless, that you have people sitting
10 around a table saying, "Here's my intuition
11 and I'm going to push my intuition into this
12 standardless set of criteria". And so it's of
13 interest to me, Norm, that you actually cited
14 Oliver Wendell Holmes because he's the perfect
15 example of the trouble.

16 DR. FOST: Frankfurt, it was Felix
17 Frankfurt.

18 DR. GLANTZ: Oh, I'm sorry, Felix
19 Frankfurt. Let me do Oliver Wendell Holmes
20 then because Oliver Wendell Holmes is also a
21 strict constructionist. It's a person who
22 intuited that it was okay to sterilize people

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1 and what he was able to do was find words in
2 the Constitution that made that okay, and so
3 you know, the idea of starting with intuition,
4 and so let me start with this way of thinking
5 about it. There seems to be around the table
6 and you could tell me, the presumption that
7 the research should be done, unless there's a
8 reason not to do it.

9 So Norm, I think that you had said
10 this protocol could be approvable under some
11 circumstances and I assume we could -- it's
12 easily have said, this protocol would not be
13 approval under some circumstances. Right?
14 And I think that both of those are probably
15 true. The question is, what's the starting
16 point and it seems to me if the starting point
17 is, it's not approvable unless there is a --
18 unless the burden of proof has been met that
19 it meets the standards, then we shouldn't do
20 it as opposed to the starting point being,
21 well, if someone has proposed doing it, we
22 should do it unless we can come up with

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1 reasons not to do it.

2 So given that, just using that as
3 my -- when I look at Skip's questions that he
4 asked us to look to, and the need to establish
5 sufficient prospect of direct benefit, that if
6 that were a requirement for some reason,
7 whether it was a 52 or something else, that
8 based on what we've seen so far, and you're
9 quite right, Skip, that it's fact dependent, I
10 can't see -- I would not use structural
11 changes as a prospect of direct benefit. It
12 seems to me that to directly benefit a
13 subject, there has to be some clinical
14 improvement in some way.

15 So I'm not saying that we couldn't
16 approve something like this if it wasn't a
17 direct benefit. I think it would be harder to
18 do, but I think that we shouldn't use that as
19 a rationalization to approve something that
20 otherwise might not be approvable under that
21 standard and rather move it into the more
22 appropriate review process.

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PARTICIPANT: Two things, one with

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