

1 the asthma kid, I don't see how they're worse
2 off in being in a trial with a 75 percent
3 chance of getting treatment when their
4 previous option was no treatment. I don't see
5 how anybody's worse off from that.

6 MR. GLANTZ: Yes. I think you're
7 talking about social justice issues. You're
8 talking about desperate parents doing what
9 they need to do, and that creating a group of
10 people who are subjects because they're poor,
11 that's the reason.

12 And the reason why it's done in the
13 United States is because people would get the
14 076 regimen because it was available to
15 people.

16 Can I ask actually a separate
17 question though a little bit? And I don't
18 know if we're going to get to this later. But
19 the question that I have about this trial is
20 benefit, whether or not there is any benefit
21 at all in this trial. And again, I don't know
22 if you want to put that on the table for later

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1 or if we're moving into that.

2 DR. FOST: I think we're on it. Go
3 ahead.

4 MR. GLANTZ: Okay. Because it
5 seemed to me that if the issue is one of
6 velocity as opposed to sort of the end result
7 of kids' development being pretty much the
8 same, why do this trial at all? And I'm not
9 asking it rhetorically. When I read it, I
10 just couldn't see why this was a useful thing
11 to do since the kids will be the same height
12 one way or the other, if I read the background
13 paper correctly.

14 DR. FOST: The theory is that the
15 new drug will have less growth retardation
16 effect.

17 MR. GLANTZ: But I thought what I
18 had read -- and again, this is why I'm asking
19 it as a question -- that I thought this was a
20 velocity question as opposed to an ultimate
21 growth retardation question.

22 DR. FOST: Alex?

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1 DR. KON: Yes. That's how I read
2 it as well.

3 But I think the benefit is that
4 there's a sense that delaying growth had some
5 negative psychological ramifications in the
6 child, even if their ultimate adult height is
7 unchanged, but having a delay in their growth
8 has some negative repercussions. So if they
9 could be on a medication which would allow
10 them to continue growing similar to their
11 peers, they would never have a period of
12 shortness, so to speak, and that that is the
13 proposed benefit. That's my understanding.

14 MR. GLANTZ: Because I thought that
15 the numbers were somewhere between .3
16 centimeters and 1.-something centimeters,
17 which I assume on a yearly basis on a given
18 year -- maybe they add up in some way.

19 So when do kids catch up? I guess,
20 when do they actually reach their adult
21 height? Because I think of .3 centimeters as
22 a not noticeable difference. So when they're

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1 18 do they catch up? Are they 20 when they
2 catch up?

3 DR. FOST: Isn't the idea of catch-
4 up is that they might be able to come off the
5 inhaled steroids later, at which point they
6 will catch up if it's a low dose steroid?

7 DR. WILFOND: Right. And again, as
8 I understand it, there's a number of
9 conflicting studies also. In other words,
10 whatever decline in velocity occurs can be
11 recaptured if they're off inhaled steroids.
12 Other than the CAMP study -- which is in your
13 thing -- there have been very few studies that
14 followed people long enough to know what
15 really happens as they become adults.

16 But I think your primary question
17 is actually one that I happen to study too.
18 The reason why I thought the placebo arm was
19 troubling in this study is that I just wasn't
20 motivated by the value of this study as a
21 whole. In other words, I don't know if we
22 need a study of this new drug to see how this

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1 compares to placebo for the purposes of
2 whether you're going to be half a centimeter
3 shorter or not on a particular year.

4 And that's where I think that the
5 issue, back to Leonard's comment about the
6 poor people is it's one thing if here's a
7 study that really has very minimal value, but
8 you construct it in a way in which you're
9 saying you're offering people this potential
10 benefit because of what you're offering them.

11 It strikes me that, disanalogous from the
12 situation in Africa where there really are no
13 other options, there probably are some sort of
14 options for these families. And what you're
15 doing by enrolling them in the study is not
16 permitting them to seek out the other options
17 where they could get better therapy.

18 DR. FOST: Let me just say what I
19 thought the reasoning of the study was -- the
20 hypothetical one -- and then Skip can say what
21 it really was.

22 I thought the idea was we know that

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1 inhaled corticosteroids slow growth. We don't
2 know yet the second you can catch up if you
3 can go off them. But that gives you some
4 pressure to go off them. So you have to make
5 those judgments.

6 And if there were a drug that were
7 just as effective in controlling the asthma
8 but had no effect on growth, then you wouldn't
9 have to worry about those trade-offs. You
10 wouldn't have to worry about taking the kid
11 off.

12 Now whether in the long run there's
13 difference in adult height between the two, we
14 don't know. But other things being equal, it
15 would be better to have a drug that doesn't
16 slow growth than one that does.

17 DR. NELSON: No, I think that's
18 fair. One could consider growth velocity as a
19 surrogate marker for ultimate growth and
20 recognize that doing a one-year study is
21 really sort of within the constraints of what
22 one would do for determining information for

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1 labeling. Although of course, if everybody
2 caught up, that would be important to know.
3 So I think it's framed within that particular
4 sort of growth velocity.

5 You can see growth velocity changes
6 even within shorter periods of time as well on
7 inhaled corticosteroids. And so I would sort
8 of assume that that's the focus of the case --
9 if you will.

10 DR. FOST: Elaine?

11 MS. VINING: I wanted to just
12 backtrack for a second because the inclusion
13 benefit was something that I had understood to
14 have some -- there was definitely an inclusion
15 benefit.

16 And I think that the discussion
17 seemed to get us to the point where the
18 inclusion benefit was focused only on poor
19 people. And I don't see that as I'm looking
20 at this, because I think that there are
21 significant benefits to folks outside of the
22 poor people. People have co-pays. People

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1 have parking expenses. There are a lot of
2 things that if my child is in an ongoing
3 program that is going to have some benefit to
4 them, perhaps inclusion benefit could actually
5 be a reality.

6 There's a consistency in seeing a
7 physician or a nurse practitioner or whoever
8 the medical personnel would be on a regular
9 basis throughout this study. And whether
10 they're on placebo or not, it seems to me that
11 there is an inclusion benefit. And I just was
12 a little uncomfortable seeing this as a
13 discussion that the inclusion benefit may or
14 may not only apply to just poor people. I'm
15 uncomfortable with that premise that seemed to
16 come out of this discussion.

17 DR. FOST: Skip?

18 DR. NELSON: Just to perhaps
19 clarify the importance of the question with
20 two comments.

21 I think there needs to be a
22 distinction between the benefit of potentially

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1 going into a clinical trial as it may impact
2 on parental decisionmaking. That's a very
3 different question whether it's beneficial to
4 go into the trial for whatever reason, which
5 may or may not relate to access relative to
6 insurance. It might relate to whether or not
7 you want to get care at institutions that only
8 accept people on research trials, which
9 there's at least two I know of that do
10 pediatric research.

11 So there may be a number of reasons
12 why people would decide to do that based on
13 inclusion benefit. The question is whether
14 that inclusion benefit ought to be judged
15 against the risks of the experimental
16 intervention. That's the question. And
17 that's where this notion of the fallacy of the
18 package deal was originally brought up years
19 ago.

20 I might say that this is not a
21 trivial issue, because there have been
22 instances where IRBs have used this benefit to

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1 argue that including children who don't even
2 have the disease can be on a trial of an agent
3 that treats that disease.

4 All right? You may not want to go
5 there. But I'm just saying to say it's
6 beneficial to be on a trial as a reason to
7 evaluate the risk/benefit of that trial
8 without further clarification is problematic.

9 DR. FOST: Jeff?

10 DR. BOTKIN: Yes. I guess the
11 other angle I would take with this is that the
12 inclusion benefit -- for reasons that Skip
13 just mentioned -- is such a highly abusable
14 concept that it basically turns potentially
15 any placebo group into a beneficial group
16 because they're involved in a trial. And I
17 think even though there may be benefits in
18 participation, I think as a community we want
19 to say that we're not going to count that,
20 very much the same way we say with monetary
21 rewards.

22 Children in this study perhaps are

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1 getting 100 bucks for their participation. Is
2 that a benefit? Sure. Does that make it a
3 beneficial arm of the trial for them to be in
4 a placebo because they're getting \$100? I
5 think we've explicitly said no, we're not
6 going to count the 100 bucks because otherwise
7 it's a highly abusable set-up for the conduct.

8 And so the benefits if they accrue ought to
9 be a direct response to the experimental
10 intervention as opposed to these indirect
11 aspects of the participation.

12 DR. JOFFE: Do you think that's
13 true for competent adults also -- that we
14 shouldn't count indirect benefits including
15 monetary ones?

16 Len? And then Alex, and then
17 Steve.

18 MR. GLANTZ: Yes, Skip, I was
19 thinking about your comment that there were
20 institutions that only take people on for
21 research purposes, and that people who want to
22 go there need to be in research.

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1 I still don't see why that's a
2 benefit. It assumes that being there is a
3 benefit. The fact that somebody wants to be
4 there -- we already heard that it's an 80
5 percent of drugs or interventions that are
6 studied end up being nothing. Why is that a
7 benefit? Except that you want to do it.

8 DR. NELSON: My intent letter was
9 not to argue that it's a benefit, but only to
10 point out that the complexity of the reasons
11 parents might decide to go into trials may
12 well include inclusion benefits. It was only
13 to --

14 MR. GLANTZ: Got you.

15 DR. NELSON: -- highlight that
16 aspect.

17 MR. GLANTZ: Okay.

18 DR. KON: Coming back to the
19 inclusion benefit, I think it's one of these
20 subjects that a lot of very smart people
21 disagree about. I think there's data that
22 suggests that there is a trial effect.

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1 There's some interesting data that suggests
2 that if you only look at people at the same
3 institution who are getting excellent care at
4 an academic institution that there's actually
5 no trial effect.

6 So while I'm uncertain if I would
7 be willing to consider it as a benefit of the
8 study -- and actually I think I probably
9 wouldn't -- I think even if we were going to
10 say we'll consider this as one of the benefits
11 of being in it, certainly we couldn't argue
12 that it's any significant benefit because
13 there's a lot of data to suggest that there is
14 no such benefit.

15 So even if we were going to,
16 perhaps that would obviate a small amount of
17 risk. But if we're talking about a study
18 that's greater than minimal risk, I think
19 you'd be very hard pressed to say that there's
20 sufficient inclusion benefit to overcome the
21 risks involved with the study.

22 DR. JOFFE: So two points. One, I

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1 just wouldn't want to give the impression that
2 one needs to go to an academic center to get
3 excellent care. And I think for many, if not
4 most things, one can get excellent care in all
5 kinds of different places.

6 But the second point -- and this
7 may be one you want to table for later in the
8 discussion but I want to make sure not to lose
9 it -- which is for me thinking about the four
10 arms. The placebo arm -- I think most of us
11 have said that we would not be willing to look
12 at that arm under the prospect of direct
13 benefit category, but rather would look at it
14 as no prospect of direct benefit. And then
15 just exactly how great is the risk? And how
16 does that relate to questions of scientific
17 necessity?

18 The arm where I struggle frankly --
19 and this raises very general questions -- is
20 what Skip called the positive control arm --
21 the 200 micrograms of budesonide arm. So
22 that's essentially -- if I understand the

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1 treatment recommendations correctly -- exactly
2 the same treatment as most pediatricians --
3 most good pediatricians would recommend for a
4 kid with this level of asthma. And many if
5 not most randomized trials in pediatrics will
6 have a standard care arm like that whether
7 it's viewed as a positive control for an
8 equivalency or noninferiority kind of design,
9 or whether it is sort of the baseline arm in a
10 superiority study trying to show that
11 something else is more effective -- or some
12 other combination is more effective.

13 And how we should think about the
14 prospect of direct benefit in the standard
15 care arm -- which is essentially what this is
16 -- to me is the hardest question on the table
17 here -- is since this is what a kid should get
18 anyway outside of the study, is getting that
19 within the context of a study something that
20 offers a prospect of direct benefit or not?

21 DR. FOST: Say again why not.

22 DR. JOFFE: Because it's exactly

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1 analogous to what you get outside of the
2 study.

3 And the answer may very well be
4 yes, it does offer a prospect of direct
5 benefit -- a prospect of direct benefit that
6 is exactly commensurate with what good care
7 would offer outside of the study. But at
8 least I think it's worth being explicit about.

9 DR. FOST: Ben, you had a comment?

10 DR. WILFOND: Well, I was thinking
11 about Steve's comment. I think your answer
12 was a very reasonable one, because that's
13 actually the arm that I had the least trouble
14 with.

15 And again, I guess I had a question
16 for Skip getting back to this more broader
17 question of the study design and the question
18 of whether there's a sense that it's necessary
19 to have a placebo arm in this sort of trial to
20 conduct the trial because it seems like the
21 answer to the question about how this new drug
22 does in terms of growth velocity could be

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1 compared to the act of control. Let me
2 finish.

3 That maybe wasn't true initially.
4 And we actually have a number of studies that
5 did that. But at some point, there ought to
6 be accumulating evidence to say look, we don't
7 keep having a placebo control at this point
8 because we've seen how things work.

9 DR. NELSON: To respond to that,
10 first I'm not a statistician. But let me give
11 you what I presume would be the answer.

12 The difficulty under that kind of
13 design where you've only got the three arms --
14 the 100 micrograms, 200 micrograms, and then
15 the standard-of-care arm -- would be that if
16 in fact you've not chosen the study population
17 well, you've not conducted the trial well.
18 All of the issues and trial design that
19 undermine the ability to see a signal between
20 the two arms would lead one potentially to
21 conclude that the study intervention and the
22 control arm are in fact equivalent.

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1 Now, there's some issues one could
2 assess that tries to get at that. But you're
3 effectively then putting yourself into the
4 mercies of the historical control. It goes
5 back to the assay sensitivity.

6 The purpose of the placebo arm is
7 not necessarily against the new one. It's
8 also to make sure that the active control is
9 in fact doing what it should do within that
10 trial.

11 So a long discussion of those
12 issues within choice of control group about
13 how problems in trial design -- just sloppy
14 work, for example -- if it's an active control
15 trial with no placebo, may if it's designed as
16 an equivalence trial give you the wrong
17 impression that the two interventions are the
18 same when in fact you've undermined the
19 ability of your control drug to function as it
20 ought to. And the absence of the placebo
21 makes you unable to assess the assay
22 sensitivity -- if you will -- of our current

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1 trial. So that's the reason it's in there.

2 I think the issue is the risk as
3 people have been talking about, and
4 justification I think scientifically. Do you
5 need that all the time? No.

6 The question would be then if you
7 have an intervention where you are always
8 assured of assay sensitivity, meaning that the
9 historical controls are robust, it's entirely
10 possible you might get away with a placebo. I
11 don't think we necessarily have to answer the
12 scientific questions around when and can that
13 be done. As I went through those choices of
14 control group, that's directly from ICH E10.

15 DR. KON: So getting back to
16 Steve's point, I think your point is an
17 interesting one because I would agree I'd have
18 a hard time viewing the standard ICS arm as
19 having direct benefit.

20 But I guess when I read through the
21 case, I interpreted that arm as actually a
22 minimal risk arm, because we're not -- all

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1 that we're doing is sort of following these
2 kids and seeing what they're doing, giving
3 them the same care that presumably they would
4 be getting anyway.

5 So I didn't have a problem with
6 that arm, because I really viewed it as a
7 minimal risk arm.

8 DR. JOFFE: I didn't raise it to
9 suggest that I have any problem with it
10 whatsoever. But I just am raising the
11 question of whether it is a minimal risk arm
12 as you interpreted it or an arm that's
13 approvable under the concept of prospect of
14 direct benefit.

15 And it seems to me that arguments
16 could be made on both sides.

17 DR. FOST: I wanted to go back to
18 try and understand why indirect benefits are
19 morally problematic.

20 Let's just start with adults,
21 because Jeff said he thought the principle
22 applied to adults too.

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1 So in our ordinary life, we allow
2 competent adults to do far more risky things
3 than clinical trials -- join the army, join
4 the police, and so on -- for things that have
5 no direct to them other than the money and
6 whatever satisfaction they get.

7 So just for openers, if it's okay
8 to do that to take a high-risk of dying or
9 permanent disability by playing football, why
10 shouldn't you be allowed to join a clinical
11 trial just for the money? People do that.
12 That's what the private sector phase 1
13 companies are for. Do we think that's an
14 immoral apparatus to pay people?

15 Len?

16 MR. GLANTZ: I don't think Jeff
17 said -- and I wouldn't say -- that they
18 shouldn't be able to do it. I just think he
19 said it shouldn't be considered a benefit of
20 the research.

21 When we talk about research
22 benefit, it should come from the --

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1 DR. FOST: It's definitely an
2 indirect benefit. Buy why shouldn't we allow
3 that to be weighed in to the decision about
4 whether it's appropriate to offer it to people
5 and let them choose to accept it?

6 Start with adults first, and then
7 we'll come to --

8 MR. GLANTZ: Well, I guess it
9 depends on whether or not you see research
10 with human subjects differently. So if we
11 could find people who would jump off a roof
12 for \$1,000, is it okay for doctors and
13 clinicians to suggest that they do that?

14 And so again, we're not talking
15 about the nature of contract, which is what I
16 think you're talking about. I think we're
17 talking about the nature of when we talk about
18 benefits in the context of research and
19 whether or not the research provides benefits,
20 that you're talking about whether or not
21 employment provides benefits. And employment
22 does. It doesn't mean the research provides

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1 benefit.

2 DR. FOST: I'm not talking about
3 benefit. I'm talking about indirect benefit.

4 MR. GLANTZ: Or any benefit. Yes.
5 I wouldn't see it as part of the benefit of
6 coming out of research. Because employment
7 benefit, you're just taking things like any
8 other employment.

9 DR. FOST: Is that morally
10 problematic in a research setting?

11 MR. GLANTZ: I just wouldn't count
12 it as a benefit when you're doing risk --

13 DR. FOST: The money is the
14 benefit?

15 MR. GLANTZ: Yes.

16 DR. FOST: It's okay?

17 DR. BOTKIN: Here's my response. I
18 would say you've got a protocol that involves
19 taking healthy individuals and doing liver
20 biopsies on them. IRB says I don't think so.
21 That's excessive risk.

22 And so you say all right. I'm

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1 going to pay them 5,000 bucks each. Now does
2 that make that unacceptable research protocol
3 because some people might do it for \$5,000. I
4 think you'd still say no. It's the
5 risk/benefit of the intervention that makes
6 this an unacceptable protocol. And the fact
7 that they're getting money doesn't then change
8 your risk/benefit ratio for your assessment of
9 the protocol.

10 DR. FOST: I'm trying to understand
11 why that is since we do think it's morally
12 appropriate to offer them the same amount of
13 money to do things that are much riskier than
14 that.

15 DR. WILFOND: Let me try to help
16 with that.

17 I agree with Jeff's example. I
18 think the distinction that we're trying to
19 make is the initial assessment of the benefits
20 and risks of the research, whether the
21 research should even be offered. And the
22 issue of payment is actually what's motivating

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1 it to be in the research.

2 So imagine instead the IRB actually
3 thought that whatever the liver biopsy was
4 acceptable to do -- in other words, they
5 actually the benefit risk was such that it was
6 acceptable to do -- it just turned out that
7 nobody actually decided to sign up because who
8 wants to have a liver biopsy. And so they may
9 have increased the price to \$5,000 and people
10 signed up. That's different than the initial
11 evaluation of the IRB to change its view
12 because of the payments.

13 MR. GLANTZ: I think if we're
14 asking if the research has benefit -- what
15 you're saying is that the research doesn't
16 have any more benefit than getting a job
17 sweeping the streets. Then it's all the same.
18 I just don't see why it's considered a
19 benefit of the research.

20 DR. FOST: I'm not discussing that
21 at all.

22 MR. GLANTZ: Okay.

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1 DR. FOST: I'm asking why research
2 that has no benefit whatsoever to the person
3 who's volunteering for it -- let me put it
4 another way.

5 We ask somebody if they're
6 interested in a nontherapeutic liver biopsy.
7 We're not claiming at all that it has any
8 benefit to him. It's just a way of us to
9 advance knowledge. It has a social benefit.
10 He can make some money from it.

11 We think it's okay for him to join
12 the police force and have a one percent chance
13 of dying. Why is it not okay for him to have
14 a liver biopsy to make money with a .1 percent
15 chance of dying?

16 MR. GLANTZ: Because you're
17 focusing on him. And I'm focusing on the
18 doctors -- that you're focusing -- it seems to
19 me -- on the wrong party.

20 So this is like the conversation
21 about should I be able to sell my kidney.
22 Shouldn't I be able to sell both my kidneys,

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1 that if I'm willing to go on dialysis for the
2 rest of my life for \$100,000 -- so you're
3 making really a contract argument, I think,
4 what you can contract for as opposed to an
5 argument about what is it okay to do to a
6 human being.

7 DR. FOST: Why should we not think
8 of it as a contract?

9 MR. GLANTZ: You can think of it as
10 a contract. I'm just saying you shouldn't see
11 it as a benefit of the research.

12 DR. FOST: I'm not claiming it is.

13 DR. NELSON: Norm, since I was in
14 Wisconsin for a while -- this is an issue you
15 and I have debated for years. I haven't heard
16 anything new around the table, and I guess at
17 this point I'm just wondering if it makes
18 sense -- we are close to the break -- whether
19 we want to transition via break. But I think
20 we've heard enough of the diversity of views
21 around this particular issue that I'm not sure
22 it's productive -- particularly since it

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1 involves mainly adult decisionmaking -- to go
2 a lot further.

3 DR. FOST: I'm happy to drop it.
4 Because it's clearly a majority view on it.

5 But I think it does have extensions
6 to children. And I think we haven't actually
7 gotten to the bottom of it. But that's fine.
8 We can move on.

9 So since we are approaching the
10 break, let's see if I can sum up what I think
11 we have so far. And people can correct me or
12 modify it.

13 It sounds like there's clearly a
14 nearly unanimous view that placebo groups
15 cannot be considered to have prospect of
16 benefit, at least in studies such as this one.

17 There may be different situations.

18 Number two, it sounds like
19 inclusion benefit is not something that this
20 group thinks in general is sufficient to
21 warrant a study, that there either has to be
22 direct benefit of the components or it has to

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1 be minimal risk.

2 Did I get that right? Again,
3 there's a minority view on all these things.
4 But that's clearly the nearly unanimous view.

5 Three, that the questions about
6 placebo apply also to whether it's a placebo
7 group over the course of the trial or run-in
8 and run-out, the same questions arise that it
9 has to be minimal risk to justify it.

10 Four, some questions have been
11 raised with some support about whether having
12 an active control of standard therapy should
13 be considered a prospect of benefit. Again,
14 not to say it's wrong to do, but that it may
15 not be appropriate nomenclature.

16 Did I get all that right?

17 Any other conclusions that anybody
18 thinks we reached from what we talked about so
19 far?

20 If not, this might be an
21 appropriate place to break. And then we can
22 move on to some of the other issues.

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1 Good. Okay. Thank you.

2 DR. NELSON: So what time would you
3 like people to come back?

4 DR. FOST: 3:20. Thanks.

5 (Whereupon, the above-entitled
6 matter went off the record at 3:06 p.m. and
7 resumed at 3:20 p.m.) DR. FOST: The
8 next set of questions then relates to risks
9 and appropriateness of the risks.

10 So in the example at hand, the
11 placebo run-in and run-out group and the
12 control group -- but let's take the control
13 group out of it, since people think it's
14 inappropriate. But the run-in and the run-out
15 thing, and exposing these kids to risk -- oh,
16 excuse me. People didn't yet veto the placebo
17 group. They thought it might be okay on
18 grounds not of prospect of benefit but of
19 risk.

20 So let's re-visit then these three
21 placebo groups for a minute, and see if people
22 think they're ethically acceptable for other

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1 reasons than prospect of benefit, namely that
2 it's minimal risk or just a minor increment
3 over minimal. So let's start with the placebo
4 group.

5 Does anyone think the placebo group
6 is justified, not on the grounds of prospect
7 of benefit, but on grounds of acceptable risk?

8 If not, say why not. What position do people
9 have on the placebo group with a different
10 rationale?

11 DR. WILFOND: As I said before, I
12 think the biggest problem with the placebo
13 group is the number of exacerbations prior to
14 withdrawal from the study, and in a study that
15 wouldn't require that to occur. I think there
16 might be other studies in which, depending
17 upon the design, you might still allow
18 exacerbations more than one time, depending on
19 the objectives of the study, but not for this
20 study.

21 DR. FOST: Let me just understand
22 that.

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1 Because the exacerbations cause
2 discomfort, or permanent disability, or what
3 is it about the exacerbations that's
4 troubling?

5 DR. WILFOND: Discomfort. In other
6 words, I think the discomfort of having an
7 asthma exacerbation shouldn't be minimized.
8 It's disruptive to the child. It's disruptive
9 for the family. You have maybe a trip to the
10 ER, an extra trip to the doctor. I don't
11 think it should be considered to be the same
12 as just having blood drawn or some other sort
13 of minor discomfort.

14 DR. FOST: So not permanent harm
15 yet?

16 DR. WILFOND: No.

17 DR. FOST: And Alex?

18 DR. KON: I guess I have a question
19 and then a statement.

20 So I guess my first question is,
21 having seen kids die from asthma attacks, I
22 guess my question would be for a child with

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1 mild persistent asthma, is that a risk for
2 these children or not? Because I've seen some
3 kids who seem to have pretty mild asthma and
4 come in on death's door. And I'm not sure if
5 they've just been misdiagnosed as having mild
6 persistent asthma and end up dying from an
7 asthma exacerbation, or if in fact they had
8 more significant asthma and were just
9 misdiagnosed.

10 DR. WILFOND: You're raising a fair
11 question. And it's always hard to really know
12 the answer to that.

13 So one of the things that happens
14 often in trials, they'll do a number of things
15 to try to screen out people who they think are
16 likely to be really sick based upon previous
17 ICU admissions. And what also happens often
18 if there is a placebo run-in, it's actually to
19 screen out people who are too sick rather than
20 not sick enough. So I think it's plausible
21 you can do a pretty good job of trying to
22 identify those really sick patients who could

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1 run into trouble. Then the issue really is
2 just having an exacerbation.

3 But again, the exacerbation happens
4 right before the kid=s test in school the next
5 day, and he misses his field trip. There's a
6 lot of bad things that happen that I don't
7 think I'd want to trivialize.

8 DR. FOST: Alex and Steve.

9 DR. KON: So then my second would
10 be the statement half which is I think, given
11 our previous discussion that many reasonable
12 parents and good physicians might, for a child
13 just like this, opt to take them off of
14 inhaled corticosteroids and try them on a
15 leukotriene inhibitor or something else, makes
16 me believe that, while I'm still uncomfortable
17 saying that the placebo arm has the potential
18 for direct benefit, I don't think it's
19 unreasonable to say that the placebo arm might
20 be consistent with the standard-of-care, in
21 which case I think it would be reasonable to
22 say that perhaps it meets the criteria for

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1 minimal risk because it's still within the
2 bounds of standard-of-care. It's still
3 consistent with what the child might otherwise
4 encounter in their routine care. And so I
5 think that it might be reasonable under 404.

6 DR. JOFFE: So I'm just looking at
7 the New England Journal paper that was
8 included in our packet from the CAMP group
9 that was published in 2000.

10 And so this was a study comparing
11 200 micrograms of budesonide, so the standard
12 care intervention to placebo. And then there
13 was a third nedocormil. And these were kids
14 with mild to moderate asthma. So the disease
15 spectrum in there included kids who were more
16 ill than the kids in our hypothetical study.
17 So that is a caveat.

18 And so the primary endpoint was
19 FEV1. And there was no difference in FEV1 or
20 FEC. However, there were a lot of differences
21 in clinical endpoints -- children given
22 budesonide also had lower airway

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1 responsiveness to methacholine, fewer
2 hospitalizations -- 2.5 versus 4.4 per 100
3 person-years -- fewer urgent care visits to a
4 caregiver -- 12 versus 22 per 100 person-years
5 -- greater reduction in the need for albuterol
6 for symptoms, fewer courses of prednisone, and
7 a smaller percentage of days on which
8 additional asthma medications were need.

9 So if that's an estimate of what
10 could be expected in this study and this
11 caveat I think about this being milder kids is
12 important. And it doesn't look like this
13 article breaks out the mild kids versus the
14 moderate kids. And those would be helpful
15 information. Then that at least gives a sense
16 of the magnitude of sort of excess risk that
17 we can expect that kids assigned to the
18 placebo arm will be exposed to. And that does
19 seem to be nontrivial.

20 On the other hand, it's hard to
21 argue that one couldn't include a control arm
22 in a study that was consistent with acceptable

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1 if not recommended care out in the community.

2 DR. FOST: Would a more aggressive
3 rescue strategy solve that problem? Or would
4 that screw up the design because you'd have
5 too many dropouts?

6 DR. WILFOND: Yes. There's a
7 number of studies.

8 Again, this is not my specific area
9 of focus. But my impression is that there's a
10 number of studies now that are being designed
11 where often the endpoints will be time to
12 first exacerbation as a way of trying to do
13 comparisons between things. Again, this data
14 as Steve pointed out, was really very helpful
15 because we now know this as well as other
16 studies gives us a pretty clear sense of the
17 natural history for a cohort of people who
18 remained untreated for a year. And so I think
19 the idea is we don't need to repeat this
20 study, but we can use placebos when we need to
21 but just have appropriate rescue approaches so
22 they don't stay on more than they need to.

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1 DR. FOST: Alex, you likened this
2 possibly to the risk that a child might
3 encounter in the course of routine care, which
4 is within the definition of minimal risk. But
5 that's one of the criticisms of the definition
6 of minimal risk is that it gets interpreted to
7 include things like that. And there's some --
8 maybe you can tell us where SACHRP is going on
9 this -- but there are some who think that what
10 was intended was a well-baby check or health
11 supervision for a healthy child because
12 otherwise you wind up with nephrologists
13 saying routine care in my office is a kidney
14 biopsy, an asthmatoologist saying routine care
15 includes a lot of exacerbations.

16 Jeff, can you illuminate us on
17 where SACHRP is headed on that?

18 DR. BOTKIN: Yes. I think SACHRP
19 agreed with the Institute of Medicine in
20 suggesting that the definition ought to be not
21 relative to the status of the child, but an
22 absolute. So minimal risk in the context of

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1 average healthy child living in a safe
2 environment. So the idea that because some
3 kids play football that the risks of football
4 are acceptable in a minimal risk trial, we
5 wanted to say that's not an appropriate way to
6 think about that definition.

7 DR. FOST: Alex?

8 DR. KON: So I agree. And I didn't
9 mean to imply that we would be looking at the
10 risk relative to a child with asthma.

11 But I think what we're talking
12 about or what I meant to be discussing was
13 that we're talking about doing something that
14 would be considered within the standard-of-
15 care for that child, which I think if we're
16 talking about for example a child with
17 pyelonephritis, if the standard-of-care is
18 giving that child steroids, I think, while
19 we're not talking about then judging the risk
20 of putting this child on steroids vis a vis
21 their position as being a child with
22 glomerulonephritis, I think if what we're

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1 saying though is that the current standard-of-
2 care is to put that child on steroids, that
3 doing so does not place them at higher risks
4 than they would otherwise be. I think that
5 that's perhaps a subtle but a very real
6 distinction.

7 DR. NELSON: It would be helpful to
8 try to move away from a particular discussion
9 of whether this hypothetical case is or is not
10 acceptable more towards the analytical
11 questions of what standard would one hold it
12 to.

13 What I actually hear Alex arguing
14 is that the incremental research risk -- not
15 minimal risk -- that the incremental research
16 risk between standard-of-care and going into
17 the trial, which is clearly related to the
18 budesonide arm, might apply to the placebo
19 arm. I personally think that's a debatable
20 factual assertion since here it's a 12-month
21 placebo. But putting that aside, the broader
22 question is if in fact the incremental

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1 research risk is no different than what you
2 might receive in standard-of-care, one could
3 approach that as an analytical principle. I'd
4 be more interested in asking the question and
5 hearing people reflect on if that's not the
6 case rather than saying it is the case in this
7 case because I'd prefer to hear how one might
8 expand that to other cases.

9 I might also point out, the CAMP
10 trial was a four-year placebo-controlled
11 trial. So the data that was cited that was,
12 quote, nontrivial, it did reach statistical
13 significance. It was a four-year trial. And
14 so one of the questions is, what's the
15 standard that we would hold a placebo-
16 controlled arm that's withholding known
17 effective treatment -- what standard would we
18 use to apply that in the context of Subpart D,
19 independent of whether we think this arm in
20 this hypothetical case does or doesn't meet
21 that standard, which is less helpful.

22 DR. FOST: Ben?

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1 DR. WILFOND: In terms of
2 standards, I want to come back to actually one
3 of your points about scientific necessity.
4 And I want to distinguish between scientific
5 necessity in the way that you responded to one
6 of my earlier questions about why we needed a
7 control group which had to do with sort of the
8 ability to do a study well.

9 I want to bracket that aside and
10 talk about the issue of the justification for
11 a placebo, because the question being asked is
12 one of real significant importance. And I
13 think what I see is that there's a real range
14 of asthma trials, some of which are really
15 designed to answer questions that will
16 actually guide clinicians in how to treat
17 asthma better, whereas other ones are just
18 trying to find out how this drug works
19 compared to other drugs and things that are
20 actually probably not terribly relevant to the
21 actual clinician or patient trying to make
22 clinical decisions. So that would be one

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1 justification that I would want for placebos
2 will be one that answers a really important
3 clinical question.

4 DR. BOTKIN: Yes, which is why I
5 think I'd look at the placebo group under a
6 406-type category for the component analysis.

7 From my perspective, putting kids
8 at increased risk for asthma exacerbation and
9 having every expectation that that's going to
10 happen with these kids potentially multiple
11 times is more than minimal risk, more
12 questionable whether it's a minor increase
13 over minimal risk. And if it fits that risk
14 criteria, then you still have to fit the other
15 criteria, which is it has to be of significant
16 or critical value to the understanding of the
17 condition that the kids have.

18 And I guess I would question this
19 study or this hypothetical on that basis as
20 well if indeed there's at least preliminary
21 evidence that the growth inhibition that
22 inhaled steroids provide is transient and of

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1 small magnitude, then the question would be
2 whether one could expose kids to a minor
3 increase over minimal risk for the purposes of
4 demonstrating an agent that has at best small
5 or negligible clinical value.

6 DR. NELSON: Norm, just two
7 comments.

8 For the 406, it's 50.53 since this
9 is an FDA panel.

10 And all of the data about whether
11 it is or is not an important clinical question
12 is not the point on the table. So I would
13 just leave that as an open question.

14 DR. FOST: But since Jeff raised
15 50.53, I'd like to ask. It's a good
16 opportunity to talk about one other
17 problematic part of that which is commensurate
18 with the child's other experiences. And this
19 seems to me a good example of why that's been
20 problematic, just because he's had ten
21 exacerbations before and knows what they're
22 like, it doesn't follow that therefore it's

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1 okay.

2 And the way that was intended was
3 for nontherapeutic research in which the
4 notion was that the child's use to having
5 venipunctures or used to having spinal taps.
6 But even there, it seemed to me problematic to
7 assume that because the child's had ten of
8 these that the 11th one is going to be more
9 okay for him than it would be for somebody
10 who's had none.

11 One more comment about that which
12 seems to me might be a generalizable
13 principle. It appears elsewhere in the
14 documents.

15 But I think IRBs commonly weigh
16 these matters as whether they're true of the
17 study in general or not, rather than whether
18 they're true of each individual child who's in
19 the study. That is, I think it might make
20 sense if it were a case-by-case analysis. If
21 Junior -- and this is -- it really boils down
22 to an assent issue -- if Junior's not bothered

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1 by these, and there's no objective medical
2 harm, then it's commensurate with his
3 experience and he doesn't mind. And that's
4 the spirit in which it was intended. But if
5 he's very troubled by his exacerbations and
6 gets very anxious by them and so on, then he
7 should be excluded.

8 Steve?

9 DR. JOFFE: So two points.

10 I think on this issue of
11 commensurability, a recent publication from
12 some of the leadership of the SACHRP group
13 argued that the reason for this
14 commensurability requirement was not for sort
15 of risk/benefit purpose, but rather because if
16 it was commensurate, then children and their
17 parents would be more likely to be able to
18 give valid permission, consent, assent --
19 whatever you want to call it -- to doing it to
20 participation because they have a better
21 chance of understanding what the risks are and
22 what the procedures will be like to go through

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1 than other children -- other families -- who
2 have no idea what the particular risks and
3 experiences would be like.

4 And then the second point I want to
5 make -- I don't know if this at least a
6 partial answer to your question a moment ago,
7 Skip -- is again looking back at the CAMP
8 studies. So if this is reflective of the
9 experience in our hypothetical study, the
10 incremental risk is essentially two
11 hospitalizations for 100 person-years or over
12 the one-year period of this study, an excess
13 risk of 1 in 50 chance that any individual
14 child will require hospitalization.

15 So I feel comfortable saying that
16 that's not minimal risk. Whether that's minor
17 increment over minimal risk I think is a
18 harder conversation. I need to be convinced a
19 little bit that that is consistent with what
20 we mean by a minor increment.

21 So both the thought process of what
22 is the incremental risk to the population as

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1 compared with what their experience is likely
2 to be -- what standard-of-care -- and then how
3 do we assess that incremental risk in terms of
4 the various risk standards that we have, I
5 think is the generalizable approach that I
6 would take to assessing a case like this were
7 I sitting on an IRB.

8 DR. FOST: Where do you come out on
9 it?

10 DR. JOFFE: Well, I come out
11 wanting to hear why it should be considered --
12 it's not a trivial risk. I'm comfortable it's
13 not minimal risk. So for anybody who wants to
14 argue that it is a minor increment or minimal
15 risk, I'm open to the arguments.

16 DR. FOST: Does anybody want to
17 make the case? Ben?

18 DR. WILFOND: I don't want to make
19 the case, but I want to ask Skip to make the
20 case. I'll explain why I'm asking it.

21 Skip, remember the paper that you
22 wrote with Laney a couple years ago? My

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1 recollection of this two-page paper that was
2 in I think -- was it JPeds -- that I thought
3 what you were trying to do in that paper if I
4 recall was really try to argue against that
5 distinction between a minor increase or
6 minimal risk and say we really ought to be
7 thinking of these as it relates to the
8 benefits. But I don't recall if I got that
9 right. And I hope you know which I'm
10 referring to.

11 DR. NELSON: It's a commentary in
12 response to another article that basically
13 suggested that the issue of minimal risk and
14 minor increase over minimal risk could be
15 viewed from the standpoint of parental
16 decision-making.

17 On the other hand, at this point I
18 do not think that the IRB system as a whole is
19 reliable enough to basically be able to make
20 these distinctions in a way that would not
21 open -- even based on my own recommendations
22 -- to more serious abuse.

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1 So I would take that paper and file
2 it in the interesting ethical discussion
3 category as opposed to a meaningful regulatory
4 proposal, if I can be clear on that.

5 And I don't think it's my purpose
6 here -- again, I want to emphasize, these
7 cases are meant -- hearing how people would
8 approach the assessment of risk, I think we've
9 gone far enough. I don't really care to
10 comment on what my own view of the particular
11 risk of this particular hypothetical protocol
12 is.

13 DR. KON: So Steve, I think to me
14 the crux really comes down to -- in reading
15 through the New England Journal article, I was
16 sort of struck that what they were really
17 talking about were the children with moderate
18 persistent asthma. And I may be wrong about
19 that. And I think therein lies the crux,
20 because I would agree that if we're talking
21 about those types of incidents, I have a hard
22 time saying that that would be merely a minor

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1 increase over minimal risk. But I'm not sure
2 100 percent. I need to think more about it.

3 I think I was more struck with the
4 concept that for these children with mild
5 persistent asthma that you could actually find
6 a cohort of these children who was receiving
7 standard-of-care and care that pediatric
8 pulmonologists would say yes, they're
9 receiving excellent care, who were not on
10 inhaled corticosteroids. And to me, therein
11 lies the bigger crux.

12 And thank you, Skip, for pointing
13 out. I think really what we're talking about
14 is the incremental risk. And so if you could
15 find a cohort that fit in with the category of
16 the placebo arm, for example, that were
17 receiving what would be considered standard-
18 of-care, that the only incremental risk to
19 those individuals of being in the study was
20 that people were following them to look at
21 their growth velocity. To me, that is where I
22 would think that it fits into minimal risk, or

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1 certainly a minor increase over minimal risk.

2 But I think the key question is,
3 are those children really receiving the
4 standard-of-care, and what's the incremental
5 risk for those children to be in the study.
6 And I know, Skip, you were looking more for
7 sort of general concepts, but to me that's
8 really the hallmark of the general concept is
9 whether or not the children who are on that
10 arm would still be considered to be receiving
11 the standard-of-care.

12 And based on that New England
13 Journal article, for those children that were
14 in that cohort, I certainly don't think that
15 you could say that they were. But I think
16 therein lies the crux of the question.

17 DR. NELSON: But Alex, let me press
18 you on the distinction.

19 The arguments of the clarified
20 Declaration of Helsinki and of ICH E10 is that
21 there can be a deviation from the standard-of-
22 care as long as it meets the language that I

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1 had put up there and suggested that that meets
2 the minor increase over minimal risk. So it
3 might be the case that one could design a
4 trial where there is no incremental research
5 risk. If you could, then I think everybody
6 would agree, wonderful, that makes it easy.

7 The example -- although perhaps it
8 wasn't clear -- is to say is you could easily
9 take kids on inhaled corticosteroids and stop
10 them for the purpose of the run-in of the
11 placebo, if that would meet an acceptable
12 standard. What I've heard from others is that
13 it would if it only was no more than a minor
14 increase over minimal risk. That's a very
15 different argument from saying the incremental
16 research risk is only minimal risk. Those are
17 really two different standards. And we seem
18 to be kind of bouncing back and forth a little
19 bit between them.

20 So I just want to keep those clear.

21 DR. WILFOND: To respond to Alex, I
22 think one of the challenges of using the

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1 standard-of-care as a blanket term is that the
2 standard-of-care constantly changes. In fact,
3 back to using clinical analogies, one thing I
4 often do tell my patients with asthma is that
5 one of the few things I'm confident of is that
6 whatever is working on them now, in five years
7 will be completely wrong. In other words, the
8 standard-of-care is always evolving. And it
9 only evolves because we do research that
10 challenges a standard-of-care.

11 I think the issue is figuring out
12 how to sort of push the envelope safely to
13 answer those questions that don't expose
14 people to too much risk. And at some point
15 and under some circumstances, that might
16 involve using placebos. So it's not just
17 standard-of-care, it's what the risk is for
18 those folks.

19 DR. FOST: Len?

20 MR. GLANTZ: So in terms of
21 standard-of-care, what we've heard is that
22 some kids are taken off of corticosteroids

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1 just to see how they do. And what I'm
2 thinking of is a circumstance which is not
3 completely analogous but has to do with
4 removing people from anti-psychotic
5 medications to see how they do. And that's
6 done differently depending on the population.

7 So a psychiatrist might say, gee, you seem to
8 be doing very well for the last year or two.
9 Let's see if we could wean you off. Right.
10 As opposed to a research study where we say
11 every third patient will be weaned off.

12 And so the fact that some people
13 get weaned off doesn't mean that it's a
14 standard-of-care in the context of a research
15 study. I don't know if this is making any
16 sense or I just made some sort of a leap. But
17 the fact that we sort of randomize kids into
18 coming off of corticosteroids seems to me to
19 not be a standard-of-care, because I think the
20 standard-of-care has to do with a physician
21 exercising his or her judgment in a particular
22 case.

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1 DR. WILFOND: This is the second
2 time you made that version of this point. And
3 I actually think that's a very well taken
4 point. Because it seems to me whether it's in
5 asthma or in psychiatric research, if you're
6 thinking about a trial that involves placebos,
7 perhaps one of the ways that you can actually
8 support the study ethically would be if you
9 could to actually only be enrolling those
10 folks who otherwise, because of their personal
11 circumstances, are thinking hey -- you know --
12 I'm actually thinking of going off this
13 medicine. And so regardless of which arm
14 they're randomized to, they'll have an
15 opportunity to be taken off the medicine in a
16 safe environment.

17 The problem is most studies don't
18 really work that way. We don't recruit that
19 way. But if we could recruit that way, those
20 would be the patients who I would be
21 recommending to clinical trials -- those folks
22 who want to get off the medicine.

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1 DR. FOST: It seems to me this is
2 another example of how there is a possible
3 prospect of benefit from being in a placebo
4 group.

5 The tendency in medicine is to
6 treat too much and for too long. The
7 evolution of many clinical trials is that less
8 was just as good -- I'm thinking of UTIs,
9 which when I was a medical student was six
10 weeks, then it was two weeks, then it was one
11 week. Then somebody found one dose of
12 amoxicillin could cure an uncomplicated UTI.

13 And convulsions. Children first
14 seizure 30 years ago were on for a decade or
15 more until John Freeman said, let's see if
16 that's really necessary. And it turned out
17 for the overwhelming majority, they never had
18 another seizure again, that is, in the placebo
19 group.

20 And there are many, many examples
21 of this. And this may be one of them in which
22 inhaled corticosteroids are good for you.

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1 Yes. But maybe you don't need to be on them
2 for five years or ten years. And being in a
3 trial in which there's a sort of you agree to
4 take a look. It's not a wild or crazy idea.
5 It's not irrational. And it may turn out to
6 be a benefit.

7 But I don't know how you find out
8 unless you have a placebo group.

9 MR. GLANTZ: Well, it wouldn't be
10 this trial. It would be a trial of a non-
11 treatment versus a treatment --

12 DR. FOST: I understand. I
13 understand. I agree with that.

14 Steve?

15 DR. JOFFE: I want to just point
16 out, Skip, in your comments to Alex and
17 pointing out the sort of different way that he
18 was framing things versus the ICH guidelines,
19 for example. That those ICH guidelines as I
20 understand them are written for adults, or not
21 written specifically with children in mind.
22 The Declaration of Helsinki's comments on

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1 placebos are not written specifically with
2 children in mind.

3 So it may well be that there are
4 trials that are ethical and acceptable to do
5 that involve placebos and withholding of known
6 effective therapy among consenting adults that
7 are not ethical to do among children on the
8 basis of proxy permission. And maybe this is
9 an example of such -- without coming to any
10 conclusions on that, there may be a gap
11 between what's permissible to do in adults
12 with respect to placebos and what's
13 permissible to do with children.

14 So I do think that the regulatory
15 language, which I think has a great deal of
16 value that we use to think about what's
17 acceptable to do in pediatrics needs to
18 layered on top of what might be considered
19 acceptable for an adult population.

20 DR. KON: So getting back to what
21 Leonard was saying just a couple of minutes
22 ago, I think that's an excellent point.

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1 And I think it sort of comes back
2 to this question of whether or not that arm is
3 truly standard-of-care. And I think your
4 point is very well taken that it may not be
5 standard-of-care for all kids with mild
6 persistent asthma, but that there is some
7 subsection of that group for whom coming off
8 would be standard-of-care. And I think this
9 goes back to what Ben was just talking about
10 that it has to be tailored to the individual.

11 And if you could only find those patients who
12 are already planning on going off, then you
13 would make the argument then that for those
14 children it is standard-of-care, which comes
15 back to this question of the incremental risk
16 of being in the study would be, I would
17 consider, minimal risk, because you're saying
18 that that's standard-of-care.

19 But I think therein lies the big
20 question is, what is your study population and
21 who are you really talking about. And if
22 you're talking about a group for whom coming

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1 off of steroids really is consistent with the
2 standard-of-care, then you're not increasing
3 the risk. But if you're saying well, it's not
4 really, then I think that becomes the much
5 bigger issue.

6 And then how do you parse out? Is
7 it merely a minor increase over minimal risk
8 or more than that really becomes the very
9 large question.

10 DR. FOST: But the way that would
11 work in the real world I think is if you ask
12 doctors in an asthma center do you have any
13 kids who you're thinking of taking off
14 steroids, we're doing a study. Given the
15 incentives of being in a study, they would
16 have no trouble finding kids who they think
17 should be considered to take. And I'm not
18 saying they'd be irrational or crazy in doing
19 so. But they probably would find many more
20 kids who were eligible for the study than left
21 to their own devices.

22 Steve?

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1 DR. JOFFE: I think there's a
2 general point here that maybe we can agree on,
3 which is that in some cases, doing less rather
4 than doing more may offer a prospect of direct
5 benefit.

6 So if the standard-of-care for
7 inhaled corticosteroids is indefinite,
8 preventative treatment, and there are credible
9 reasons to believe that after a year or two of
10 stability one can safely come off and we
11 decide to test that in a randomized trial
12 where half the participants are randomized to
13 come off and half of them are randomized to
14 stay on, and then we look at differences in
15 exacerbation rates, I have no difficulty
16 saying that treatment withdrawal in that
17 setting offers a prospect of direct benefit to
18 those kids who are assigned to that group.
19 That seems to me an intervention. The
20 intervention is to back off on something.

21 And we'll find out when the
22 experiment's over, that that may very well be

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1 better for those kids on average, all things
2 considered, than continuing on the steroids.

3 Again, of course that is a
4 different study than the one we're talking
5 about here. But I think the general point of
6 --

7 DR. FOST: Couldn't you combine
8 those two questions in one study?

9 DR. JOFFE: To go on and then to
10 come off? I suppose you could if you wanted
11 to do a study that looked at alternative
12 treatment pathways from beginning to end.

13 So the initial question is, for the
14 first year, do you do better if you go inhaled
15 corticosteroids and there's a comparator, and
16 then amongst those who were on the inhaled
17 corticosteroids, you then randomize them to
18 either come off or not. But I think then you
19 look at each component separately.

20 MR. GLANTZ: But withdrawal studies
21 don't necessarily have a placebo on them. You
22 withdraw because you want people to know that

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1 they're off the medication.

2 DR. FOST: You could randomize them
3 to a placebo inhaler.

4 MR. GLANTZ: Right. But I'm saying
5 if you wanted to see the effect of withdrawal
6 -- again, you would have almost the opposite
7 of the placebo effect. The people do worse
8 when they don't have an inhaler.

9 DR. FOST: Skip?

10 DR. NELSON: Just a comment on
11 study design.

12 The FDA's not that interested in
13 knowing if there is or is not a placebo
14 effect. They want to know if the drug works.

15 Randomized withdrawal has been used
16 a lot in hypertension, for example. And I
17 don't know if the paper's out on that.

18 Well, there's a couple of papers
19 that are in preparation or in press around
20 hypertension. And one particularly looked at
21 the adverse effects of the placebo groups.
22 Those are placebo-controlled trials. They

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1 start everybody on treatment, and then
2 determine efficacy by looking at the
3 difference when randomized to different doses.

4 And they're in a manuscript that's in
5 preparation and perhaps even in press. So
6 there were no increased adverse events in the
7 placebo group. It was just fine to be on
8 placebo in that context.

9 Again, these are short-term trials
10 of hypertension where you're looking at
11 basically at three to five millimeters of
12 mercury changes. So it's not a large context.

13 Norm, on the issue of risks, I'm
14 looking at some of the issues. You've really
15 touched on the first three under question 2, I
16 think -- those issues -- but haven't touched
17 on d. And I'm not sure if it's sort of clear
18 why I threw that in there as a question or
19 not, if you look at question 2 around the
20 risks of any monitoring procedures made
21 necessary.

22 You made the observation that

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1 there's not that many risky procedures in this
2 case. And I think that's true. But I had a
3 particular thing in mind when I put that
4 there. So --

5 DR. FOST: I'll give some other
6 examples in which you're --

7 DR. NELSON: Well, it's hard for me
8 to come up with a concrete case that I can
9 think of that's actually been included in a
10 research protocol.

11 But let's go with me on the
12 assumption that in fact if a placebo group is
13 thought to represent no more than a minor
14 increase over minimal risk relative to no
15 prospect of direct benefit, if that's in fact
16 the proper way to analyze not all perhaps, but
17 certain placebo-controlled trials. The
18 question would be if there is in fact a
19 monitoring procedure itself that exceeds that
20 level of risk if it's only made necessary
21 because you received the active intervention.

22 In other words --

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1 DR. FOST: A common one in asthma
2 is methacholine challenges. Do you want to
3 try that?

4 DR. NELSON: Well, if you read the
5 CAMP data, there's in fact no evidence that
6 any of that created a problem. So I think the
7 data would suggest that that's pretty
8 straightforward.

9 I was thinking of things more such
10 as whether there's an oncology example where
11 if you didn't receive active treatment,
12 there'd be no need for particularly invasive
13 biopsy or something. In other words, where in
14 fact you'd say the monitoring procedure made
15 necessary by the active intervention, if
16 you're on placebo you just would feel very
17 unsettled -- if you will, about having a
18 blinded trial that would have that kind of
19 monitoring procedure in it. That's the sort
20 of issue I was interested in hearing some
21 discussion about.

22 I don't have good examples. I

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1 personally don't think the methacholine
2 challenge is a good example.

3 DR. FOST: Terry and Ben?

4 MS. O'LONERGAN: I have an example.

5 Some of the humanized monoclonal antibody
6 studies in Type I diabetes that are designed
7 to delay destruction of beta cells, we now
8 have a trial that's going to be run with a
9 placebo arm with a placebo infusion over a
10 five-day period, twice in one year.

11 Routinely what we do is we put PICC
12 lines in these kids who are getting infusions
13 and are going to come back. So this is one
14 I'm that struggling with right now is that
15 what about the kids who are on a randomized
16 placebo, and it's blinded. Routinely these
17 kids would get a PICC line for monitoring
18 different functions. So is that an example
19 that would suffice?

20 DR. FOST: You had something.

21 DR. WILFOND: I've got two others.

22 One's not a placebo, but it does raise the

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1 issue of risk with no benefit. And these are
2 these phase 0 oncology trials who are giving
3 one dose of some sort of new agent that the
4 only way they can determine whether or not
5 there's any effect would be by doing a biopsy.

6 So that would be an example of one which
7 there's a risk of the intervention without
8 there being any benefit.

9 But that's not exactly the question
10 you asked. I think the one that's perhaps
11 more analogous might be there are a number of
12 studies in CF looking at gene transfer
13 research where they were placebo-controlled
14 and bronchoscopies were done, and the
15 bronchoscopies were done in everybody
16 regardless of whether they got the active
17 agent or the placebo.

18 The question's whether you think
19 bronchoscopy -- which I think is debatable --
20 where that would fit into that realm of
21 interventions.

22 DR. NELSON: Yes. My interest in

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1 asking is not to get us into debating the
2 risk/benefit of different procedures. I think
3 depending on how you do it, who does it, how
4 it's structured, the procedural sedation, et
5 cetera, et cetera, would impact on that.

6 I guess it was more to at least
7 raise in this group if you decide to break out
8 the placebo group based on the absence of a
9 prospect of direct benefit, there's more to
10 that than just looking at the risk of the
11 withholding of a treatment that they might
12 otherwise receive. There's also then the
13 risks of the various monitoring procedures
14 that are then thrown into the protocol, most
15 of which are usually are minimal risk or minor
16 increase over minimal risk. But
17 theoretically, potentially not.

18 So it was just to say that that's
19 another -- if you will -- twist on this story.

20 And that's why that d) is in there.

21 DR. FOST: I don't see it in my
22 outline, unless I've got the wrong one.

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1 Question 2?

2 DR. NELSON: Yes. Question 2. The
3 formatting got it under -- yes, it's down
4 there under c). It got somehow formatted and
5 didn't get it's own line.

6 DR. FOST: So monitoring procedures
7 obviously have to be subjected to the same
8 risk analysis, but it would be the same
9 considerations as for other risks. Right? Is
10 there any reason to think of them differently?

11 DR. NELSON: No, I don't. But I
12 honestly don't think that this degree of
13 sophistication is often applied to these kinds
14 of trials. But I guess that's the whole
15 purpose of our discussion.

16 DR. FOST: Steve and then Alex.

17 DR. JOFFE: So monitoring
18 procedures could be monitoring for efficacy or
19 surrogate efficacy endpoints. Or they could
20 be monitoring for adverse effects. And so I
21 guess both are on the table.

22 So let's talk about monitoring for

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1 adverse effects for a second. So if we have a
2 procedure to monitor for adverse effects, and
3 we don't know who's in the placebo group, but
4 if we did know we would be able to say with a
5 fair confidence that they're not at risk for
6 those adverse effects, that seems to me to
7 raise one set of issues.

8 If we're looking at efficacy or
9 surrogate efficacy kinds of endpoints, then I
10 guess the question is do we need to think
11 about that differently for those who are in
12 the placebo arm or the standard care arm
13 versus those who are in the intervention or
14 the new therapy arm. Because my understanding
15 of components analysis as applied to
16 deconstructing a study like this is one looks
17 at each intervention separately.

18 And so for example if we have a new
19 drug that offers a prospect of direct benefit
20 and half of those in the study are getting
21 that, then we are not allowed to use that
22 prospect of direct benefit related to that new

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1 drug to justify the risks of procedures that
2 might be done to measure study endpoints. So
3 is it really any different for those on the
4 placebo arm versus those who are on the active
5 treatment arm?

6 DR. NELSON: Maybe, maybe not. I
7 think if you've got -- and that goes to one of
8 two possibilities.

9 One possibility would be
10 considering that monitoring procedure or the
11 risks thereof against the prospect of direct
12 benefit under 50.52. In other words, the
13 risks and benefits need to be comparable.
14 Depending on the risks of the intervention
15 itself, let's imagine it has potential for
16 great benefit but in and of itself, it's not
17 risky, but then the monitoring procedures are.

18 You may have a little -- if you will --
19 benefit cash to spend to offset the monitoring
20 risks. So you may consider it that way.

21 Or if you've already spent all your
22 benefit on the risks of the intervention

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1 itself, then I agree that it's not too big of
2 a different issue whether you're on a placebo
3 group or got the active intervention if you've
4 got this monitoring procedure downstream.

5 But I could see it depending on the
6 case potentially playing out either way. That
7 was the intent of asking the question. And if
8 people think that that's a reasonable
9 approach, we don't necessarily have to explore
10 it in any more detail.

11 DR. WILFOND: Skip, if I can --
12 actually I want to tell people a story of a
13 trial that raised some interesting related
14 issues to risk and was motivated by when you
15 asked the last question about risk of
16 monitoring procedures. This was a study that
17 I reviewed about ten years ago because it
18 involved doing methacholine challenges and the
19 concern was that this was too risky. And of
20 course, like you said, after some discussion,
21 I said my recommendation was that this was not
22 a problem.

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1 But what was interesting in the
2 study is that this was a study that involved
3 recruiting people with asthma exacerbations
4 coming in to an ER for recruitment to a sort
5 of nontherapeutic trial that was trying to
6 look at the ability of video clips of
7 different movies to induce asthma
8 exacerbations based upon the emotional stimuli
9 of the video clips.

10 But the issue was that there was no
11 attempt at verifying whether or not they were
12 receiving appropriate asthma therapy. In
13 other words, so a patient came in and was not
14 on inhaled corticosteroids, no attempt was
15 made to think about whether they should or
16 shouldn't be on them because that was not the
17 purpose of the trial.

18 And so, that's not one of the
19 examples that you've given here. But it is
20 one that struck me as being relevant that
21 there can be risks of -- not directly related
22 to study, but risks related to the failure to

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1 offer what otherwise would be appropriate
2 treatment.

3 DR. NELSON: Quick question. Was
4 this an adult or a pediatric study?

5 DR. WILFOND: This was in
6 pediatrics.

7 DR. NELSON: Because I think that
8 would sort of begin to fit into the
9 alternative category. We haven't talked much
10 about that -- a little bit in alluding to it.

11 But the second component of 50.52
12 is that the risks/benefits are comparable to
13 the alternatives which implies that you're
14 informed about those.

15 Just FYI, the article that I
16 mentioned on the safety of placebo controls
17 and pediatric hypertension trials was
18 published in April in the journal
19 Hypertension. The first author Smith, P.B.
20 "B" is for Brian. I know him as Brian Smith.

21 DR. KON: So I think in some ways -
22 - and maybe I'm misunderstanding -- but I

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1 think some of what you're asking, Skip, sort
2 of comes back to something that Norm was
3 talking about a little bit earlier, was this
4 question of do we look at the risks and
5 benefits pre- or post-randomization. And I
6 think in many ways, that becomes very relevant
7 to this question of risks associated with
8 monitoring procedures, because in some
9 respects the way that I look at that then is
10 if we look at the risks and benefits pre-
11 randomization, that it's not really so much of
12 an issue. But if we look at the risks and
13 benefits post-randomization, that's where we
14 start running into the real problems.

15 And so I wonder if that might be
16 something interesting for us to think about a
17 little bit or not.

18 DR. FOST: I'm glad you raised it
19 because we didn't really pursue it.

20 My view is that after
21 randomization, it's easy to say, especially
22 if you have a pre-judgment that it's bad to be

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1 in the placebo group, which I don't.

2 Obviously you can't run the trial
3 if you allow people to start making judgments
4 after they're randomized. That is, they agree
5 to be in the trial or not to be in the trial.

6 They don't agree to be in the treatment
7 group, or in the new treatment group versus
8 the standard treatment. They agree to be in a
9 study where, by definition, there are going to
10 be winners and there are going to be losers
11 probably. Somebody is going to come out
12 better and somebody's going to come out worse.

13 And you think it's okay to invite people to
14 be in that trial because it meets other
15 criteria of an ethically sound trial.

16 But once you agree to be in it,
17 blinding is a component of it. And blinding
18 means blinding to who gets the biopsies and
19 who doesn't get the biopsies, and the whole
20 thing.

21 So it seems to me self-evident, but
22 maybe not to others, that it has to be handled

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1 as a package or not.

2 DR. WILFOND: Norm, help me
3 understand why is it that you would -- I
4 assume that you would believe that a placebo-
5 controlled trial of antibiotics for meningitis
6 is problematic. So explain why that's
7 problematic, given what you just said, because
8 there's a 50/50 chance of getting an
9 antibiotic and that's better than if I didn't
10 get anything.

11 DR. FOST: Well, first in a
12 population that had access to standard care,
13 obviously it would be exposing them to a
14 phenomenal risk of harm. But if you're
15 talking about a study -- Len's going to leave
16 the room -- but if you're talking a population
17 where nobody gets any care, that's what the
18 AZT short-course trials were. They were
19 withholding proven effective reducing
20 maternal-fetal transmission.

21 I didn't think there was anything
22 wrong with it. The CDC didn't. Lots of other

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1 people didn't. And people died. People died.

2 DR. WILFOND: Back to the one here.

3 Why is it problematic to do it in Madison?
4 Why would that study be wrong to do in
5 Madison?

6 DR. FOST: Because children -- none
7 of whom would die otherwise -- would now
8 suffer brain damage -- would be put at very
9 high risk of brain damage. That is, the trial
10 itself would be introducing a risk into those
11 children that previously didn't exist, whereas
12 in Biafra, the trial itself would not be
13 introducing a risk. It would be introducing a
14 benefit.

15 You'd be better off in Biafra being
16 in the trial and in Madison you'd be more
17 likely to be worse off by being in the trial.
18 The risk/benefit ratio is reversed.

19 DR. WILFOND: Of the whole trial?

20 DR. FOST: Of being in the trial.

21 DR. WILFOND: Got it.

22 DR. FOST: Steven?

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1 DR. JOFFE: So the conventional
2 answer to this -- which for the moment I
3 accept but maybe I'll be talked out of it by
4 the end of this meeting -- is that you look at
5 this post-randomization and you look at it arm
6 by arm.

7 And I think it gets to what Ben was
8 just trying to say, which is that the danger
9 is that if there's a very great potential for
10 benefit to the kids who happen to get
11 randomized to arm B, I would be uncomfortable
12 allowing that very great potential for benefit
13 to kids in arm B to outweigh or justify a very
14 great potential for harm to the kids in arm A.

15 So you'd have to come up with a situation
16 where there's a partially effective therapy
17 for a serious condition and somebody proposes
18 to do a trial comparing a new potentially
19 highly effective new therapy to placebo. And
20 nobody gets the old partially effective
21 therapy.

22 And I'd be very hard to imagine

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1 doing that because the excess risk that the
2 kids in the placebo arm get exposed to are
3 judged as excessive.

4 DR. FOST: Let me just make sure.
5 We're talking about a population that
6 previously had access to this treatment?

7 DR. WILFOND: Right.

8 DR. FOST: Right. No question.

9 Let me remind Ben that you were
10 part of a study in which 50 percent of the
11 children were exposed -- and their families --
12 to substantial harm.

13 DR. WILFOND: Oh, absolutely. But
14 again, it's this issue of the baseline. And
15 your answer was very helpful.

16 But just to follow that through,
17 let's replace meningitis again with asthma in
18 Madison. Again, we have a group of patients
19 who otherwise would all be on inhaled steroids
20 with all the caveats we've talked about
21 before.

22 So again, that trial that offered

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1 people a 50/50 chance of either on inhaled
2 steroids or placebo, wouldn't that make them
3 potentially worse off as a trial compared to
4 what they otherwise were getting?

5 DR. FOST: Well, possibly. It's
6 possible they might be better off if the
7 parents are making a truly informed choice,
8 they would join the trial because they see
9 some potential upsides, some potential
10 downsides. If the rescue strategies are sane,
11 the downsides are minimized.

12 I can see how an intelligent parent
13 might choose -- just like an intelligent
14 parent might choose to go off corticosteroids,
15 they might choose to not go on it in the first
16 place.

17 DR. WILFOND: But similarly, you
18 could also see how some studies could actually
19 make people worse off though, of that nature.

20 DR. FOST: Yes. Not this trial.

21 DR. WILFOND: No, not this trial.

22 DR. NELSON: With all due respect,

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1 we're getting back into the debate over the
2 inclusion benefit, which I don't think they'll
3 be anymore light rather than just more heat
4 shed by debating it, because I think the
5 positions are well articulated. And I don't
6 see a resolution of that.

7 But I don't see that as the issue
8 that was raised in the pre-randomization
9 versus both randomization analysis. That's
10 not the issue.

11 The question that's raised and the
12 distinction under, please consider this
13 distinction, I will confess; I used to a pre-
14 randomization advocate. In other words, to
15 argue that one group benefits, the other
16 doesn't, I would say sort of already pre-
17 judges the very nature of the scientific
18 conclusion that one's attempting to draw.

19 I'm not so sure of that argument,
20 because that argument at this point is
21 directed more towards the issue of the
22 efficacy of the intervention, not to whether

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1 or not the intervention itself offers the
2 prospect of direct benefit to any individual
3 child, which gets into what's the data around
4 that intervention which isn't data that would
5 then be available on the placebo, which is
6 very different than at the level of the
7 inclusion benefit, very different at the level
8 of the efficacy conclusions and the like.

9 So I am no longer, I'll confess, a
10 pre-randomization advocate in spite of what
11 I've said in the past at times. It's not
12 clear to me that that's the right way to parse
13 out a trial where the potential for direct
14 benefit is very different in the different
15 arms at the level of the nature of the
16 intervention itself, not at the level of the
17 inclusion benefit or at the level of the
18 outcome of the trial, which I think is
19 precisely why you're doing it in the first
20 place. You can posit that there's an
21 appropriate scientific uncertainty. But that
22 doesn't address in my mind the question of

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1 prospect of direct benefit and how you analyze
2 it.

3 So that's where that question is
4 coming from. This has been a big debate over
5 the years in the literature, as you all know.

6 And I'm not saying we'll necessarily decide
7 and agree at the end of the day about it. But
8 that's precisely the area I wanted to kind of
9 get some concentrated focus on, to see if we
10 can provide anymore light on it beyond what's
11 already been debated in the literature about
12 that topic.

13 DR. FOST: Alex?

14 DR. KON: So let me throw this out
15 there, because I think in many respects if
16 there's true equipoise, then one would argue
17 that both groups are at equal risk and have
18 the potential for equal benefit to some extent
19 because there's true equipoise.

20 But it seems to me that there are
21 certainly cases where we can look at the
22 children who are in one of the arm's study and

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1 say that for those children, the risk/benefit
2 ratio is very high, and that the potential for
3 that child to benefit doesn't come close to
4 the potential for that child to be harmed.
5 And so then I think from a theoretical
6 perspective, say we're taking 100 kids and 50
7 of them get randomized to one arm and 50 to
8 another, so then what we're saying is we're
9 going to put 50 kids at significant risk of
10 harm, and we're okay with that. And I'm not
11 so sure that I'm okay with that.

12 DR. NELSON: Well, I think there
13 needs to be two points of clarification.

14 First of all, your use of equipoise
15 precisely combines the two concepts in a way
16 that doesn't make clear how you're using it.
17 In a placebo-controlled trial, there is
18 scientific uncertainty about the intervention
19 compared to the placebo. So there's equipoise
20 in the first sense.

21 But the placebo-controlled group
22 may well be not receiving a treatment that is

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1 known to be effective, even if we've
2 restricted it to only a minor increase over
3 minimal risk. You decided to introduce
4 significant risk. I did not. All right? So,
5 that's where the -- if you will -- I use this
6 in a true, Greek, rhetorical sense or the
7 rhetoric of equipoise I think needs to be
8 unpacked in a way that helps clarify the
9 issue.

10 I think I agree with the way you
11 ended up. But the issue is how do you analyze
12 that trial, even if there's scientific
13 uncertainty between the two arms, and so
14 therefore there is, quote, equipoise in a
15 scientific sense. But yet, there's not
16 equipoise in that one has appropriately in a
17 situation of either incremental research risks
18 -- as we've already discussed -- where we
19 consider the risk of withholding appropriate
20 because it has a scientific justification.
21 And then how do we analyze that trial? Are we
22 still going to lump them all together? Or are

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1 we going to split them apart? That's, in my
2 mind, the question.

3 DR. BOTKIN: Well, I've certainly
4 come around to the post-randomization point of
5 view. But I would say that it depends on the
6 study.

7 You can get obviously the same
8 endpoint through two different analyses. And
9 to see if I understand how Norm would take a
10 look at the randomization, pre-randomization
11 process -- you've got some kids who are -- so
12 a therapeutic trial let=s say, because there's
13 therapy involved, prospect of benefit. Some
14 kids are going to get an intervention. Some
15 kids are going to get placebo.

16 Or if you assess that pre-
17 randomization, then everybody has some
18 prospect of benefit. But in some
19 circumstances, that won't be acceptable
20 because the risk/benefit ratio may be too
21 great between the intervention group and the
22 nonintervention group, like with the

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1 meningitis trial. Right?

2 The problem I see in analyzing it
3 that way rather than post-randomization is
4 that there becomes no ceiling on the level of
5 risk that you can pose to the kids in the
6 placebo arm of that trial. As long as the IRB
7 becomes convinced that the benefits to half of
8 the group -- the intervention group -- justify
9 the risk posed to the other kids, whereas in a
10 post-randomization analysis, your group that
11 is randomized to the placebo has to fall
12 either under minimal risk or a minor increase
13 over minimal risk. So there's a ceiling to
14 that assessment, which is, from my point of
15 view, more protective and more appropriate for
16 the kids rather than trying to lump them all
17 together under the 405 or 52 criteria.

18 Am I making sense with that line?

19 DR. FOST: Yes. That makes sense
20 for a population that has access to standard-
21 of-care. But I think the question as Ben was
22 raising it was, might there be populations in

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1 which that's not the case and the analysis
2 would be different.

3 Skip, could I just ask you and
4 Jeff, does the post-randomization perspective
5 then prohibit monitoring procedures that are
6 more than minimal risk because you will never
7 know whether you're applying them to somebody
8 who might be in the placebo group?

9 DR. NELSON: No. It would be under
10 the minor increase over minimal risk.

11 And that's precisely where that
12 question emerged is, if you think the placebo
13 group appropriately falls under that category
14 in any given trial, then the monitoring
15 procedures themselves could be no more than
16 that level of risk.

17 Now, I'll be honest. I can't come
18 up with many examples in my own mind that
19 necessarily meet that kind of situation,
20 personally. I don't think we don't need to
21 start debating the different procedures and
22 decide whether we do or don't. But that would

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1 be the implications from the standpoint of the
2 standard that would be applied using this
3 approach.

4 DR. FOST: Examples that come up
5 are biopsies, not just cancer patients, but
6 kidney trials and liver trials. Do you
7 consider those a minor increment over minimal?

8 DR. NELSON: Yes. I'd have to look
9 at trials -- once we've stated the standard,
10 I'm not sure it's that productive to begin to
11 debate individual procedures, Norm, because
12 that's really not part of the focus.

13 DR. FOST: Len?

14 MR. GLANTZ: You know, I feel like
15 I'm not really understanding the question or
16 the issue, because it seems to me isn't the
17 question the totality of the risks -- without
18 breaking them down into individual procedures
19 -- whether a monitoring exercise in some way
20 increases the risk. Don't you look at all the
21 risks together? So if you had a whole bunch
22 of minor increases over minimal risk, couldn't

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1 that amount to more than minimal risk?

2 I'm not understanding why we're
3 just looking at the monitoring issue as
4 opposed to looking at what does that add to
5 the entire nature of the research that's being
6 done on the kid.

7 DR. NELSON: I think you have to
8 look at both.

9 MR. GLANTZ: Yes. I'm saying would
10 you look at all of these.

11 DR. NELSON: Right. I'm just
12 focusing on sort of trying to give a
13 particular case.

14 One implication in oncology, I do
15 know of a particular protocol that decided to
16 limit the approach of procedural sedation to a
17 certain biopsy so that it fit a minor increase
18 over minimal risk because it was a research-
19 only procedure, whereas what they would
20 routinely do for anesthetic during a
21 clinically-indicated biopsy was different. So
22 that was a decision made based on whether it

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1 was a prospect of direct benefit procedure or
2 not.

3 So that in my mind is an example
4 where a decision was made to do that. This
5 was years ago, and not FDA knowledge in my
6 prior IRB chair experience. So this has
7 nothing to do with an FDA-regulated produced
8 in my knowledge.

9 I have to always put that caveat in
10 everything I say.

11 DR. FOST: Yes. Steve?

12 DR. JOFFE: So if one adopts the
13 post-randomization approach, then your
14 justification process of risk/benefit is an
15 intrapersonal risk/benefit justification.
16 It's within the individual child who is
17 assigned to arm A or arm B or whatever. It's
18 -- I'm sorry?

19 DR. NELSON: Well, by group. It's
20 not Johnny versus Susie. It's just --

21 DR. JOFFE: A judgment for all the
22 kids assigned to arm A, all the kids assigned

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1 to arm B.

2 DR. NELSON: Right.

3 DR. JOFFE: And judging the risks
4 versus benefit within the child for all the
5 kids assigned to a particular group.

6 On the other hand, if one adopts
7 the pre-randomization approach, then you get
8 into an interpersonal risk/benefit
9 justification where you're suggesting that the
10 risks to kids in group A -- or the benefits to
11 kids in group A -- may justify the risk to
12 kids in group B, which is something that is 1)
13 very hard to do, and 2) unless one tries to in
14 sort of a consequentialist sense try to weigh
15 those risks and benefits on the same scale --
16 which we all know the difficulties with doing
17 that -- that's really the only way you can go
18 about making those sorts of interpersonal
19 judgments. Otherwise, we get into issues of
20 incommensurability of risks and benefits that
21 I think are very hard to parse out.

22 And I think it's very difficult to

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1 claim that we can allow benefits to group A to
2 justify risk to group B, which is what the
3 pre-randomization approach forces you to do.

4 DR. FOST: So let's see where we
5 are. Let me try to summarize some points of
6 agreement. This is post-break issues.

7 So placebo arms -- whether they're
8 long-term or wash-in or wash-outs -- can only
9 or should be justified on grounds of being of
10 minimal risk or a minor increment over
11 minimal. There's some uncertainty whether
12 that was the case in this study. But that's
13 not central.

14 Monitoring procedures should be
15 assessed in the same way and that, therefore -
16 - and that would be independent of which arm
17 that it's in the placebo group -- the child
18 may be in the placebo group. That would
19 require being minimal risk or minor increment
20 of risk.

21 And those two things lead to the
22 third conclusion, which is this. What we're

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1 calling the post-randomization view -- that
2 assessments of whether risks are appropriate
3 or not have to include the possibility of
4 being in the placebo group. So therefore,
5 risk calculations have to be adjusted to that
6 group.

7 Are there other issues about which
8 people might say there's consensus? We can go
9 back over Skip's questions.

10 Inclusion benefit was rejected more
11 or less as a relevant consideration both on
12 empiric grounds and conceptual grounds.

13 Stop me when I'm going astray here.

14 Monitoring procedures, we talked
15 about. And the same analysis would apply to
16 discontinuation studies.

17 Other questions that we have not
18 addressed, or other conclusions that people
19 want to say we drew? Steve?

20 DR. JOFFE: I want to go back to a
21 point that Skip raised and just pose it as a
22 question to the group because we let it go

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1 past, but maybe there's controversy there
2 which is, you alluded to this idea of benefit
3 cash. So if you're in the intervention group
4 that offers a prospect of direct benefit, so
5 we haven't spent that entire prospect
6 justifying the risks that come along with that
7 intervention. And so maybe we have some extra
8 benefit cash to spend on monitoring procedures
9 of other risk-bearing procedures that go along
10 with it.

11 And I was struck by that concept of
12 having benefit cash to spend on other things.

13 So maybe you could say more about what you
14 mean by that and maybe people want to take
15 issue with it, or maybe endorse it.

16 DR. NELSON: Well, I guess this is
17 a little bit at the edge of my thinking. So
18 if you'll allow me to think about it and if I
19 say something stupid, admit that I said
20 something stupid.

21 Imagine how you make decisions
22 about clinical interventions. If you think,

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1 say, in the oncology setting and you're sort
2 of justifying -- there's a lot of things that
3 are done to sort of follow up on the results
4 of an intervention, biopsy. I mean, there's a
5 lot of things that are done to assess
6 response, to then guide further therapy and
7 those kinds of things.

8 So what I'm really raising is in
9 many ways those could be lumped -- if you will
10 -- under monitoring procedures. There's
11 information that is gleaned that we often
12 might say that they offer the prospect of
13 direct benefit, I think is often how an IRB
14 may evaluate that. But some of them may
15 simply be to assess are you in the right place
16 with that therapy. There may be a clinical
17 decision downstream that that will affect.

18 So part of it is saying that maybe
19 the risks of a monitoring procedure itself may
20 well be wrapped up in the sort of risk/benefit
21 assessment of the very nature of the
22 intervention that you've done in the first

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1 place that are sort of part of that
2 risk/benefit evaluation, which is fairly
3 standard relative to what we do clinically.
4 And in fact, if you remember the quote, the
5 National Commission suggested that that same
6 kind of risk/benefit in the case of
7 interventions that offered the prospect of
8 direct benefit is in fact how we ought to
9 think about those risks and benefits.

10 So that's kind of what I was
11 raising there that a monitoring procedure
12 might fit into those kinds of risk/benefit
13 considerations in the way that we do it
14 clinically, which would be very different than
15 something that's just in there because there's
16 a research question that needs to be addressed
17 -- what happened to the biomarkers --
18 whatever. We could come up with just --
19 research question -- period. Absolutely no
20 impact. The data may not even feed back to
21 the individual setting. It may not even be
22 available to clinicians. It's not an issue

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1 that would have any impact on the judgment of
2 response or triage or further response, et
3 cetera. That, in my mind, is very different.

4 And if one has this kind of
5 clinical risk/benefit going on within a
6 protocol and someone's on placebo -- I like
7 your comment about using the benefit to one
8 group to justify the risk to another -- it
9 gets you into that kind of quandary.

10 So that was kind of what I was
11 getting at. Maybe that was controversial.
12 Maybe not.

13 DR. JOFFE: So if we separate out
14 things that are done -- maybe in your most
15 recent clarification you suggested that you
16 wouldn't be willing to spend your benefit cash
17 on measuring scientific endpoints that have no
18 potential benefit to feed back to the
19 participant.

20 So there has been a vigorous debate
21 in the oncology setting of we're studying an
22 early drug. It's targeted at a particular

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1 pathway. And it becomes important to know,
2 for example, if kids with a certain
3 somatically-acquired mutation in their tumor
4 tissue are more or less likely to respond to
5 the drug, or whether the pathway is
6 successfully targeted and you need a biopsy to
7 do either of those things. And so can you do
8 a deep biopsy on a kid in the context of
9 either looking at predictors of the
10 effectiveness of a new drug or monitoring the
11 surrogate sort of biological effectiveness of
12 the new drug. And there are some in our
13 oncology world who want to say you just can't
14 do that -- period.

15 Now it's becoming relatively
16 routine to do that, hopefully with the high
17 level of informed consent in the adult world.

18 And there's I think often scientific value to
19 doing that in the pediatric world. But it
20 obviously does raise serious considerations.

21 And then there are some of us who
22 want to be able to say well, if the scientific

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1 question is really important and the drug
2 development really hinges upon being able to
3 answer this question of predictive markers or
4 evaluating the effect of the drug on a
5 pathway, then if it's absolutely necessary, we
6 should be able to do that, although some of
7 those studies, because of that measurement
8 procedure may need -- I guess it's 50.54, 407
9 review. So some of them may need to go to a
10 federal panel.

11 So that's part one.

12 DR. NELSON: Yes. And I think you
13 brought up that category which is not the
14 topic of this conversation.

15 But I also just want to say that
16 just because one may argue that there are
17 ethical constraints -- if you will-- that are
18 framed within the three categories that -- the
19 main one we're focusing on -- prospect of
20 direct benefit -- the other two that have
21 come in indirectly -- minimal risk and minor
22 increase over minimal risk -- that's not to

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1 say that there may not be good ethical
2 justifications for proceeding under the fourth
3 category.

4 So I'm not foreclosing that in
5 terms of ethical justifications, but that then
6 becomes a different pathway.

7 DR. BOTKIN: Let me be clear about
8 what you're saying with that particular
9 example, which I think may be a good one.

10 It seems to me that in that
11 context, the relative value of the new agent
12 or of the science becomes, to a large extent,
13 irrelevant because of the ceiling that the
14 pediatric risk criteria includes. So if it is
15 a biopsy that's not going to be used for any
16 clinical decision-making, then it's not within
17 the prospect of direct benefit. And component
18 analysis I think requires you to keep the risk
19 of that to a minor increase over minimal risk.

20 Right? And if you're above that, then we're
21 talking 407 or 55. Am I right?

22 DR. JOFFE: The other possibility

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1 is a monitoring procedure, because your new
2 agent requires some monitoring for safety.
3 And you feel like you can't safely give this
4 agent unless you have some tests. Let's say
5 it's an imaging procedure. And let's say that
6 because it's a population of very young
7 children, you require general anesthesia or
8 deep sedation in order to be able to keep the
9 kids still for the imaging procedure.

10 So if you've got a blinded study,
11 you can't just do the imaging procedure and
12 the half that are getting the drug because
13 that will un-blind the study. So in order to
14 keep the blind, you have to do it in both
15 groups.

16 So that I think gets directly to
17 the kind of issue that you were raising. The
18 general anesthesia probably would be judged
19 more than a minor increment, though people may
20 want to disagree with that. But that would be
21 my impression.

22 And there it is very closely tied

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1 to being able to -- there's a benefit to doing
2 it to the kids in the intervention group
3 because that's part of being able to do the
4 intervention safely, but there's not a
5 corresponding benefit to doing it with the
6 kids in the placebo group.

7 So can you justify doing that
8 simply to maintain the blind? Is that an
9 example?

10 DR. NELSON: You've put your finger
11 right on the crux of the problem, I think.

12 DR. JOFFE: And it may be that that
13 is not approvable within 50.52, that because
14 if we're taking a post-randomization approach,
15 then that is exposing kids in the placebo
16 group to an intervention that imposes more
17 than a minor increase over minimal risk. And
18 therefore, if it's sufficiently important, we
19 ought to go to 50.54 review and maybe if the
20 case is compelling, we'll be able to go ahead.

21 DR. FOST: So if you were on the
22 50.54 panel -- as you will be -- how would you

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1 address it? How would you think about it?
2 Let's say it was somebody else's study and
3 they were coming to this group for that
4 question. And it's general anesthesia.

5 DR. FOST: You'd have to have a
6 very just extraordinary, compelling case made
7 that it was critically important to the safety
8 of the study and the intervention group, that
9 the whole study was sufficiently important to
10 impose this level of risk on the half of the
11 kids who ended up in the placebo group --
12 questions like that.

13 So I wouldn't want to rule it out,
14 but it seems to me there would be a pretty
15 substantial kind of burden of proof that would
16 be involved in justifying imposing general
17 anesthesia on a group of kids merely to
18 maintain a blind.

19 DR. FOST: But that's what the reg
20 said. That's why you come to this group
21 because the investigator's arguing that it's
22 compelling. Otherwise, they wouldn't be here

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1 and wouldn't go through all the effort.

2 So you can imagine circumstances if
3 it's a very important scientific question that
4 really could advance.

5 DR. JOFFE: I can imagine
6 circumstances. But I guess the proof is in
7 the specifics of the individual study that
8 comes forward.

9 DR. FOST: Alex?

10 DR. KON: Yes. I would agree. I
11 think therein lies the whole point is, you
12 really need the facts of the individual case.

13 And the other issue that comes up
14 is the informed permission and assent process
15 at that point I think would require
16 significantly more scrutiny than otherwise
17 would. But I think that those two issues
18 become very large.

19 DR. FOST: Terry?

20 MS. O'LONERGAN: This is the very
21 thing I was talking about with putting in a
22 PICC line in a kid to use anesthesia.

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1 In talking to parents, these are
2 parents who have two or three children with
3 Type 2 diabetes. They have younger kids that
4 have the potential to have their frank onset
5 delayed. And the parents are very well aware.

6 And they're still willing to take the risk.
7 They think that it's justifiable, even if
8 their kid is in the placebo arm.

9 And as a scientific advisory
10 committee, we struggle quite a bit with this
11 because we did sort of the post-randomization,
12 that there is no direct prospect of direct
13 benefit for kids who are in the placebo, who
14 are subjected to sedation, and the PICC line
15 and the blood draws. And it's quite high
16 blood draws. There are five, six percent over
17 about three weeks.

18 Our IRB passed it. But it's a
19 consideration. What about blood draws that
20 are really not doing anything for the placebo
21 group over the short course?

22 DR. NELSON: Well again, I would

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1 hesitate for us to begin to provide advice
2 around specific questions that is somewhat
3 decontextualized from a full analysis of the
4 protocol. Although I hear your pain.

5 So I guess the question is, what
6 else can be said to explore it. Around this
7 case, but then talking about these sort of
8 general principles, the separation of a
9 placebo group separate from the inclusion
10 relative to scientific necessity uncertainty,
11 which is assumed to be the case, the post-
12 randomization analysis of whether that group
13 benefits within the context of prospect of
14 direct benefit, and then if you've broken them
15 apart, how you assess risk I think is just an
16 important conceptual approach that, just
17 having outlined that conceptual approach is
18 useful beyond then saying, well how do you
19 drive that downstream into individual
20 protocols.

21 I have no idea personally. I don't
22 think it would impact on this case. That's

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1 partly why I chose the case. The analysis is
2 important, but in this case you'd probably end
3 up in the same place. But there may well be
4 other protocols where that would not be the
5 case that you would end up in the same place
6 depending on which approach you took.

7 MS. O'LONERGAN: I'm interested in
8 Alex's comment about how we would do consent,
9 or would we approach consent and assent
10 differently in cases where the post-
11 randomization analysis comes up with a
12 situation like this. I'd like to hear more
13 about what you would do.

14 DR. KON: Well, I think from my
15 perspective that would need to be -- I do
16 think it would need to go a federal panel.
17 And I think if it did so, and it was approved
18 because it was very important, then I think
19 what becomes crucial is for parents to
20 understand very clearly that X percent of the
21 children who are involved in the study are
22 actually going to be in a study that would not

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1 be approvable by a local IRB because the risks
2 are significant without the prospect of direct
3 benefit. And that they need to have a very
4 clear understanding that their child is at
5 very real risk of being in that group and
6 being harmed without the prospect that they
7 would benefit.

8 And I think that that needs to be
9 made very clear in language that people would
10 understand and separate it in a way that makes
11 it not just part of a 30-page consent
12 document, but that really stands out so that
13 people understand that this is something
14 that's significantly different.

15 DR. FOST: Well, I'd think you'd do
16 more than that. I think this would be an
17 example of where consent monitoring should be
18 required. And we do that for things far short
19 of 50.54 proposals, that is, if you think it's
20 really important that parents and the kids --
21 if they're old enough -- understand it, then
22 you ought to check and make sure they

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1 understand it.

2 Steve?

3 DR. JOFFE: So I think to amplify
4 what was said, one of the important
5 implications for the consent/assent permission
6 process is presenting risks and benefits by
7 arm. If we've said that we need to assess
8 them by arm, then we also need to present them
9 and help parents and kids think about them by
10 arm.

11 There's one other set of procedures
12 that is going to raise similar issues which
13 is, any time sham procedures are needed to
14 administer the intervention, I think the same
15 issues will come up. So I don't foresee that
16 we're going to do a pediatric analogue of the
17 sham arthroscopy trial that was published in
18 the New England Journal about six years ago on
19 adults. But to think back to the growth
20 hormone -- the human growth hormone for
21 idiopathic short stature -- that was a
22 randomized trial, and half of them got sham

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1 injections and half of them got active
2 injections of growth hormone. And this was
3 for a prolonged period of time. And the
4 question that came up in that trial was how to
5 justify the sham injections.

6 And this will come up again with
7 drugs that need to be given parenterally and
8 for whatever reason need placebo controls or
9 need to be blinded. And so I think the
10 thought process around the sham intervention
11 will have to be the same as the thought
12 process around monitoring procedures that you
13 don't blind.

14 DR. NELSON: I agree. And I think
15 the trial you just mentioned is one of the
16 first articles that came out that raised this
17 post-randomization, pre-randomization analysis
18 question.

19 Just for people's information, some
20 of this you may know. Others may not know.
21 To date, the only referrals that have come to
22 this panel -- I mention this is the fourth

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1 meeting; there have been three previous
2 meetings -- there were referrals prior to that
3 that were not part of a public process because
4 we didn't have a procedure at that point in
5 time. But the majority of those also fit in
6 this category, but not all of them.

7 All of them have been non-
8 beneficial research that involves a research
9 procedure thought to be only a minor increase
10 over minimal risk, but the children did not
11 have a condition. And so they were felt to be
12 healthy. And therefore, it didn't fit on that
13 category.

14 There has been no referral to date.

15 There could be tomorrow for all I know. But
16 there has been no referral that falls into the
17 category that we've been talking about where,
18 in fact, the sort of risk elevates above that
19 for children with a condition. I think it's
20 an important issue, but I just want to make it
21 clear to people that there have to date not
22 been referrals that fit into that category.

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1 They've all been in that other category.

2 I would welcome, personally,
3 referrals that expand us beyond that health
4 children getting minor increase over minimal
5 risk procedures so we can begin to develop
6 more experience with that. But to date, none
7 of that has happened.

8 DR. FOST: Skip, are there other
9 questions that we haven't either addressed or
10 tried to identify consensus on?

11 DR. NELSON: I don't think so. I'm
12 open to people feeling there are. I do sense
13 a lagging of the spirit. Maybe I'm just
14 projecting.

15 DR. FOST: Call it task
16 accomplished.

17 DR. NELSON: Well, that plus it
18 seems a little warmer in here, et cetera, et
19 cetera.

20 I don't see issues that have not
21 been put on the table. I think we've got
22 another take on these issues tomorrow which

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1 will be very different. And unless there's
2 something other people think we haven't
3 addressed, I don't have any further topics I
4 would want you to explore.

5 So it's the Chair's prerogative
6 what you want to do at this point.

7 DR. FOST: Any other issues the
8 group wants to raise? If not, we're reconvene
9 at 8:30 in the morning, or --

10 DR. NELSON: It's eight o'clock.

11 DR. FOST: Eight o'clock.

12 DR. NELSON: The opening portion is
13 a public comment period. I'm not sure if
14 we've had any people to sign up at this point.

15 But if not, then we'll just launch into our
16 discussion and the case is scheduled sort of
17 late morning. And then there'll be time to
18 sort of generalize. And whether we finish at
19 1:00 or earlier, my view is we'll finish no
20 later than 1:00. But depending if we exhaust
21 the topic, then we could finish earlier.

22 But I will say I thank everyone for

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1 their participation and discussion. And I
2 think this has been quite helpful.

3 (Whereupon, at 4:44 p.m., the
4 hearing was adjourned, to be reconvened at
5 8:00 a.m., Tuesday, June 9, 2008.)
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