

1 raised that we ought to be working towards
2 approval of a vaccine for at-risk populations
3 at the same time, rather than bringing them
4 into clinical practice -- adults first, and
5 adolescents at some later date. Because I'm
6 not sure I can see the counter-argument.
7 There are obviously questions about how best
8 to get there in terms of designing the
9 research trajectory, but I certainly endorse
10 the objective.

11 DR. WILFOND: There is, I think,
12 one possible counter-argument, which is that -
13 - I'm actually looking at the graph that I
14 guess was from Alan Fix's paper that he was an
15 author on, which is this really nice table
16 that I guess not everybody here has, but he
17 has this wonderful table that tries to make
18 that point about the involvement of
19 adolescents in phase 3 trials such that, at
20 the time of licensure, all that's happening
21 together.

22 But what occurred to me is that

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1 there could be some circumstances where,
2 depending upon when you start those trials, or
3 how those trials are recruiting, that it may
4 very well be that there=s a -- even though
5 they're happening simultaneously, there is
6 enough evidence in the adult population that
7 one could actually otherwise approve the drug
8 earlier than waiting for the rest of the data
9 to come in. And so you could imagine -- so
10 you would actually be delaying the adult
11 licensure in order to make sure that the
12 adolescent got caught up. And I guess that
13 would be the counter-argument.

14 DR. FOST: Alan?

15 DR. FIX: With the Committee=s
16 permission, I=ll lay in on this one, because I
17 don't think the argument was sure that the
18 indications are there for adolescents when
19 they're made for adults. Things may come up,
20 and maybe that kind of situation is one we
21 have to think about, and work on how it would
22 play out. But the ultimate aim is to make the

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1 indication available for both as soon as it's
2 possible to make it.

3 I think the scenario we were given
4 this morning was one in which there would be a
5 phase 2b study first, which would give you the
6 indications of whether there's sufficient data
7 to enroll adolescents, as well, when you get
8 to that pivotal study. And it's either the
9 involvement of adolescents in that pivotal
10 study, or acceptance that you'll be able to
11 use the data in adults only to go back and
12 extrapolate to adolescents.

13 DR. FOST: Steve?

14 DR. JOFFE: If it were to come to
15 pass that a vaccine were approved for 18 and
16 up, let's say, and there was still a
17 perception of a need to do efficacy studies in
18 adults before licensing, or an indication for
19 that population, I predict we'll be back in
20 this room having arguments about whether it's
21 acceptable to be doing a placebo-controlled
22 study in adolescents when the vaccine is being

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1 widely used in the adult population.

2 DR. FOST: Skip?

3 DR. NELSON: I thought it might be
4 helpful to just make a general comment about
5 pediatric product development not specific to
6 this particular arena. And it allows me also
7 to at least introduce to people the notion
8 that we now have similar legislation
9 stimulating pediatric product development in
10 Europe, where companies can get an additional
11 six months of - they don't call it exclusivity
12 - but basically to do pediatric studies.

13 What's interesting in that setting
14 is they now have a requirement that a
15 pediatric investigational plan be submitted to
16 the European Medicinal Agency at the end of
17 phase 1. Now, that doesn't say you start
18 doing your pediatric testing at the end of
19 phase 1, but it at least says you're thinking
20 about, and then you can begin to have a
21 discussion about what information do you need
22 out of adult phase 1, adult phase 2 to begin

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1 to sort of sequentially develop it. There are
2 circumstances where you may develop things in
3 pediatrics earlier. There are circumstances
4 where you may do it later. I just wouldn't
5 want people to come away with the impression
6 that, simply because one is saying you need
7 certain information in adults, whether it's
8 efficacy or other information prior to
9 initiating pediatric studies, that that=s
10 always going to be post-marketing or post-
11 licensure studies. I think that would be an
12 inappropriate conclusion.

13 The ideal circumstance is that
14 these two are sort of coming forward, and have
15 been thought about in a coherent and
16 consistent fashion so that the idea of, at the
17 point that it's on the market, you've got the
18 appropriate pediatric information available,
19 is there. Sometimes that will be post-
20 marketing; sometimes it doesn't necessarily
21 have to be.

22 But just to say that this is just

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1 some general comments on that. I wouldn't
2 interpret asking for a certain degree of
3 evidence that is promising to imply that it
4 would only be post-licensure.

5 DR. FOST: Other comments? If not,
6 I think we can start on our afternoon session,
7 which begins with a presentation by Skip
8 Nelson on choice of control group, and then
9 segueing into a presentation of the second
10 hypothetical case.

11 DR. NELSON: I'll stand anyway,
12 since it's nice to stand a little bit.

13 DR. FOST: I agree. Ben suggested
14 that we read this comment from the person who
15 couldn't be here, because it may help orient
16 our discussion, and we can read it again
17 tomorrow.

18 This is from Dr. Bernard Yablin,
19 and it's an email.

20 "Since I don't have medical
21 clearance, wheelchair needs, or arrangements
22 for remuneration in travel and hotel, I would

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1 like to submit the following questions:

2 1) In any pediatric study on
3 asthma, how would it be possible to account
4 for genomic variations in response to
5 medications, e.g., antileukotrienes, in each
6 treatment arm?

7 And 2) In the periventricular
8 injury study, would there be different time
9 tables for imaging studies to hopefully
10 determine the onset as soon as possible? Dr.
11 Bernard Yablin."

12 Okay. Carry on.

13 DR. NELSON: Thank you, Norm.

14 Now, the intent of this
15 presentation is to lay out before you some
16 concepts that you may find helpful, or you may
17 not find helpful, as you tackle the
18 hypothetical asthma case, because this case,
19 even though there was, presumably, a control
20 group in your last case, raises much more
21 explicitly issues around choice of control
22 group. And so I wanted to put some of these

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1 ideas before you, assuming -- there we go.

2 Now of course, choice of control
3 group - this is taken from ICH E10, published
4 in May, 2001 - is a critical decision which
5 impacts on the scientific validity and ethical
6 acceptability of clinical investigation. The
7 proper control group allows for discrimination
8 between patient outcomes caused by the test
9 treatment, and outcomes caused by other
10 factors, such as the natural progression of
11 the disease, observer or patient expectations,
12 or other treatments.

13 Now, there are a number of
14 different types of control groups. The one
15 that generates the most interest is placebo,
16 and that could be either a two- or three-arm
17 study. I might point out that the basic
18 distinction is between a concurrent control
19 group, in other words, a control group that's
20 selected from the same population, usually by
21 randomization, although not necessarily, and
22 treated concurrently. The other approach

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1 would be a nonconcurrent control group, which
2 is referred to as an external. It could
3 include historical controls, since they may
4 not be temporally related, regardless of
5 comparative treatment.

6 Among concurrent control groups,
7 there are four types of control groups: a
8 placebo control group; an active or positive
9 control group; a dose response - in other
10 words, you could give a low dose and a high
11 dose of the drug, and if you demonstrate
12 differences, that could be considered evidence
13 of efficacy. That could also be a short
14 course versus a long course, which might be a
15 fairly standard antibiotic trial design,
16 assuming that you could determine a non-
17 inferiority margin, which we'll get to. And
18 then, of course, no treatment. The problem
19 with no treatment is it's not blinded, and one
20 of the issues of reducing bias within the
21 assessment of clinical trials is to design it
22 in a way that you can minimize bias, both in

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1 terms of those that are enrolled in the trial,
2 but also the investigators who are conducting
3 it.

4 Now, this notion of assay
5 sensitivity, what that basically means is that
6 the clinical trial that you have before you is
7 able to distinguish an effective treatment
8 from a less effective or ineffective
9 treatment. And often the way that this is
10 assured is you either add a known positive, or
11 a known negative, which often, most likely, is
12 a placebo, since adding a negative that has
13 activity often doesn't make sense. Or adding
14 a negative that is, in fact, negative, would
15 be considered harmful. As a third study arm,
16 this can serve as a measure of assay
17 sensitivity, because then you can assess
18 whether the observed difference between your
19 study drug and the other controlled
20 interventions is, in fact, reproduced with
21 that known active or negative control. So
22 there you'll often have a three-arm study to

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1 assure that kind of assay sensitivity.

2 Now, the concept of equipoise is
3 one that has been around for a number of
4 years. There's a fair amount of discussion in
5 the literature about equipoise, including two
6 different notions that I've divided into these
7 two principles, if you will, of either
8 scientific or ethical. Now I don't mean by
9 that that the scientific component is not an
10 ethical aspect, but as a way of just trying to
11 identify these two components.

12 The first is the notion that, if
13 you're doing a research study, you should be,
14 in fact, genuinely uncertain, or at least have
15 a certain amount of indifference about the
16 relative merits of the interventions being
17 compared in the clinical investigation. Now
18 that doesn't mean you individually don't have
19 to believe in what you think might happen.
20 But the point is, there should be no data that
21 would already have answered the question. In
22 other words, you're uncertain about the answer

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1 to that question, which is precisely why
2 you're asking it. I think that notion of
3 scientific equipoise is fairly
4 uncontroversial. The amount of data you might
5 need to reach the point where you're not in
6 equipoise is a whole separate question.

7 The ethical one is the notion that
8 no patient subject should be randomized to an
9 intervention known to be inferior, either to
10 the study intervention, or to the known
11 effective treatment. The requirement for
12 scientific uncertainty and an ethical
13 obligation to provide proven effective therapy
14 are separate claims, and one should carefully
15 distinguish between these two senses when
16 using the concept of equipoise. So to the
17 extent that we want to use that term, I think
18 we need to specify how we're using it.

19 Now this is tied up closely with
20 the debate over placebo controls, which I'm
21 not going to discuss in any great detail. But
22 to at least illustrate that debate, the

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1 starting point for that debate, at least more
2 recently, is around the Declaration of
3 Helsinki, Version 2000, which paragraph 29
4 states, "The benefits, risks, burdens and
5 effectiveness of a new method should be tested
6 against those of the best current
7 prophylactic, diagnostic, and therapeutic
8 methods. This does not exclude the use of
9 placebo or no treatment in studies where no
10 proven prophylactic, diagnostic, or
11 therapeutic method exists."

12 Over the years, since that
13 statement and its inclusion in earlier
14 versions, there was a discussion about the
15 limits, if you will, of the extension to which
16 you would apply paragraph 29. And in 2002,
17 the World Medical Association General Assembly
18 adopted a note of clarification of paragraph
19 29, where they reaffirmed this position that
20 extreme care must be taken in making use of a
21 placebo-controlled trial, and that, in
22 general, this methodology should only be used

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1 in the absence of existing proven therapy.

2 However, a placebo-controlled trial
3 may be ethically acceptable, even if proven
4 therapies are available under the following
5 circumstances. Those circumstances are two.
6 The first is, where for compelling and
7 scientifically-sound methodological reasons,
8 its use is necessary to determine the efficacy
9 or safety of a prophylactic, diagnostic, or
10 therapeutic method - that refers back to that
11 principle of assay sensitivity - or, and I'll
12 comment on the or in a second, where a
13 prophylactic, diagnostic or therapeutic method
14 is being investigated for a minor condition,
15 and the patients who receive placebo will not
16 be subject to any additional risk of serious
17 or irreversible harm.

18 I'm going to show you the language
19 around the choice of control group from ICH
20 E10, which basically replaced the or - or
21 didn't replace it, since I think that actually
22 was written before this clarification - uses

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1 the word and. If you look closely at this,
2 this would mean that scientific assay
3 sensitivity would be more important than
4 avoiding the risk of a minor condition.

5 In fairness to the World Medical
6 Association, they're in the process of
7 revising the Declaration of Helsinki. And I
8 believe, although, since I'm not part of that
9 process, can't make any comments on it, that
10 this is one area that they're looking at as to
11 whether that small word, or, ought to be
12 altered to and.

13 Now, if you look at ICH E10, it
14 also starts with the notion that, as a general
15 rule, research subjects in the control group
16 of a trial of a diagnostic, therapeutic or
17 preventive intervention should receive an
18 established effective intervention. So that's
19 the default position. However, in some
20 circumstances, it may be ethically acceptable
21 to use an alternative comparator, such as a
22 placebo, or no treatment.

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1 And it goes through the
2 circumstances where a placebo may be used as
3 when there is no established effective
4 intervention. I think that's fairly
5 uncontroversial. Second, when withholding an
6 established effective intervention would
7 expose subjects to, at most, temporary
8 discomfort or delay in relief of symptoms.
9 And finally, when use of an established
10 effective intervention as comparator would not
11 yield scientifically reliable results, and the
12 use of placebo would not add any risk of
13 serious or irreversible harm to the subjects.

14 And that's the difference between the
15 clarification of the Declaration of Helsinki,
16 which would have the word or at that location.

17 A brief comment about component
18 analysis. The idea here is that you have a
19 protocol that includes a number of different
20 interventions, and you need to parse out those
21 interventions that offer the prospect of
22 direct benefit, and those interventions that

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1 do not offer the prospect of direct benefit.
2 There are those who see this as a recent
3 clarification, if you will.

4 The quote I give you is from the
5 National Commission's report on research
6 involving children that was published in the
7 Federal Register in 1978, but dates from 1977.

8 What I've done here is replaced their
9 recommendations two and five with the
10 regulatory references that now contain those
11 recommendations. And as you will see, the
12 National Commission saw component analysis as
13 a part of Subpart D, our existing pediatric
14 regulations.

15 Here's the quote: "To determine
16 the overall acceptability of the research, the
17 risk and anticipated benefit of activities
18 described in the protocol must be evaluated
19 individually, as well as collectively, as in
20 done in clinical practice. Research protocols
21 meeting the criteria of 21 CFR 50.52,@ which
22 we're discussing at this meeting, "regarding

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1 risk and benefit may be conducted or supported
2 provided the conditions of 56.111," which is
3 the more general recommendations," and the
4 requirements of 50.55," which is the assent
5 and permission, "will be met. If the research
6 also includes a purely investigative procedure
7 presenting more than minimal risk,@ in other
8 words, no prospect of direct benefit, "the
9 research should be reviewed under 21 CFR 50.53
10 with respect to such procedure." That's the
11 minor increase over minimal risk.

12 My only point in here is to just
13 have us be aware of component analysis, but
14 also recognize, as a historical point, that
15 this dates back to the very inception of the
16 pediatric regulations.

17 So the general ethical principles
18 of Subpart D, "Research involving children
19 either must present a balance of risks and
20 potential benefits comparable to the available
21 alternatives," which is 50.52, which is what
22 we're discussing, "or be restricted to minimal

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1 or low risk, absent direct benefit to the
2 child," which is 50.51 or 53, as I'd gone
3 through this morning. "Under 21 CFR 50,
4 Subpart D, withholding known effective
5 treatment from children enrolled in a control
6 group must present no more than a minor
7 increase over minimal risk,@ which would be a
8 way of harmonizing Subpart D and the ICH E10
9 choice of control group.

10 So having laid those out, and
11 perhaps before I just read through the case
12 that will guide our afternoon discussion, I
13 can stop there and see if there's any points
14 of clarification.

15 DR. FOST: Or comment.

16 DR. NELSON: Well, you're welcome
17 to comment, but you could also save your
18 comment to your own discussion.

19 DR. FOST: Steve?

20 DR. JOFFE: Skip, I wonder if you
21 could go back to the slides comparing the
22 Declaration of Helsinki "or" framework to the

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1 ICH "and" framework.

2 DR. NELSON: So there's Helsinki.

3 DR. JOFFE: So there's Helsinki,
4 and now go forward one or two.

5 So it seems one, placebo may be
6 used. So there's three bullets on that slide,
7 and I take it that the conjunction between
8 those three bullet is "or." So condition
9 number one, when there's no established
10 effective treatment may be met, or --

11 DR. NELSON: Yes, it's "or."
12 Right.

13 DR. JOFFE: And it seems that
14 number two is analogous to -- I forget if it
15 was the first or the second Helsinki
16 condition.

17 DR. NELSON: Well, it is, but it's
18 not totally inclusive. I mean, the Helsinki
19 one is basically adding the first one of assay
20 sensitivity and the second one about a minor
21 condition in a way that is -- and I apologize
22 for the directions here, because I'm not -- in

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1 a way that is more similar to the third
2 bullet. I realize the second bullet there is
3 similar to the second half of the third
4 bullet.

5 DR. JOFFE: Yes. So to me, it
6 seems like the third bullet here is simply
7 putting a risk -- it's very much analogous to
8 the Declaration of Helsinki assay sensitivity
9 point, but putting a risk cap on that, whereas
10 the Declaration of Helsinki one doesn't put an
11 explicit risk cap if you're going to go
12 forward with something under this assay
13 sensitivity consent of considerations.

14 DR. NELSON: Correct.

15 DR. JOFFE: Okay.

16 MS. VINING: Could you just comment
17 on the word compelling in the World Medical
18 Association definition -- the clarification on
19 page 29? How are they defining compelling in
20 order to use a placebo?

21 DR. NELSON: I don't think it's
22 appropriate for me to speculate on what they

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1 might have thought about compelling evidence,
2 because it's not my document, nor was I there
3 for any discussion of that.

4 That's the language they're using.

5 Maybe it's something along the lines of
6 exciting, or promising. I'm not sure.

7 I wouldn't have any particular
8 advice about how to interpret that.

9 DR. FOST: Other comments?

10 DR. NELSON: Not to make light of
11 it. It's an important question, but I can't
12 comment.

13 DR. FOST: I just want to hope that
14 our discussion here will not start with the
15 assumption that any of these documents are
16 ethically correct. That is -- Helsinki,
17 obviously, has been changed so often as to
18 show that it was imperfect from the beginning.

19 And similarly, the ICE documents and the
20 National Commission's documents are all what
21 groups of people thought at one time. But for
22 our purposes today, they all should be thought

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1 of as up for grabs.

2 DR. NELSON: Yes. And Norm, my
3 intent here was to sort of lay these on the
4 table as tools you may or may not choose to
5 pick up and use.

6 DR. FOST: It's a useful framework
7 for our discussion.

8 If there aren't any other general
9 comments, let's move on to the hypothetical.

10 DR. NELSON: Carlos, I think you
11 need to make this change. There we go.

12 So again, I'll just be going
13 through the case that is before you. The case
14 description, which is in prose on a couple of
15 pages, has been translated into slides.

16 But again, this is a hypothetical
17 case description, which uses published
18 information to construct a generic description
19 of a typical clinical investigation that is
20 not unique or specific to any particular
21 product, involves the study of inhaled
22 corticosteroid in children with mild

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1 persistent asthma.

2 The background is that a sponsor
3 has developed a new inhaled corticosteroid
4 that may have a decreased steroid-induced
5 effect on bone growth based on results from
6 cell culture and animal models. The
7 investigational or study inhaled
8 corticosteroid has been shown to be safe and
9 effective for the treatment of adolescents and
10 adults, meaning 12 years of age and older,
11 with asthma. The sponsor now wants to
12 demonstrate that the study ICS is both safe
13 and effective for the treatment of children
14 with asthma, and minimizes the adverse effect
15 on growth as measured by prepubescent growth
16 velocity.

17 As part of the pediatric clinical
18 program, the sponsor is proposing a year-long
19 growth study. The proposed study is a
20 randomized, double-blind, double-dummy
21 parallel group, placebo-controlled - a lot of
22 buzz words in there - 56-week study to

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1 evaluate the safety and efficacy of two
2 different doses of the study ICS when
3 administered via metered-dose inhaler to
4 children between five to eight years of age
5 with mild persistent asthma. To assure assay
6 sensitivity, the study design also includes an
7 approved inhaled corticosteroid with known
8 effects on linear growth as a positive control
9 group.

10 After a placebo run-in period,
11 children with a history of mild persistent
12 asthma for a minimum of the six months will be
13 randomized in equal ratios to one of four
14 treatment arms. The first arm would be one
15 puff from the inhaler, which would give 100
16 micrograms twice a day of the study inhaled
17 corticosteroid, two puffs twice a day, which
18 would give 200 micrograms BID of study ICS,
19 200 micrograms BID of the comparator ICS,
20 which is the positive control, and then
21 matching image placebo for each drug. The
22 doses of the study ICS are chosen not to

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1 exceed the lowest dose found to be safe and
2 effective in adolescents. I might say there
3 is also a fourth arm in there, which would be
4 placebo-controlled.

5 In addition to meeting the 2007
6 National Asthma Education and Prevention
7 program criteria for mild, persistent asthma -
8 it has other criteria, but one of which is a
9 FEV1 at greater than 80 percent - enrolled
10 patients are required to be in Tanner stage 1,
11 and with heights and weights in the fifth to
12 95th percentile range for age. Those criteria
13 are there to allow it to be a study that
14 assesses growth. In addition, bone age, as
15 measured by wrist radiograph, should be less
16 than one year different from the patient's
17 chronological age. Children who used and
18 inhaled corticosteroids within six weeks, and
19 systemic corticosteroids within three months
20 of the first baseline visit, and during the
21 placebo run-in period, will be excluded.

22 Concurrent medications that are

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1 allowed include an approved leukotriene
2 modifier, whose effect on linear growth has
3 already been well characterized, provided that
4 this treatment was prescribed at least four
5 weeks prior to the study, and the dosing
6 regimen remains constant following
7 randomization. All subjects will be allowed
8 to use beta-agonists as needed throughout the
9 study.

10 Primary endpoints include a primary
11 safety endpoint of linear growth velocity
12 measured using a stadiometer. And a primary
13 efficacy variable is the forced expiratory
14 volume at one second, which is the FEV1.

15 For safety reasons, standard-of-
16 care guidelines based on the national
17 guidelines will be followed in the management
18 of all acute asthma exacerbations. Subjects
19 are allowed up to four rescue treatments with
20 oral corticosteroids during the trial before
21 being converted to open-label inhaled
22 corticosteroid. In addition, any subject

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1 experiencing one episode of life-threatening
2 asthma will also be converted to open-label
3 inhaled corticosteroid. These subjects will
4 remain in the study for the purpose of the
5 primary safety endpoint, and be considered a
6 treatment failure for the primary efficacy
7 variable.

8 The questions which I'll lay before
9 you, the first one starts with asking the
10 question about the potential benefits. Please
11 discuss the assessment of the potential
12 benefits of this clinical investigation for
13 the enrolled children.

14 Issues you may want to consider
15 include whether the potential benefits would
16 apply equally to both the intervention and
17 control groups, including the placebo group;
18 the distinction between benefits that may
19 occur as the direct result of the experimental
20 intervention, versus those that may occur from
21 inclusion in the clinical trial independent of
22 the experimental intervention - what's often

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1 called the inclusion benefit - and whether any
2 additional monitoring procedures required by
3 the administration of the experimental product
4 would be considered a direct benefit, or
5 evaluated as a risk that must be balanced by
6 the potential direct benefit of the
7 experimental product.

8 Question two, please discuss the
9 assessment of the risks of this clinical
10 investigation for the enrolled children.
11 Issues you may want to consider include the
12 risks of withholding the known effective
13 inhaled corticosteroid comparator from the two
14 experimental IC-inhaled corticosteroid arms
15 and of the negative placebo control arm, the
16 impact of the selection of subject population
17 on those risks, such as mild or moderate
18 persistent asthma; the role of other study
19 modifications, such as the use of other rescue
20 and/or controller medications, and d) the
21 risks of any monitoring procedures made
22 necessary by the experimental intervention.

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1 Question three asks you to then put
2 this all together. Please discuss the
3 analysis of this proposed trial under Subpart
4 D. In your discussion, please address whether
5 the different study arms should be evaluated
6 together. In other words, is one cohort
7 before randomization or separately, as
8 separate cohorts after randomization. Issues
9 you may want to consider include the
10 distinction between prospect of direct benefit
11 for each arm of the clinical study, and
12 efficacy as the primary objective of the
13 clinical study.

14 And that's the end of the
15 presentation.

16 Norm, if there's factual
17 clarifications about the case, I'm happy to
18 address those before you get into your
19 discussion.

20 DR. FOST: I had one.

21 DR. NELSON: If you don't mind, I'd
22 like to sit down to address it.

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1 DR. FOST: Please do.

2 A couple of your questions refer to
3 risks of monitoring, and the only monitoring I
4 saw - I may have missed it - is height with a
5 stadiometer - presumably riskless - and FEV1s,
6 which is certainly low risk. Was there some
7 other monitoring of this study that was risky
8 in some way?

9 DR. NELSON: The question is not
10 meant to imply that the risks of monitoring in
11 this case are worrisome. That would be
12 something you could discuss. But it's a
13 question then that could be perhaps
14 generalized to sort of look at the analysis of
15 other trials that might include riskier
16 monitoring.

17 DR. FOST: Yes. Okay. Other
18 factual questions? Steve?

19 DR. JOFFE: I'd like to ask Skip,
20 or Ben, as a pulmonologist, or anybody else
21 around the table who could answer this: if a
22 child who is eligible for this study went with

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1 his parents to a pediatrician, a really
2 outstanding pediatrician who is conversant in
3 the guidelines, and talked about therapeutic
4 options - let's put aside the study for the
5 moment - what would a first-class pediatrician
6 recommend to the family about appropriate
7 therapy for their child?

8 DR. FOST: Ben?

9 DR. WILFOND: It would depend on a
10 number of factors. It would depend on the
11 age, depend on other risk factors in the
12 child's history, number of exacerbations. But
13 assuming that some threshold of those were
14 met, then a decision would probably be made to
15 place that person on inhaled corticosteroids.

16 DR. JOFFE: As I read the case
17 first of all, it was prepubescent children, so
18 five to nine, or something like that.

19 And secondly, it was called mild
20 persistent asthma. I assume that is according
21 to the definition in the national guidelines,
22 for example. So for that subcategory of age

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1 and severity of disease.

2 DR. WILFOND: Okay. Yes. For
3 that, it would be inhaled corticosteroids.

4 DR. FOST: From your answer, I
5 assume that is what a good pediatrician should
6 do, not necessarily what they do do.

7 DR. WILFOND: And that is a
8 recommendation that's in the documents that --

9 DR. FOST: I didn't mean it
10 facetiously. That is, we know that standard-
11 of-care doesn't comport to guidelines more
12 often than not. So in the real world, the
13 child actually might not be exposed to
14 whatever the risk of steroids are. But the
15 presumption is that that's not in his or her
16 interests to be omitted.

17 Alex, and then Len.

18 DR. KON: So it's actually on the
19 same line as Steve's question, because I was
20 looking through the national guidelines, and
21 I'm just looking on page 54 of the guidelines
22 for diagnosis and management of asthma. And

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1 it looks like, you know, we're talking about
2 step 2, which is where patients this age with
3 this diagnosis would come in.

4 And it says the preferred treatment
5 is low-dose inhaled corticosteroids, but
6 alternate treatments include cromolyn, long-
7 acting beta-agonists -- I'm having a hard time
8 reading because it's small here --

9 DR. FOST: Leukotrienes.

10 DR. KON: -- leukotrienes or
11 theophylline.

12 And so my question was sort of
13 really on the same vein of how much preferred
14 are the inhaled corticosteroids, and how
15 alternative are the alternate therapies? You
16 know, how strong is the evidence that that's
17 really important? I guess what I'm trying to
18 understand is, if rather than being on inhaled
19 corticosteroids, a child were placed on
20 cromolyn instead, how big of a risk would that
21 be if we're trying to parse out risk?

22 DR. WILFOND: I think, particularly

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1 for someone who's been described as having
2 mild persistent asthma in which you're trying
3 to control daily symptoms, and actually, this
4 is done in practice, people, particularly with
5 leukotriene antagonists, often some parents
6 may prefer to try that first, and see what
7 effect that has, and whether they can achieve
8 the goals of control with that. So I would
9 say that there certainly is flexibility to try
10 arranges of things to see whether or not you
11 can reach the goals.

12 DR. KON: So it wouldn't be
13 unreasonable then - even saying standard-of-
14 care, best care - it wouldn't be unreasonable
15 for a child to be started on one of these
16 other therapies rather than inhaled
17 corticosteroids? That would still be
18 considered within the standard-of-care, if
19 that's what the physician and parent wish.

20 DR. FOST: But don't the
21 guidelines, I don't know if strongly is the
22 word, but they recommend inhaled

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1 corticosteroids first, unless there's some
2 contraindication?

3 DR. WILFOND: Yes.

4 DR. FOST: And isn't that based on
5 -- you know, none of us has access to this
6 copious literature, but aren't there not head-
7 to-head studies showing that inhaled
8 corticosteroids are better than the
9 antileukotrienes?

10 DR. WILFOND: Well, there's no
11 question that they're better. And in fact,
12 actually there was a recent study doing a
13 head-to-head comparison, and it clearly showed
14 that inhaled corticosteroids were better than
15 the leukotriene antagonists. But as the study
16 pointed out, there was a significant number of
17 people who did just fine on leukotriene
18 antagonists alone.

19 So for those people who are
20 particularly worried about this type of
21 treatment, regardless of whether they should
22 or shouldn't be, this would not be an

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1 inappropriate or unreasonable thing to do.
2 That's the guidelines I was speaking to.

3 DR. JOFFE: Len?

4 MR. GLANTZ: One of the inclusion
5 criteria is that children not have used ICS
6 within six weeks. Is that right? So my
7 understanding of that, this is usually done
8 prophylactically, isn't it? That this is used
9 -- so I sort of don't understand which
10 population of children would not have used
11 this for six weeks, and then be enrolled.
12 Does this make any sense?

13 So children who aren't inhaling
14 steroids right now, as part of being in this,
15 will now be invited to use inhaled steroids.
16 Is that right? And they may not need them at
17 the moment because they seem to be controlled
18 without them at least for six weeks. Yes?
19 No?

20 DR. WILFOND: This is hypothetical,
21 so I don't know how this study is being
22 intended to be designed.

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1 But what typically happens is there
2 may be many kids who have some symptoms who
3 have not been on inhaled steroids. I mean,
4 most of the patients I see in clinics will
5 have a one, two, three, four, six-month
6 history of asthma where I would have started
7 inhaled steroids six months ago, but finally,
8 at this point, we're making a decision to do
9 that. So it's quite plausible you would have
10 patients who have not been on them who would
11 still meet the criteria for enrollment.

12 But again, back to Steve's original
13 point is that the normal answer would be, in
14 terms of the issue of alternatives, without
15 much difficulty, you could say to a person,
16 clinically, this is what we ought to do, and
17 the question is, does the trial offer any sort
18 of special benefit that's different from what
19 they would get in the standard of clinical
20 practice.

21 MR. GLANTZ: And the other question
22 I have is that this is to determine growth

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1 velocity, so that has to do with the speed
2 with which kids attain -- but if I read the
3 background literature correctly, it doesn't
4 tell you what the ultimate height differential
5 is. Is that correct?

6 DR. FOST: Yes.

7 DR. JOFFE: Just one thing to note
8 is, so we're going to be focusing on the
9 comparison of the four arms, and the issues
10 that are raised in each of the four arms, and
11 then relatively, but the hypothetical case
12 does specify a placebo run-in for everybody.

13 And it doesn't actually say it in
14 the case, I don't think, but in the guidance
15 on choice of comparator for these studies that
16 was included with our materials, there's a
17 recommendation for a placebo run-out period.
18 So at the end of some 16 weeks or whatever is
19 on study drug that all of the children are on
20 a placebo for some period of time to look at,
21 I guess, catch-up on those sorts of things.

22 DR. FOST: Let's open, not with the

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1 run-in and the run-out placebo group, but ask
2 the question whether this study offers the
3 prospect of benefit to children in all groups.

4 And let's start with the hard one, whether
5 you think children who are assigned to the
6 placebo group can be said to be in a study
7 with a prospect of benefit.

8 DR. KON: Well, I mean, my initial
9 impression is no. And I think this is when we
10 start talking about component analysis, and I
11 think we really need to say, well, these
12 children in the placebo arm don't have a
13 prospect of direct benefit, because they're
14 receiving something that we've decided is not
15 perfect standard-of-care.

16 But I think the question then
17 becomes this issue of, where do we put the
18 risk. Would that be considered minimal risk?

19 Would that be a minor increase over a minimal
20 risk? And I think, personally, it seems as
21 though I think you'd have a very hard time
22 selling that they have a prospect of direct

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1 benefit in the placebo arm.

2 DR. FOST: Hold off on how much
3 risk it is. Let's just get other comments on
4 whether people agree or disagree about whether
5 there's prospect of benefit.

6 Ben, you wanted to say something?

7 DR. WILFOND: I would say, in this
8 study, no.

9 But that's not meant to imply that
10 there would be no studies in which the placebo
11 arm would offer a prospect of direct benefit,
12 and actually, it does relate to this run-in,
13 run-out issue, which is that one of the
14 biggest challenges is, even though we know
15 that people who have these symptoms should be
16 on inhaled steroids, we're still faced with
17 the decision, exactly when do we start them,
18 and when do we stop them. And so there's
19 still lots of uncertainty about those
20 questions.

21 And it may very well be that there
22 are patients who otherwise would be on them

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1 who really don't need to be on them, and in
2 fact, there are some circumstances where the
3 placebo group could actually be having a
4 prospect of direct benefit in comparison to
5 the active group, because they'll do just fine
6 with nothing. And we won't know that until we
7 do the study.

8 DR. FOST: Yes. My reaction is
9 more along those lines. I think there's
10 several ways in which you could say there's a
11 prospect of benefit.

12 First, this is a new drug, as I
13 understand it -- a new inhaled corticosteroid.

14 So even though it's the same class, who
15 knows? It may turn out worse than its
16 predecessors, not just in terms of efficacy,
17 but safety, and may turn out to have some
18 unanticipated adverse effect, and you may wind
19 up being better off in the placebo group.

20 Second, 90 percent of drugs
21 introduced into human testing fail. I don't
22 know about how many entered into phase 3

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1 testing, what the number is, but I think it's
2 around 50 percent, or something like that. So
3 that, as Dave DeMets, the chair of our
4 Statistics Department says, if I'm in the
5 emergency room unconscious, and there's a
6 study going, I want to be in the placebo
7 group. That is, more often than not, you're
8 better off in the placebo group. And we don't
9 know. That's why we have a placebo group.
10 It's not just - as has been observed here -
11 not just for the -- lots of hands going up,
12 but let me finish. It's not just to see if
13 there's a placebo effect, but to see if no
14 treatment, essentially, might make you better
15 off.

16 And then third, I think we do have
17 to talk about whether component analysis is
18 appropriate, that is, whether it's fair to ask
19 whether it was in your interests to be in this
20 study just because you wound up. Even if your
21 hypothesis is that the new drug is going to be
22 better than the old ones in terms of growth,

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1 and just as good in terms of asthma control,
2 you still, being in this study, have a 50
3 percent chance of being better off.

4 And that's the question that I
5 think the regs are supposed to be asking, is
6 does this research study have a prospect of
7 direct benefit, not -- and I think, for
8 various reasons, it's inappropriate to require
9 that every component must have the prospect of
10 benefit, because, as we know, there are
11 components of the study, including monitoring,
12 that may have no benefit at all -- that may be
13 nontherapeutic.

14 So I stimulated discussion, which
15 is useful, but I also meant what I said. So
16 we have Jeff and Alex, and maybe some others.

17 DR. BOTKIN: In response to your
18 comments, Norm, I would say that in this
19 hypothetical, we do have a proven therapy arm.

20 And so in that context, the fact that you're
21 assigned to the placebo versus assigned to the
22 experimental inhaled steroid, you might be

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1 better off in the placebo group. In that
2 context, you simply failed to harm somebody.
3 You actually haven't benefitted them.

4 So I think there's a distinction --

5 DR. FOST: I think I kind of meant
6 -- while it's fresh.

7 To say that there are drugs that
8 have proven efficacy, of course, doesn't mean
9 that everybody who gets them benefits. It
10 means that there's a probability that you're
11 more likely to benefit than not.

12 But there will always be
13 substantial numbers of children who get these
14 drugs who don't benefit from them, even the
15 so-called proven ones -- not to mention the
16 experimental one.

17 DR. BOTKIN: But that's the
18 prospect of benefit.

19 So I think your comments are most
20 pertinent to the situation where you have a
21 placebo versus an unproven intervention. And
22 can you say the placebo is beneficial? Well,

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1 it's perhaps beneficial compared to being
2 harmed by the experimental alternative. But
3 you haven't really benefitted them over
4 baseline.

5 And I think particularly in this
6 context where you have one arm of the therapy
7 that is proven therapy, it seems to me you
8 can't make the argument that the placebo group
9 offers benefits simply because you have
10 avoided potential harm with the experimental
11 agent.

12 DR. KON: So two things. First of
13 all, I agree with Jeff. I think what you're
14 talking about in this case is you have a
15 disease process with a known treatment with
16 national guidelines saying that you should be
17 getting this known treatment. And so when
18 you're talking about then taking children who
19 are in the situation and there are guidelines
20 saying this is the drug you should be getting
21 and saying well, now we're going to randomize
22 you to placebo, I think that that's very

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1 problematic.

2 And so I do think that it's
3 fundamentally different. I think that this
4 bigger question of do you judge potential for
5 direct benefit before or after randomization
6 becomes sort of the big issue to me.

7 DR. FOST: Ben?

8 DR. WILFOND: Again, as I said
9 before, I think there are some circumstances
10 where placebo controls are appropriate in mild
11 persistent asthma even in comparisons for
12 inhaled corticosteroids.

13 But in this particular study in
14 which you're trying to look at a new inhaled
15 corticosteroid, it seems to me that you could
16 use the known corticosteroid as the
17 appropriate comparison rather than a placebo,
18 because we already know that in general this
19 class of medicine is efficacious in the
20 setting.

21 DR. FOST: Steve?

22 DR. JOFFE: So it raises for me in

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1 making judgments about prospect of direct
2 benefit what the appropriate comparator is.

3 And I wonder, we've been talking
4 about comparators within the study -- the
5 various arms within the study. I wonder if it
6 isn't sort of best available therapy to the
7 prospective participant outside of the study,
8 which in this case we were told was a
9 recommendation for inhaled corticosteroids
10 although with some potentially reasonable
11 alternatives available as well. In that
12 context of recommended therapy outside of the
13 study being inhaled corticosteroids or
14 alternatively a nonsteroid anti-inflammatory,
15 it is hard for me to understand how
16 randomization to a placebo could be viewed as
17 a prospect of direct benefit.

18 DR. FOST: One more time, and then
19 I'll shut up.

20 If you take 100 children with mild
21 asthma, some of them will do just fine with no
22 long-term sequelae, and will do well on beta-

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1 agonists and so on. So that's a number.

2 Second, of those who get put on
3 standard treatment, most of them will do
4 better but not all of them will do better.
5 Some of them it will have no benefit. So
6 they'll have risks and no benefits. And some
7 other number will have both -- will do better
8 and will not get the side effect of retarded
9 growth.

10 I don't know going in that it's
11 certainly not the case that every child in the
12 placebo group is a child who would have done
13 better had he had steroids. So it may be that
14 his probability is substantially higher of
15 doing better. That's why the recommendations
16 are there. That's why the studies had a good
17 P value.

18 But there certainly will be kids
19 who have a prospect of benefit. That is it's
20 not just plausible. It seems to me likely
21 that in a group of 100 there will be kids who
22 will do better in the placebo group, or who

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1 will do just as well in the placebo group, and
2 who therefore benefitted by being in that
3 group because they didn't have to incur the
4 growth risk.

5 Len and Ben.

6 MR. GLANTZ: So given that, do you
7 think it will be appropriate for a practicing
8 pediatrician to flip a coin when a kid comes
9 in to determine whether they get
10 corticosteroids or not since some of them will
11 do just fine anyway and you can't determine
12 which ones?

13 DR. FOST: Not flip a coin. But
14 get informed consent from the parent, just
15 like --

16 MR. GLANTZ: Okay, get informed
17 consent to flip a coin.

18 DR. FOST: No. No. Not to flip a
19 coin. We see parents turning down vaccines
20 that are proven effective. I'm talking about
21 standard --

22 MR. GLANTZ: No, I thought you said

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1 that because some kids getting standard
2 therapies may not benefit from it, and some
3 kids would do well if they didn't get the
4 standard therapies. That means putting them
5 in a placebo arm is okay plus you don't know.

6 But I'm saying we know well enough
7 not to randomize kids who come in when they
8 have asthma and we're trying to treat them.
9 We don't just flip a coin. That there is
10 proven therapies and they're not perfect. But
11 that doesn't mean that randomizing to a
12 placebo arm doesn't present the prospect of
13 harm.

14 DR. FOST: I'm not sure what the
15 relevance of going from the practice situation
16 to the research setting is.

17 In the practice setting, an
18 informed parent who's risk averse to drugs
19 might choose not to have her child on an
20 inhaled --

21 MR. GLANTZ: Right.

22 DR. FOST: It wouldn't be neglect.

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1 I don't think we can go to court over it.
2 The pediatrician would not be guilty of
3 malpractice for not doing it.

4 MR. GLANTZ: But you would suggest
5 corticosteroids, assuming they met the
6 criteria for asthma?

7 DR. FOST: Yes. Just like I would
8 suggest measles vaccine. But some people
9 might choose not to get it.

10 MR. GLANTZ: But here the
11 researchers are not suggesting it, for some
12 population they're suggesting placebos.

13 DR. FOST: But that's because their
14 purpose is not treating patients. Their
15 purpose is to advance knowledge.

16 MR. GLANTZ: And that's the
17 concern. Right? I think you've stated the
18 concern is that we're withholding a known
19 treatment to advance knowledge. And that's
20 why it doesn't seem to be --

21 DR. FOST: Well, we're just asking
22 a very technical question about whether the

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1 children in the placebo group in this project
2 who advance knowledge might benefit from being
3 in a placebo group.

4 MR. GLANTZ: Might benefit. Yes.

5 DR. FOST: Alex, Theresa, Ben.

6 DR. KON: So I think that the
7 measles analogy is actually very good.

8 If we were talking about designing
9 a study where we're going to randomize kids to
10 get MMR or not -- and we know that there are a
11 lot of parents who opt out of MMR vaccinations
12 for their kids -- and we as a profession of
13 pediatricians say that's a really bad idea.
14 And we really don't suggest it. But we're not
15 going to go and call child protective services
16 to make you vaccinate your children.

17 But if an investigator were
18 proposing a study to randomize children, and
19 one arm wasn't going to get MMR, we would -- I
20 would think -- I would find that very
21 troubling, because I think that even though
22 there is some theoretical risks of MMR, it

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1 seems as though we have national
2 recommendations because we as a profession
3 believe that this is what's in children's best
4 interests.

5 And while there may be some
6 children who might avoid some negative
7 repercussions from vaccination, the reality is
8 I think you'd be very hard pressed to say that
9 randomizing a child not to get MMR is somehow
10 in their best interests. And I think this is
11 very analogous.

12 There's no question that there are
13 some children who do okay not on inhaled
14 steroids. And in fact, there are some
15 children that on balance would do better not
16 on inhaled steroids than on inhaled steroids.

17 But I think in general when we're looking at
18 these children as a class, the recommendation
19 of the profession is that they be placed on
20 standard-of-care medication. And to withhold
21 standard-of-care medication -- I think it's
22 very difficult to argue that that is somehow a

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1 prospect of direct benefit.

2 DR. FOST: Theresa?

3 MS. O'LONERGAN: I have the same
4 point, that the possibility that they might do
5 okay is not the same I don't think as a
6 prospect of benefit. And I think some kids do
7 okay. Some kids might not do okay. But
8 that's not the same as prospect of benefit.

9 DR. FOST: What else would benefit
10 me other than that you might be better off?

11 MS. O'LONERGAN: It's too
12 theoretical, I think. I think we have enough
13 understanding of probability, the reason again
14 why we make this a suggestion in a guidance is
15 that the probability is higher that you will
16 do better on this than not on it.

17 DR. FOST: Ben, Len, and Steve.

18 DR. WILFOND: I'm going to say two
19 things. One that kind of is meant to sort of
20 disagree with you, and another part that will
21 agree with you.

22 But the part that disagrees is that

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1 it's not so much an issue of standard-of-care
2 or that they'll do better, but I think we can
3 be pretty specific. In a 52-week study, the
4 concern would be based upon all other studies
5 in this packet that we know that the kids in
6 the placebo group will have a much higher rate
7 of asthma exacerbations. Now these will be
8 self-limited exacerbations. They probably
9 won't wind up in the hospital. They're not
10 going to die. They're just going to have the
11 experience of having a number of additional
12 asthma exacerbations.

13 Now the question is whether that
14 experience is sufficient to try to avoid
15 circumstances of doing that unless it's
16 necessary. And I think to find out whether a
17 new inhaled corticosteroid will have impact on
18 growth by this type of study is not in and of
19 itself a compelling reason to do it.

20 Now also the opposite side. I
21 think one place where a placebo control makes
22 sense, or a placebo make sense is actually in

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1 that run-in stage, because one of the things
2 we have to decide is do we have the right
3 population of people to be enrolled in the
4 study so that we will be able to observe
5 whether there's a benefit or not. And if we
6 didn't have that placebo, we'd have all those
7 people initially. We wouldn't know who is
8 going to have enough asthma to actually
9 warrant being in the study. So that's why I
10 think the placebo is necessary in the
11 beginning.

12 DR. FOST: I thought the purpose of
13 the run-in was to establish a growth rate.

14 DR. WILFOND: Well, it's probably
15 also to establish that they're sick enough. I
16 would imagine in most of these studies, people
17 get kicked out during that period of time if
18 they actually have no symptoms because a lot
19 of folks who we think have symptoms turn out
20 not to when you stop their steroids.

21 DR. FOST: Len and Steve?

22 MR. GLANTZ: Yes, I was just going

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1 to say that I think we're stuck on the word
2 prospect again, and what that means, whether
3 or not it's a bare possibility or a likelihood
4 or a probability.

5 So some kids who don't get the
6 measles vaccine may end up doing better as a
7 result of that because some rare group of
8 children react poorly to it. But to argue
9 that the whole group has a prospect of direct
10 benefit by not getting it seems to not give
11 meaning to the word prospect.

12 DR. JOFFE: I guess maybe I'm just
13 saying what others have said.

14 But it seems to me that in making
15 treatment recommendations, we're always making
16 inferences from average benefits, average
17 risks in a population to the next patient in
18 front of us who we think is represented by
19 that population.

20 And so clearly, any individual may
21 have a risk/benefit profile usually unknowable
22 to us that is different from the average in

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1 the population, but we don't have the
2 information to judge that. So to take an
3 extreme example, in my world when we treat
4 kids for acute leukemias, the vast majority of
5 kids are going to be much better off receiving
6 treatment for their newly-diagnosed
7 lymphoblastic leukemia than not receiving
8 treatment.

9 There however will be the
10 occasional child who has fatal toxicity from
11 that initial treatment. And in fact, if we
12 could have known that up front, would have
13 been better off not getting that treatment.

14 Does that mean that we could argue
15 that a placebo-controlled trial of
16 chemotherapy for acute leukemia is that
17 randomization to the placebo arm would offer a
18 prospect of direct benefit to the child? I
19 think the answer to that has to be no.

20 That's clearly a more extreme
21 example than the inhaled corticosteroid. And
22 that's not to say that it would be unethical

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1 to have a placebo arm. I'm not ready to
2 conclude that. But nonetheless, I think the
3 reasoning follows.

4 DR. FOST: Well, I think the
5 analogies including MMR are not good analogies
6 with leukemia, obviously the outcome is very
7 dire. And MMR's a bad example because the
8 sequelae of measles can be so profound. But
9 maybe rotavirus vaccine would be a better
10 thing in which the benefits are not life-
11 saving for most kids in the United States.
12 And even though it's standard-of-care and
13 recommended by the AAP, it wouldn't follow
14 that a parent who chose to be in a trial in
15 which they did something else to prevent
16 diarrhea, or to prevent rotavirus where
17 diarrhea was doing a bad thing.

18 One more point and then I'll drop
19 it. I wasn't yet reaching the conclusion --
20 nor have any of you -- about whether the
21 placebo group is appropriate or wrong or a
22 good idea or a bad idea. But if we're asking

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1 technical questions about what prospect of
2 benefit means, it seems to me there is a
3 prospect of benefit, whether it's big enough
4 to justify including them in the trial is a
5 separate question.

6 Terry was up, and then Skip.

7 MS. O'LONERGAN: So I have a
8 question for Ben.

9 It's been a while since I was at
10 National Jewish, so I don't know the answer to
11 this. Isn't one of the justifications for
12 using inhaled corticosteroids in mild
13 persistent asthma the idea that it prevents
14 further progression so that there's not only
15 the utility of preventing exacerbations, but
16 that there's some structural remodeling that
17 it prevents? Or is that out of vogue?

18 DR. WILFOND: It's still in vogue,
19 but I would say there's lots of different
20 views about how true that is and there's still
21 people trying to push that.

22 Norm, you never really answered

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1 Steve's question. In other words, would you
2 say that a leukemia trial that included a
3 placebo arm, would that offer a prospect of
4 benefit to those children?

5 DR. FOST: Yes. But the balance of
6 risk in that prospect are so extreme that it
7 would be inappropriate to include them in a
8 trial in that regard, because the risk you're
9 taking there is so enormous. The risk we're
10 taking here with these children I don't think
11 is so enormous.

12 We could argue more about the
13 design of this, but waiting for four episodes
14 is three too many. But you could do a trial
15 in which maybe one relapse was enough. I
16 would call that extremely low risk of anything
17 serious happening to the child, not remotely
18 related to getting measles or the other.

19 Skip?

20 DR. NELSON: Norm, just to
21 reinforce a concept that was part of the
22 discussion this morning and to see how that

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1 plays into your thinking. And that's a
2 distinction that I raised, partly because it's
3 one I'm thinking about more, which is the
4 difference between prospect of direct benefit
5 and evidence of efficacy.

6 My impression is all of the
7 questions that you ask are actually questions
8 about the results of the trial. It's true in
9 many cases, it would be better off to have
10 been on the placebo. But it's not clear to me
11 that the basis for that argument is that the
12 placebo offered prospect of direct benefit.

13 And so at the heart of asking this
14 question is that distinction, which as I
15 listen to the discussion, there's a number of
16 threads that are all weaving together. But
17 trying to focus on the prospect of direct
18 benefit alone, I see as a very different
19 question than whether at the end of the day
20 those people randomized to placebo are better
21 off, which is in fact the very question if you
22 have scientific uncertainty, the trial is

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1 intended to answer.

2 So I'd like that distinction to
3 sort of maybe be explored a little bit to see
4 if that begins to clarify why there is a
5 considerable disagreement with the originally
6 stated position.

7 DR. FOST: Yes. Let's come back to
8 it, because I want to discuss the run-in and
9 the run-out and see how people feel about
10 prospect of benefit of those phases also.

11 But Jeff had a comment. And then
12 we maybe can tie it up.

13 DR. BOTKIN: Well, two comments.
14 And I'm forgetting the second at the moment.
15 But I hope it will come to me.

16 I would go back to the prior
17 comment which was I think there is a
18 difference between benefitting a patient and
19 failing to harm them. And so it gets back to
20 what's the comparator. And if you're
21 comparing it with other kids who do poorly in
22 the clinical trial, then the kids are better

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1 off. It's not clear to me that you've
2 benefitted them but you've failed to harm
3 them.

4 So I guess I'm not ending up buying
5 the idea that the placebo group in this
6 context can fit under the prospect of benefit,
7 other than something that I haven't spent much
8 time thinking about. But it seems to me again
9 the issue of compared to who. And placebos
10 work pretty well. In fact, placebos are
11 remarkably effective in a lot of circumstances
12 compared to doing nothing.

13 So if you in fact compare the
14 placebo group to the group for whom you're
15 doing nothing, then can you claim that a
16 placebo has prospects of benefit? And I'm not
17 willing to go there. But it seems to me at
18 least raises a question of interest.

19 DR. FOST: Let's go back to the
20 other two placebo groups -- the run-in and the
21 run-out, which have different motives. And I
22 think the answers might be separate.

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1 So let's start with the run-in
2 first. Do people think that even if you wind
3 up in the -- let's assume there were no
4 placebo arm in the trial. It was a three-arm
5 trial, all with an active intervention. But
6 all three of them had placebo run-in phases of
7 how many weeks in this trial?

8 DR. WILFOND: Was it three I think
9 in this one?

10 DR. FOST: No. I thought it was
11 much more.

12 DR. WILFOND: It was longer. Six.

13 DR. FOST: Because I think one of
14 the purposes was to establish a growth rate,
15 not just to confirm that you had asthma.

16 DR. NELSON: The period was not
17 specified in the case.

18 DR. FOST: Well, let's assume like
19 in some of the other trials, the run-in
20 periods were quite long because they wanted to
21 establish normal growth.

22 So let's assume a run-in of three

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1 months during which a child would plausibly
2 get an exacerbation. If you're going to do
3 component analysis, would you call that
4 component to have a prospect of benefit?

5 DR. BOTKIN: Can I ask a quick
6 clarification question?

7 Does it matter whether it's a
8 placebo run-in or just a run-in, when you can
9 just take kids off inhaled steroids altogether
10 for a period of time, and you know nobody has
11 to be fooled about what they're on because
12 it's a run-in period? I'm not sure that makes
13 a difference in terms of --

14 DR. FOST: Why would it matter --

15 DR. BOTKIN: Right.

16 DR. FOST: -- not having the
17 effective drug?

18 Alex?

19 DR. KON: Well, I guess my concept
20 of component analysis -- and maybe I'm
21 mistaken -- is to separate out components that
22 can be completely separated. And so the

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1 question becomes could you do the second part
2 of the study without doing the run-in portion?

3 And not being a pulmonologist -- at
4 least the way I'm thinking about it -- I don't
5 see how you could do the measurements without
6 doing a run-in so that you get a baseline. So
7 I'm not sure that we can really separate that
8 as a separate component because it seems part
9 and parcel of what one does next.

10 And maybe I'm mistaken and just
11 don't understand it well. But that's my
12 impression.

13 DR. FOST: Ben and Len.

14 DR. WILFOND: I was -- just to
15 comment on the original question -- as I
16 mentioned before, I don't think that a placebo
17 run-in is problematic primarily because this
18 is a decision that clinicians and parents make
19 all the time to stop medications and see what
20 happens. And so this is sort of a fairly
21 routine activity that happens with many kids
22 at some point in time. And this is a chance

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1 to find out how they're going to do.

2 DR. FOST: But five minutes ago, we
3 were outraged that some children might not be
4 on steroids for a while.

5 DR. WILFOND: No. No. You
6 misunderstood me.

7 The issue is how long and when and
8 why. So in other words, I think the concern
9 would be in somebody whom -- let's say you
10 stop their inhaled steroids and you make it
11 pretty clear that they're having daily
12 symptoms, and possibly even an exacerbation.
13 And say okay, now that we know that you're
14 moderately sick, we'll go ahead and put you on
15 our placebo for a year, or until you have four
16 exacerbations. I think that's a little bit
17 too much.

18 But it's how long and why you're
19 doing it.

20 DR. FOST: Len?

21 MR. GLANTZ: Yes. I think the run-
22 in certainly provides no prospect of direct

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1 benefit. The way I would think about the run-
2 in is that it's a risk. And it's a risk that
3 goes into deciding the risk versus the
4 benefits. But how can it be anything other
5 than risk, since we're subjecting kids to
6 doing worse.

7 The risk may not be great enough by
8 the way to say that you can't do the study.
9 But I would see it as a risk, not as a
10 benefit.

11 DR. FOST: Steve?

12 DR. JOFFE: I was going to make the
13 same point.

14 But I would just add that the way
15 the case is stipulated, these are kids who are
16 not yet on an inhaled -- there's no stopping
17 of corticosteroids at this point. They're not
18 yet on a corticosteroid. There is a
19 population of kids for whom it is recommended.

20 It's certainly not mandatory by the
21 guidelines.

22 But the question is do you start?

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1 Do you start now versus do you start six weeks
2 from now, three months from now?

3 DR. FOST: But the reason they're
4 not on steroids is because they were being
5 cared for by somebody who didn't know what the
6 guidelines were.

7 DR. JOFFE: Well, presumably either
8 because they have newly-met criteria or
9 because they've been undertreated up until
10 now.

11 DR. FOST: But they're now in the
12 hands of an expert. And the expert is asking
13 the child to go an extended period of time and
14 be exposed to risk.

15 Let's assume that you had a much
16 more conservative rescue strategy. One
17 episode and you're rescued. So if I
18 understand your comment, if it's a three-month
19 run-in, that's okay with some rescue strategy.

20 But a 12-month period is not okay.

21 But in both cases, one bad episode
22 and you get removed from the study. What's

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1 the difference. In both groups -- the three-
2 month group and the 12-month group -- they're
3 both at risk for one exacerbation and no more.

4 So why are we any more worried about the 12-
5 month than the three-month?

6 DR. WILFOND: Well, actually in the
7 first plan, I think your point was very well
8 taken that with the lower threshold for
9 removing somebody from the study, then the
10 duration becomes less problematic. Your
11 point's well taken.

12 DR. BOTKIN: I would just go back
13 quickly to the idea of component analysis and
14 I'm really agreeing I think with what most
15 folks said here, which is that run-in period.

16 And some of the other studies that are
17 included in the packet here do involve taking
18 kids off steroids for the run-in period. So I
19 think we have both phenomena going on.

20 But that can be very much a
21 separate component. And as I think as folks
22 have been saying, that run-in period might be

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1 justifiable under either minimal risk -- 404
2 or 406 sort of criteria. But it wouldn't be a
3 405 consideration.

4 So whether it's acceptable or not
5 would be determined by whether it fits
6 adequately the other criteria.

7 DR. FOST: Does anyone think the
8 run-out period raises any different questions
9 than the run-in period given a) that it's
10 longer, if I'm understanding it correctly, and
11 it has a slightly different -- well, as I
12 understood it --the purpose was to see if
13 there was catch-up growth. So it wasn't to
14 help the kids' asthma certainly in any way.

15 Does anyone think that's more
16 problematic than the run-in? Or why is it
17 less problematic than a 12-month placebo
18 group?

19 I take it that people are
20 comfortable with a prolonged run-out period.
21 And I'm not quite clear why.

22 DR. BOTKIN: No.

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1 DR. FOST: You're not comfortable
2 with it.

3 DR. BOTKIN: No. I think it
4 follows the same analysis we talked about.

5 DR. FOST: Okay.

6 DR. BOTKIN: But it's not
7 necessarily acceptable.

8 DR. FOST: And the difference
9 between the run-out and the run-in?

10 DR. BOTKIN: Ethically, I don't
11 think there's any difference. So you'd still
12 look at the same set of criteria. Is it
13 minimal risk? Or is it a minor increase over
14 minimal risk? And if you can fit it within
15 those categories, then that's potentially
16 approvable. If you think it's a substantial
17 risk to the kids, then it wouldn't be an
18 approvable design.

19 DR. FOST: So I'm just trying to
20 sum this up now. There was a lot of head
21 nodding.

22 Everybody seems to think that the

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1 run-in and the run-out are okay, not because
2 they offer a prospect of benefit, but because
3 it's minimal risk.

4 DR. KON: Yes. I'm not sure that
5 we've gotten there. I think what we've agreed
6 to is that the run-in and the run-out would be
7 handled similarly. But whether or not they
8 meet criteria for approvability, I don't think
9 that we've agreed on.

10 DR. WILFOND: I think the question
11 for whether it's in the run-in or the run-out,
12 or even during a study itself is a question of
13 at what point do you remove somebody from the
14 study because of an increase in their
15 symptoms. I think that would apply to all
16 three of those circumstances.

17 DR. FOST: So none of those three
18 would be any more risky than any other if you
19 had the same rescue strategy for each one?
20 Yes? Skip?

21 DR. NELSON: Just to kind of
22 encourage people to focus on the analysis,

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1 because I think what's of most interest is the
2 ability to take how one would approach the
3 analysis and application of this category to a
4 case such as then to then apply to other
5 cases. So that I think as people begin to say
6 well, this is how I would begin to evaluate or
7 analyze the case, that would be helpful to
8 unpack that at different points as opposed
9 just sort of summary judgments -- if you will
10 -- of the case itself.

11 MR. GLANTZ: Yes. I think if I
12 hear a consensus, the consensus is that people
13 would handle the run-in and the run-out as a
14 risk as opposed to a benefit, and then
15 determine how much of a risk it is depending
16 on how far down the road we let kids go before
17 we begin to rescue them, whether it's a long
18 time or a short time, but that it should be
19 handled as a risk as opposed to a benefit. Is
20 that right?

21 DR. WILFOND: Every time I speak I
22 actually say the opposite. But it's because -

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1 - I'm not quite sure whether this is
2 appropriate. But I'm thinking about this
3 really from the perspective of a parent in a
4 non-research setting.

5 When they make the decision to stop
6 their child's medication, they're thinking of
7 this both as a potential risk but also as a
8 potential benefit at the same time, because it
9 may turn out if the child does fine with
10 nothing, that's a huge benefit to them.

11 And so I think it's two sides of
12 the same coin, and it's hard to call it one
13 versus the other.

14 MR. GLANTZ: But I think it's
15 different in the clinical setting than in the
16 research setting where people are being put on
17 and putting off because of a protocol as
18 opposed to individual determinations by a
19 physician. So when the parent says I'd like
20 to take a vacation from this and let's see
21 what happens, their only purpose of doing that
22 is to try to benefit the child -- the parent

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1 and the physician working together.

2 When you're sort of randomizing
3 people according to a protocol, that's not the
4 goal. The goal is to attain something else.

5 DR. WILFOND: Leonard, I agree with
6 your comment. But so imagine we did a very
7 good job of screening the people who are
8 enrolled in the trial. And the only people we
9 enrolled in the trial were exactly those
10 parents who otherwise were interested in
11 taking these vacations from the medicine.

12 And I mean this in a really sincere
13 way, because I think those are perhaps the
14 types of patients we ought to be enrolling in
15 these types of trials, whereas typically I
16 think -- and this is where your concern comes
17 in -- is often the reason people seek out
18 trials is because they're feeling that somehow
19 their treatment's not adequate and they're
20 looking for something better. And I think
21 there's a real difference between those two
22 populations of folks and who we should be

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1 including in the trials.

2 DR. FOST: Okay. So let's just
3 turn to inclusion benefit again to discuss
4 what we mean by benefit, and then see if we
5 can tie it up in some conceptual way that's
6 useful and it's generalizable.

7 So what do people think about this
8 so-called inclusion benefit. Inclusion
9 benefit can mean many things. And Steve I
10 know has written about this. So maybe I
11 should let him say more about what it means.

12 But one thing it might mean is
13 better care overall. You're in the hands of
14 expert doctors. You're being monitored more
15 carefully. That's one thing.

16 Second, it may be the first time
17 you get diagnosed, and it's getting included
18 into the system.

19 Third, it may mean that there are
20 indirect benefits as well that you get hooked
21 up with Medicaid or reimbursements schemes or
22 something else before you get hooked up with

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1 an asthma allergy treatment center that you
2 never would have heard about and so on. So
3 even if you wind up being in the group that
4 loses, there was something to be gained by
5 being in the study.

6 But let me ask Steve to say some
7 more about this because he's thought more
8 about it, and then get some comments on
9 whether people think that should count for
10 anything. And if so, how much?

11 DR. JOFFE: The framework that
12 we've taken -- and I don't know if that's
13 helpful here -- is that we looked in a
14 systematic review of studies done in a cancer
15 setting. We looked at whether there was
16 evidence behind the claim that one often hears
17 made that patients who enroll in clinical
18 trials do better than comparable patients not
19 enrolled in clinical trials. And without
20 trying to contradict the claim, we argued that
21 the evidence for that claim was weak and
22 methodologically flawed, and so we shouldn't

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1 be so confident about making that claim.

2 We then sort of looked at if there
3 were such benefits, where might they come
4 from. And one possibility might be that they
5 would come from the advantages of access to
6 new experimental presumably on average more
7 effective therapies. And that's a plausible
8 avenue to sort of generic benefit from
9 participation in the study.

10 The other is that there might be
11 benefit from other aspects of study
12 participation, like all the things you alluded
13 to, Norm, being managed according to a
14 rigorous protocol, having sort of the best
15 expert minds designing the treatment paradigm
16 that you are participating in, more careful
17 monitoring procedures -- those sorts of
18 things.

19 And so it's certainly plausible
20 that being in a study compared to receiving
21 ordinary medical care out in the community
22 with all of the vagaries that that brings

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1 might be better for you, all things
2 considered. And we claimed that that hadn't
3 been shown in the cancer setting. But it
4 doesn't mean that it's not possible.

5 I think a question that I certainly
6 don't know the answer to is whether that
7 counts as direct benefit. And so we've spent
8 a lot of time talking about the word prospect.

9 We haven't actually spent a lot of time
10 talking about the word direct and what is a
11 direct benefit versus what's an indirect
12 benefit, or whatever the opposite of direct is
13 in this setting.

14 DR. FOST: That should be on the
15 table now also, is whether indirect benefits -
16 - has it been a problem to restrict -- to
17 interpret the common rule or to apply it as
18 meaning only direct benefits. Should indirect
19 benefits count too? Should we not consider
20 that as a valid reason to at least put on that
21 side of the scale to include children in
22 studies?

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1 So comments about this, about
2 whether inclusion benefits matter and whether
3 that is one of an example of indirect benefits
4 that we should be weighing.

5 Jeff?

6 DR. BOTKIN: That SACHRP --
7 Secretary's Advisory Committee on Human
8 Research Protections pediatric committee --
9 Skip and I are both on that -- talk about this
10 issue. And I think our thoughts at the time
11 were to say that this type of benefit is an
12 indirect benefit, and that if you're to claim
13 benefit, it really needs to be the intent of
14 the study and not a side benefit.

15 An example that was used in that
16 context was to say on occasion you'll hear
17 investigators who are doing scanning
18 procedures -- basically observational
19 research to let's see what the brain looks
20 like with various conditions -- make the claim
21 that that's potentially beneficial research
22 because who knows when you might find a

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1 nascent brain tumor. And therefore the child
2 would benefit who wouldn't otherwise
3 participate in the trial.

4 And I think what SACHRP -- the
5 subcommittee -- wanted to say was that doesn't
6 work, because really the intent of the
7 scanning has to be to benefit the kids to lead
8 to some cascade of therapeutic intervention as
9 opposed to some speculative benefit. And it
10 seems to me that this inclusion benefit is
11 perhaps both speculative based on perhaps less
12 data that we would like about it, as well as
13 indirect.

14 DR. FOST: Other comments? Len?

15 MR. GLANTZ: Is the inclusion
16 benefit really different from saying you're
17 better off going through a tertiary care
18 facility to get your treatment for asthma
19 where you have people who are the best experts
20 rather than saying it's a benefit as a result
21 of being in the study?

22 DR. FOST: That's one hypothesis.

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1 Yes. Better doctors.

2 MR. GLANTZ: That's why it seems
3 pretty speculative.

4 I can go to the doctor anyway,
5 can't I?

6 DR. FOST: Say it again.

7 MR. GLANTZ: I said we can go to
8 the doctor anyway. I can go to see Ben even
9 if I'm not in the research to have my child
10 treated for asthma.

11 DR. FOST: Well, not everybody has
12 that choice.

13 So let's take an uninsured parent
14 whose child is wheezing all the time. And
15 they're not Medicaid-eligible, and they don't
16 have a third party pay them. And they just
17 don't go to the doctor because they can't
18 afford it, or they feel they can't afford it.

19 And they see a sign, "research on
20 children who wheeze." And they're smart
21 enough to even read the fine print on the sign
22 and it says one of the four groups is a

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1 placebo group. And the parent says first of
2 all I'm going to find out if my kid has
3 asthma. I'll get some advice about
4 environmental -- these people are smart
5 advocates. You get a lot of advice on
6 environmental things. You get hooked into the
7 system. You'll get hooked up to a funded
8 study so at least for a year your kid will get
9 good treatment, and then maybe the social
10 workers will help you find some blah, blah,
11 blah. And you've got a 75 percent chance of
12 getting on a medication. And then there will
13 be phase 4 extension trials, so maybe he'll
14 get two or three years.

15 Is there something wrong with this
16 parent's way of thinking that this is in my
17 child's interest to be in this study even if
18 he winds up in the placebo group? And is
19 there some reason we should thwart that parent
20 from seeking this option?

21 DR. WILFOND: So, Norm, I don't
22 think there's anything wrong with that

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1 parent's reasoning. But I think the question
2 is whether or not that study really needed to
3 have a placebo group in the first place,
4 particularly when part of what you're trying
5 to do is to recruit people who otherwise are
6 looking for care, which is a right different
7 group than the parents who are looking for the
8 drug vacation.

9 This is a group where you'd have to
10 have really strong compelling reasons why you
11 thought that the placebo arm was necessary for
12 that study because it may be that you don't
13 need the placebo arm for that population.

14 MR. GLANTZ: So you would say it's
15 satisfactory then to have as inclusion
16 criteria children who are poor and not
17 eligible for Medicaid because that's the group
18 that would benefit?

19 DR. FOST: I'd say they certainly
20 have a prospect -- very high prospect of --

21 MR. GLANTZ: I understand. But I'm
22 saying do you think we should restrict it to

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1 that group because that's the group that could
2 benefit -- is most likely to benefit as a
3 result of sort of the social circumstances
4 they're in.

5 DR. FOST: No, I wouldn't see any
6 stronger argument for restricting it. I think
7 they may have more of a likelihood of benefit
8 than kids who are already in the system.

9 MR. GLANTZ: But for well-to-do
10 people who could go to Ben, they would not
11 receive this benefit. Right? Because they
12 would go to the best possible person.

13 DR. FOST: Well, they may receive
14 the benefit of getting the experimental drug.

15 MR. GLANTZ: But that's the
16 definition of the therapeutic misconception to
17 say that they would benefit because they might
18 get the drug. You have no idea if it works.

19 DR. FOST: Isn't that what we mean
20 by prospect of benefit?

21 MR. GLANTZ: But I'm saying when
22 you say they might benefit from that, it seems

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1 to me that's the therapeutic misconception --
2 that they might and they might not.

3 Meanwhile, if I go to Ben with my
4 kid, my kid's going to get good treatment.
5 I'm saying that's the argument it seems to say
6 that poor kids will do better than rich kids
7 if they're in here that they're more likely to
8 get benefit. I think that's a problematic
9 argument.

10 DR. FOST: Theresa -- Terry?
11 Excuse me.

12 MS. O'LONERGAN: Well, it's a bit
13 like saying that we can expose kids due to
14 their social inequities to greater risks. So
15 if a child is poor and their parents can't
16 afford this, then it's justifiable for them to
17 be in a placebo arm.

18 And I'm not questioning the
19 parent's motivation. The parent is trying to
20 do the best thing for the kid. But I question
21 your reasoning about having it be better based
22 on their social inequity.

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1 DR. FOST: It's better if they
2 presently have no access to treatment. It was
3 the rationale for the AIDS for the placebo
4 group in the AZT trial. It was to get into
5 the equipoise issue, nobody thought that trial
6 was in equipoise. Any intelligent person had
7 a high level of optimism that the AZT group
8 was going to do better. But they didn't think
9 it was wrong to withhold the standard
10 treatment -- namely the 076 regimen -- from a
11 population which previously had access to no
12 treatment, that at least parents and babies
13 who entered that trial had a 50 percent chance
14 of being better off. And of course, the
15 population had a prospect of improvement.

16 So for the impoverished parent of
17 the asthma kid, I don't see how they're worse
18 off in being in a trial with a 75 percent
19 chance of getting treatment when their
20 previous option was no treatment. I don't see
21 how anybody's worse off from that.

22 MR. GLANTZ: Yes. I think you're

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1 talking about social justice issues. You're
2 talking about desperate parents doing what
3 they need to do, and that creating a group of
4 people who are subjects because they're poor,
5 that's the reason.

6 And the reason why it's done in the
7 United States is because people would get the
8 076 regimen because it was available to
9 people.

10 Can I ask actually a separate
11 question though a little bit? And I don't
12 know if we're going to get to this later. But
13 the question that I have about this trial is
14 benefit, whether or not there is any benefit
15 at all in this trial. And again, I don't know
16 if you want to put that on the table for later
17 or if we're moving into that.

18 DR. FOST: I think we're on it. Go
19 ahead.

20 MR. GLANTZ: Okay. Because it
21 seemed to me that if the issue is one of
22 velocity as opposed to sort of the end result

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1 of kids' development being pretty much the
2 same, why do this trial at all? And I'm not
3 asking it rhetorically. When I read it, I
4 just couldn't see why this was a useful thing
5 to do since the kids will be the same height
6 one way or the other, if I read the background
7 paper correctly.

8 DR. FOST: The theory is that the
9 new drug will have less growth retardation
10 effect.

11 MR. GLANTZ: But I thought what I
12 had read -- and again, this is why I'm asking
13 it as a question -- that I thought this was a
14 velocity question as opposed to an ultimate
15 growth retardation question.

16 DR. FOST: Alex?

17 DR. KON: Yes. That's how I read
18 it as well.

19 But I think the benefit is that
20 there's a sense that delaying growth had some
21 negative psychological ramifications in the
22 child, even if their ultimate adult height is

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1 unchanged, but having a delay in their growth
2 has some negative repercussions. So if they
3 could be on a medication which would allow
4 them to continue growing similar to their
5 peers, they would never have a period of
6 shortness, so to speak, and that that is the
7 proposed benefit. That's my understanding.

8 MR. GLANTZ: Because I thought that
9 the numbers were somewhere between .3
10 centimeters and 1.-something centimeters,
11 which I assume on a yearly basis on a given
12 year -- maybe they add up in some way.

13 So when do kids catch up? I guess,
14 when do they actually reach their adult
15 height? Because I think of .3 centimeters as
16 a not noticeable difference. So when they're
17 18 do they catch up? Are they 20 when they
18 catch up?

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

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

10 But I think your primary question
11 is actually one that I happen to study too.
12 The reason why I thought the placebo arm was
13 troubling in this study is that I just wasn't
14 motivated by the value of this study as a
15 whole. In other words, I don't know if we
16 need a study of this new drug to see how this
17 compares to placebo for the purposes of
18 whether you're going to be half a centimeter
19 shorter or not on a particular year.

20 And that's where I think that the
21 issue, back to Leonard's comment about the
22 poor people is it's one thing if here's a

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1 study that really has very minimal value, but
2 you construct it in a way in which you're
3 saying you're offering people this potential
4 benefit because of what you're offering them.

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

12 DR. FOST: Let me just say what I
13 thought the reasoning of the study was -- the
14 hypothetical one -- and then Skip can say what
15 it really was.

16 I thought the idea was we know that
17 inhaled corticosteroids slow growth. We don't
18 know yet the second you can catch up if you
19 can go off them. But that gives you some
20 pressure to go off them. So you have to make
21 those judgments.

22 And if there were a drug that were

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1 just as effective in controlling the asthma
2 but had no effect on growth, then you wouldn't
3 have to worry about those trade-offs. You
4 wouldn't have to worry about taking the kid
5 off.

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

11 DR. NELSON: No, I think that's
12 fair. One could consider growth velocity as a
13 surrogate marker for ultimate growth and
14 recognize that doing a one-year study is
15 really sort of within the constraints of what
16 one would do for determining information for
17 labeling. Although of course, if everybody
18 caught up, that would be important to know.
19 So I think it's framed within that particular
20 sort of growth velocity.

21 You can see growth velocity changes
22 even within shorter periods of time as well on

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1 inhaled corticosteroids. And so I would sort
2 of assume that that's the focus of the case --
3 if you will.

4 DR. FOST: Elaine?

5 MS. VINING: I wanted to just
6 backtrack for a second because the inclusion
7 benefit was something that I had understood to
8 have some -- there was definitely an inclusion
9 benefit.

10 And I think that the discussion
11 seemed to get us to the point where the
12 inclusion benefit was focused only on poor
13 people. And I don't see that as I'm looking
14 at this, because I think that there are
15 significant benefits to folks outside of the
16 poor people. People have co-pays. People
17 have parking expenses. There are a lot of
18 things that if my child is in an ongoing
19 program that is going to have some benefit to
20 them, perhaps inclusion benefit could actually
21 be a reality.

22 There's a consistency in seeing a

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

11 DR. FOST: Skip?

12 DR. NELSON: Just to perhaps
13 clarify the importance of the question with
14 two comments.

15 I think there needs to be a
16 distinction between the benefit of potentially
17 going into a clinical trial as it may impact
18 on parental decisionmaking. That's a very
19 different question whether it's beneficial to
20 go into the trial for whatever reason, which
21 may or may not relate to access relative to
22 insurance. It might relate to whether or not

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1 you want to get care at institutions that only
2 accept people on research trials, which
3 there's at least two I know of that do
4 pediatric research.

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

14 I might say that this is not a
15 trivial issue, because there have been instances
16 where IRBs have used this benefit to

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