



Presidential Commission
for the Study of Bioethical Issues

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TRANSCRIPT
Trial Design and International Standards

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Meeting 6, Session 7
August 30, 2011
Washington, DC

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3 DR. GUTMANN: Welcome back, everybody. We are
4 now in session seven of this two-day commission
5 meeting, and I am very pleased to welcome our two
6 guests, Ruth Macklin and Robert Temple. And I
7 would -- will briefly introduce both of them. They are
8 widely known and respected, and will present us with
9 two different views on the topic of trial design and
10 international standards.

11 Ruth Macklin is Professor of Bioethics in the
12 Department of Epidemiology and Population Health at
13 Albert Einstein College of Medicine in New York. She
14 currently co-directs an NIH Fogarty International Center
15 training program in research ethics, which takes place
16 in Buenos Aires, Argentina. She is a member of the
17 research protocol review panel in the Human
18 Reproduction program at the WHO, and she also serves on
19 the Vaccine Advisory Committee at WHO.

20 She has published more than 200 scholarly
21 articles and chapters in bioethics, law, medicine,
22 philosophy, and the social sciences. She is also
23 author or editor of 11 books, including "Against

1 Relativism," and, most recently, "Double Standards in
2 Medical Research in Developing Countries." Ruth,
3 welcome.

4 I will also introduce Dr. Robert Temple, who
5 is Deputy Center Director for Clinical Science at the
6 FDA's Center for Drug Evaluation and Research. He is
7 acting Director of the Office of Drug Evaluation, which
8 oversees the regulation of cardiorenal,
9 neuropharmacological, and psychopharmacological drug
10 products.

11 Dr. Temple has a long-standing interest in the
12 design and conduct of clinical trials, and has written
13 extensively on the subject, especially on the choice of
14 control groups in clinical trials, evaluation of active
15 control trials, trials to evaluate dose response, and
16 trials using enrichment designs. He also has a
17 long-standing interest in the hepatotoxicity of drugs—I have to
18 confess I'm not sure what that is-liver?-Okay, now I know what that
19 means, I should have known that--
20 having participated in the first detailed FDA-NIH
21 outside discussion of the subject in 1978.

22 Look forward to both your presentations.

23 Ruth, would you please begin?

1 DR. MACKLIN: Thank you very much. I am going to have one
2 very simple message, and the simple message
3 is to defend a single ethical global standard, or a
4 single global ethical standard. That is a simple
5 message. But understanding it and interpreting it is
6 not so easy.

7 So, there are some complications. The first
8 complication is what counts as an ethical standard.
9 How would you frame the statement? How would you frame
10 the standard that you claim that one might claim to be
11 a single global standard? So I'm going to give a
12 couple of candidates for such standards, and I'm going
13 to throw them out -- reject them, I mean.

14 (Laughter.)

15 DR. MACKLIN: One candidate for a single
16 standard might be phrased as follows: If it's
17 unethical to carry out research with a particular
18 design in a developed country, or an industrialized
19 country, it is unethical to do that same research in a
20 developing country. That's one candidate for how one
21 would compare the design, the research design, in a
22 developing and developed country.

23 Well, I argue that that's flawed, because the

1 particular circumstances can be sufficiently different
2 to warrant different designs. So, for example -- and
3 this is the example I am going to use twice -- research
4 on a preventive or therapeutic method that could be
5 used or designed to be used in remote, rural areas with
6 poor infrastructure could require an experimental
7 intervention or comparator that would not be used in an
8 industrialized country.

9 And I want to point out here and emphasize
10 that it's the infrastructure that is the problem, the
11 inability to conduct the trial, or to bring the
12 products of the trial.

13 Here is a second example that I am going to
14 throw out, another candidate for a single standard in
15 research design might be phrased as follows. All
16 participants in research should receive the level of
17 care they would receive in a developed country.

18 Now, some people around the table may
19 recognize that statement. I'm not sure anybody has
20 ever argued for it. But this is flawed for basically
21 the same reason as the previous one, because adherence
22 to this requirement would make it impossible to do

1 research designed to develop treatments for some
2 diseases or some conditions, again, in remote rural
3 areas of developing countries. Or, even if they're not
4 rural areas, there are places even in a city where the
5 infrastructure simply doesn't allow you -- you might
6 need an ICU, for example, an intensive care unit. So,
7 such research, however, is critically important to test
8 interventions that can benefit people in countries with
9 poor health infrastructures.

10 So these are some of the reasons why those
11 descriptions, or those interpretations of a single
12 ethical standard, will not work. So let me turn to
13 placebos, because that's the area in which Bob Temple
14 and I have grappled on many occasions, and the one that
15 seems to raise -- it's not the only research design
16 question--but seems to raise the most controversy.

17 And here is the double-standard position.
18 Placebo controls are acceptable in developing
19 countries, where many people lack access to proven
20 interventions. And the ethical defense is that
21 subjects are not made worse off than they would be if
22 they were not enrolled in the research at all, since

1 the placebo control group would get the placebo, which
2 would be, let's say, equivalent to nothing, and the
3 other half would get an experimental product that may
4 or may not work.

5 A second point is that a cost -- this is the
6 defense of double standards -- a costly proven
7 intervention would never be available to the
8 population. So why include it, according to this
9 argument, as an arm in the study if it's never going to
10 be available?

11 And the final point -- and this is boiling
12 down the argument to the barest essentials -- is that
13 research subjects are treated equitably. Now, what
14 does equitably mean here? The argument is they receive
15 the level of care that patients in the same community
16 receive for the same disease, or same condition. That
17 may be nothing if it's a placebo-controlled trial.

18 So, this is basically the argument that people
19 are not being made worse off. And the question is
20 whether that is a minimal ethical standard, or
21 a -- let's call it the minimalist view of ethics--that
22 you're not making people worse off, even if you might

1 design the trial in such a way that they could be made
2 better off.

3 Here is the single standard position on
4 placebos. This holds that the same standards -- again,
5 standards for use of placebo -- in the sponsoring,
6 industrialized country should be applied in the
7 resource-poor country. And here the statement is, "If
8 patients in a developing country who are not enrolled
9 in a clinical trial would receive no treatment, that
10 cannot justify -- that alone cannot justify withholding
11 an effective treatment from subjects in the research,"
12 if, in fact, one could design the research
13 appropriately.

14 I mean there are some premises here, that is
15 that you have adequate research design that can provide
16 answers. So that is the underlying premise, that is
17 that the science is sufficient to be able to obtain
18 answers.

19 So, the third point, placebos may not be used
20 in a control group in the poor country when an
21 effective treatment for that condition exists in the
22 industrialized country. So the question of justice

1 here is global justice. On the previous slide I said
2 local justice, meaning that the people who are in the
3 trial would be treated equitably, according to local
4 circumstances. But now we're looking at something
5 broader, and that's global justice.

6 So, I'm not sure how much the commissioners
7 are completely familiar with the international
8 guidelines, since we are talking about standards. So
9 the next few slides are simply going to pull out what
10 the international guidance - several--international
11 guidance documents say about research design.

12 Declaration of Helsinki in 2008. The
13 benefits, risks, burdens, and effectiveness of a new
14 intervention must be tested against those of the best
15 current proven intervention, except in the following
16 circumstances. And the first circumstance -- these are
17 probably better known than some of the other
18 guidelines -- the first circumstance is the use of
19 placebo or no treatment is acceptable in studies where
20 no current proven intervention exists. This is
21 non-controversial. Nobody rebuts that.

22 However, here is the tricky part -- and this

1 is my italics that I inserted -- "Wherefore compelling
2 and scientifically sound methodological reasons, the
3 use of placebo is necessary to determine the efficacy
4 or safety of an intervention, and the patients who
5 receive placebo or no treatment will not be subject to
6 any risk of serious or irreversible harm."

7 Now, the reason I italicized those words,
8 "compelling and scientifically sound methodological
9 reasons," is precisely because experts may disagree on
10 what is compelling and what is scientifically sound.
11 So there is where some of the debate is going to lie,
12 not so much with the first issue -- because the first
13 question, if there are no treatments, there is no
14 problem with using placebo. So, it's in the analysis
15 and determination of what is -- what are those
16 compelling and scientifically sound reasons.

17 Here is the Council for International
18 Organizations of Medical Sciences, their statement of a
19 single standard. "In externally sponsored research,
20 the ethical standards applied should be no less
21 stringent than they would be for research carried out
22 in the sponsoring country." So this is now a statement

1 about an international standard, a global standard.

2 But it is not enough clarity on what constitutes
3 standards.

4 The UN AIDS document, which is a companion
5 document to the one that Mitchell Warren talked about
6 this morning, here is what they say. This is their
7 comment on control groups. "The use of a placebo
8 control arm is ethically acceptable in a biomedical HIV
9 prevention trial, only when there is no HIV prevention
10 modality of the type being studied that has been shown
11 to be effective in comparable populations."

12 Here, however -- and they do give a couple of
13 examples: a vaccine that is not known to be effective
14 against a virus that is prevalent, or a microbicide
15 shown to be effective for vaginal intercourse but not
16 for rectal intercourse. So it can be different
17 populations, it can be a different product. So, those
18 are examples that can show when it would be possible or
19 acceptable to use placebo.

20 I am going to skip this, because the time is
21 running, and go to the ICHGCP, which is not an ethics
22 document, but this section of their efficacy section

1 has this to say. "In cases where an available
2 treatment is known to prevent serious harm, such as
3 death or irreversible morbidity in the study
4 population, it is generally inappropriate to use a
5 placebo control." Note that it says "generally."

6 "In other situations where there is no serious
7 harm, it is generally considered ethical to ask
8 patients to participate in a placebo-controlled trial,
9 even if they may experience discomfort as a result."

10 And here are the two ethical points: "provided the
11 setting is non-coercive, and patients are fully
12 informed about available therapies and the consequences
13 of delaying treatment."

14 So, my last slide here, next-to-the-last
15 slide, is a statement from this European group. And
16 this is the point at which I want to emphasize,
17 which is that economics alone should not be the
18 determinant about -- of whether or not one may use a
19 placebo in a poor country. The European group says,
20 "Research activities involving human subjects cannot
21 exclusively be assimilated to an economic activity
22 subject to market rules."

1 On the contrary, in the context of solidarity,
2 regarding health as a public good, rather than as a
3 commodity, it needs to be regulated according to
4 fundamental principles. The general approach chosen
5 within this opinion is that fundamental ethical rules
6 applied to clinical trials in industrial countries are
7 to be applicable everywhere. So that is the global one
8 single standard.

9 And my conclusions -- I have one more slide,
10 sorry -- the basic value underlying the defense of a
11 single ethical standard is global justice. And the
12 disparity in economic circumstances is not a morally
13 relevant factor for determining ethical standards for
14 research design, when the external sponsor is a wealthy
15 country or a pharmaceutical company.

16 And in -- my critique of double standards
17 concludes that financial inequalities -- to endorse
18 double standards would be to include that financial
19 inequalities should be a significant determinant of
20 global justice in the design of research.

21 DR. GUTMANN: Thank you, Ruth. Robert?

22 DR. TEMPLE: Now, let me just say

1 preliminarily that the main issue in a lot of this is
2 -- turns on what the consequence of not getting the
3 standard therapy is, and that will come up repeatedly.

4 The major concerns in all this about the use
5 of placebo are two main issues. One is there is a
6 general concern about the use of placebos, mostly
7 raised by the 2000 Declaration of Helsinki -- I will
8 touch on that -- and then the fundamental question of
9 what a person in a trial is entitled to, best local
10 versus best global therapy, all of which Ruth has
11 touched on.

12 And a second important issue on the case where
13 being deprived of the therapy could have consequences
14 to the patient that are serious is where this is being
15 done, and whose interest the trial is serving. And I
16 will try to get to those.

17 In symptomatic conditions -- this is a long
18 story; I will be glad to dilate on it later, if you
19 want -- in symptomatic conditions with very few
20 exceptions, only a trial showing a difference between
21 treatments is going to be interpretable. If you merely
22 see no difference, that is what is sometimes called

1 equivalence or non-inferiority in symptomatic
2 conditions, it is usually impossible to determine
3 whether the drug, in fact, worked. We have a long
4 guidance out on non-inferiority studies. This was also
5 addressed in the ICH document E10.

6 The main trouble is, with symptomatic
7 conditions, you don't know whether the supposed act of
8 control actually had the effect it was supposed to have
9 in the trial. A typical example is depression, where
10 drugs we are quite sure work beat placebo about 50
11 percent of the time. So if you do a trial and you see
12 no difference from the active control in a depression
13 trial, how do you know whether this was a trial that
14 could tell, or a trial that couldn't tell the
15 difference between active and inactive treatments?

16 So, with exceptions, symptomatic conditions
17 generally need to show a difference. You can be
18 better, or you can beat a placebo. That's what you
19 have to do.

20 So, in 2000, when the World Medical
21 Association essentially banned placebos whenever there
22 was a known effective therapy -- as Ruth showed you, if

1 there is no effective therapy, placebos are fine -- had
2 people followed that advice, there would have been no
3 more development of symptomatic treatments if there was
4 an existing therapy.

5 Now, some people would say if the new therapy
6 isn't better than the old ones, who cares anyway, but
7 we can go into that. New treatments often have
8 advantages that are not in the form of superiority.
9 They may be better tolerated, there is lots of reasons.
10 They may have additive effects, when you study them
11 later. You do want new symptomatic treatments, in
12 general.

13 So, let me just go quickly through the
14 Declaration. So, from the very beginning, at least as
15 early as 1975, the Declaration said in every medical
16 study, every patient, including those in control, if
17 any, should be assured of the best proven diagnostic
18 and therapeutic method. It has always been unclear to
19 me what they meant by that, because even in an active
20 control trial people aren't getting the best therapy,
21 they are getting something somebody wants to test.

22 Anyway, there were some people -- notably

1 Rothman and Michaels in a pretty famous New England
2 Journal of Medicine article in 1995 -- said that means
3 if there is an existing therapy, you can't use a
4 placebo. And you know, in arguments on stages, Ken
5 Rothman said you can't test a new drug for baldness
6 because there was Rogaine. You can't have a placebo
7 control trial of baldness or seasonal allergic
8 rhinitis. You just can't ever do it. It's unethical
9 and unacceptable.

10 Of course, as I said, read literally, the
11 active control trial also doesn't give people a known
12 effective therapy. So, as a result, nobody took this
13 particularly seriously until 2000, when, as Ruth showed
14 you, it now said the benefits, risks, burdens, et
15 cetera, have to be compared. You can use a placebo
16 when there is no known therapy. But, otherwise, it
17 clearly says you can't. So that means if there is an
18 existing therapy, an allergic rhinitis, baldness,
19 whatever it is, you cannot do a placebo control trial.
20 Everybody noticed. IRBs were very concerned, because
21 they thought you wouldn't be able to do trials any
22 more.

1 After a lot of concern by FDA, HHS, and a lot
2 of people, the World Medical Association eventually
3 changed it. They made a mistake initially. They said,
4 "Where for compelling" -- this was in 2001 -- they
5 said, "Where for compelling methodological reasons it
6 was necessary to use a placebo, or where a prophylactic
7 diagnostic was being investigated for a minor
8 condition."

9 Well, that's not right. That first one is
10 grossly unethical. That says if you can't get
11 information, except with a placebo control trial and
12 you have to kill a lot of people to get that
13 information, it's okay. That's wrong. They fixed it
14 in 2000. It now lumps those two together, and it
15 basically says if no harm will come to people -- you've
16 seen this already, so I won't repeat it -- if no
17 serious harm will come to people, and if it is
18 methodologically necessary, placebo control trials are
19 okay. That's what it says as of 2008, and I think
20 there is pretty general agreement that that's okay.

21 ICH E-10 in 2000, in my view, got it quite
22 right, and it said the principal issue in use of

1 placebos is the ethical one. There is no issue when
2 there is no effective therapy. The question is when is
3 it acceptable not to give existing therapy to people in
4 randomized -- with a drug or placebo. And I am -- I
5 underlined "available," because that's what it said.
6 In cases where available therapy is known to prevent
7 severe harm, you cannot use a placebo.

8 The "generally," by the way, was a hedge
9 word -- I remember it, because I threw it
10 in -- referred to cases where the treatment is so toxic
11 that people won't take it. So low-dose AZT was tested
12 against placebo, because nobody would take the high
13 dose. So that was the only exception. It wasn't meant
14 to hedge too much.

15 In other situations where there is no serious
16 harm -- and, you know, Zeke Emanuel says, "Well,
17 serious harm, irreversible harm, those are all
18 ambiguous" -- I don't think it's that ambiguous. If
19 it's really bad for people not to get an available
20 drug, you mustn't not give them a placebo. And there
21 could be arguments about how much vomiting is
22 unacceptable. We all agree. ICH E-10 says that.

1 Where there is no serious harm it is generally
2 considered ethical to ask patients to participate in a
3 placebo-controlled trial, even if they may be
4 uncomfortable. You have to give them adequate
5 information, they can't be coerced.

6 One could raise debates about how much money
7 is coercive -- perfectly good question. And it points
8 out whether a particular placebo-controlled trial will
9 be acceptable to subjects, investigators -- could be
10 debated. And one country might conclude one thing
11 about highly emetogenic chemotherapy, and another place
12 might think something else. And, of course, the
13 patient is supposed to be informed enough to know.

14 This is now more or less what the Declaration
15 says. ICH E-10 refers to available therapy. It is no
16 accident they didn't address the question of whether
17 available meant in that country, or all over the world,
18 because that was just too hard. They didn't want to get
19 in -- we didn't want to get in to the best local versus
20 best global.

21 So, under ICH E-10, however, this whole issue
22 is only of interest when you're talking about a

1 treatment that prevents serious harm, because those are
2 the treatments that would ordinarily have to be given,
3 if they were available. Symptomatic treatments are
4 probably not an issue, and I don't think there is much
5 controversy on that.

6 So, suppose the treatment really is
7 important -- and we actually discussed this at a WMA
8 meeting, and I would say there was a fair amount of
9 agreement on what I am about to tell you, but we'll see
10 what you think. Suppose a clinically-important
11 treatment is not available in a developing country.
12 That actually can happen in a developed country, where
13 a country chooses not to approve a treatment. That has
14 happened from time to time.

15 And -- but let's also suppose -- you have to
16 stipulate this -- that a comparison study comparing
17 some new treatment with the established treatment would
18 not be informed, that this is a case where you have to
19 have a placebo to have it be interpretable. And that
20 could be debated, too, but the issue doesn't arise in
21 that case. If a non-inferiority study is available,
22 you just do the non-inferiority study.

1 So, can you study a new drug with same
2 therapeutic goal as existing therapy in a developing
3 country, where the standard of care is not available?

4 And I think there are two distinct cases. One
5 is the one Ruth referred to, where the trial clearly
6 serves the interest of the country, because they can't
7 deliver the standard therapy, they don't have the
8 clinics, they don't have the techniques. The other is
9 where the trial is being done solely because of a
10 commercial interest. Someone wants to make use of the
11 fact that the drug is not available in that country to
12 do a placebo controlled trial that would plainly not be
13 acceptable in his own country. And you can get into
14 whether he plans to market the drug in the other
15 country, and all that stuff.

16 So, let's consider those two issues. The
17 general view at the WMA -- and I think Ruth referred to
18 this as the things that she worried about being
19 excluded -- was if you could say that the country
20 needed the information, that it was important to them,
21 and they needed to know the results -- and remember, it
22 couldn't be obtained with an active control trial -- it

1 was okay to do the trial.

2 The famous HIV transmission study which got a
3 lot of discussion is a good example of that. If it's
4 true that a non-inferiority study would not have been
5 informative and, as Ruth and I were just discussing,
6 that a historical controlled experience wouldn't have
7 been informative, the only way to find out whether
8 short-course HIV was effective was to do the placebo
9 controlled study. And that's why Barnes and Thatcher
10 wrote that it was okay.

11 The disagreement was largely from Wolfe &
12 Lurie, because they thought an active control trial
13 would have been acceptable, and I don't agree with
14 that. But that's not the philosophical argument.

15 Another example, we've been talking about the
16 use of rectal artesunate, where it really would have
17 been better to just give, you know, IV quinine or
18 something. And, in general, this refers to any therapy
19 really needed by the county that they have good reason
20 to get.

21 So, the thought there -- I think the general
22 agreement was that it would be acceptable not to give

1 the therapy that was available in the advanced country,
2 because you had no choice; it couldn't be given.

3 Briefly take the other --

4 DR. GUTMANN: Robert, I'm going to just ask
5 you to try to wind up. I need to give --

6 DR. TEMPLE: I can do that.

7 DR. GUTMANN: You will have a chance to answer
8 questions.

9 DR. TEMPLE: Okay. The other case is the
10 famous Surfactin case, which I won't dwell on, where
11 the purpose of the trial, plainly, was to get it
12 marketed in the U.S. There was good reason to believe
13 that nobody in the trial would be better off -- would
14 be worse off than they would have been without the
15 trial, but they clearly would not have gotten standard
16 therapy. Most people did not feel comfortable with
17 that approach. It was not for the purpose of a
18 country, it was so that somebody could get the data,
19 and to go market the drug in the United States.

20 I just want to pose the question that, having
21 abandoned that trial, which the company did under
22 publicity, it's very clear that more babies died in

1 Latin America than would have died if the trial had
2 happened. Now, nobody seems to be bothered by that,
3 but it seems worth thinking about. Because they
4 weren't getting the drug.

5 And I think that may be my end. Okay. We
6 sort of addressed this. Okay.

7 DR. GUTMANN: Thank you very much. This is an
8 active issue for us to consider. And I want to open it
9 up to commission members to make comments or ask
10 questions.

11 (No response.)

12 DR. GUTMANN: I will begin, if nobody -- let
13 me just ask both of you, because you have, no doubt,
14 read the sounding board response, "The Ethics of
15 Placebo-Controlled Trials: A Middle Ground," that was
16 in the New England Journal, co-authored by Ezekiel
17 Emanuel and Franklin Miller. It would be helpful for
18 us if we could hear your response.

19 Robert, to you, the authors say psychological
20 and social harm caused by depression, for example, are
21 either not considered or dismissed. In other words,
22 when -- you began to address this, but what

1 actually -- how broad are you -- do you want us to
2 interpret harm?

3 And let me just -- I will just pose the
4 complementary -- there are many questions here, but
5 this suggests a middle ground, just for us to
6 understand how far apart you really are.

7 Ruth, the co-authors say that the dichotomy
8 you've proposed between rigorous science and ethical
9 protections is false; scientific validity constitutes a
10 fundamental ethical protection. I'm sure you would
11 agree with that. But here is the -- if placebo
12 controls are necessary or desirable for scientific
13 reasons, that constitutes an ethical reason to use
14 them. Although it may not be a sufficient reason, it
15 is a reason.

16 So, if you -- if I start, either one of you,
17 if you could, just say where you see the common ground
18 lacking here, because it does seem like once you take
19 into account the need for scientific validity, which is
20 an ethical consideration, we believe, and once you take
21 into account a range of harms that would be serious
22 harms, there is not -- it is at least hard for me to

1 see why we can't agree on this middle ground from both
2 your perspectives, unless you really are orthodox, as
3 orthodox as this suggests you are.

4 You want to start, Ruth, and then we will do
5 Robert?

6 DR. MACKLIN: I should say that where I stand
7 with regard to that claim and the article, I am not a
8 defender of active control orthodoxy.

9 DR. GUTMANN: Okay.

10 DR. MACKLIN: The middle ground is between
11 placebo control orthodoxy and active control orthodoxy.

12 DR. GUTMANN: Correct, correct.

13 DR. MACKLIN: I accept the middle ground. I
14 accept the arguments. And I also accept the examples
15 that Bob gives of the circumstances in which -- which
16 he refers to as the symptomatic cases, in which you
17 really can't tell whether it's the disease, the
18 remission, the -- I accept all of that. So -- and the
19 middle ground actually tries to work between those two,
20 and --

21 DR. GUTMANN: Right.

22 DR. MACKLIN: -- that's the middle ground.

1 So --

2 DR. GUTMANN: Correct.

3 DR. MACKLIN: -- that's where I stand on that
4 issue.

5 DR. GUTMANN: Okay, okay.

6 DR. MACKLIN: Where I -- let me say the other
7 thing is I think there may not be agreement on what are
8 the scientifically and methodologically compelling
9 reasons to use placebo. And so the challenge there is
10 to see whether --

11 DR. GUTMANN: Okay.

12 DR. MACKLIN: -- there are other
13 methodologists who might challenge Bob's view on when a
14 trial might be uninformative in the non-symptomatic
15 cases.

16 DR. GUTMANN: Right, fair enough. Very good.
17 That's very helpful to us. Robert?

18 DR. TEMPLE: There might be somebody who would
19 do that, but we haven't been exposed to them. I think
20 there is broad agreement that if, under the
21 circumstances, we say an active control is not
22 informative -- I mean we just wrote a long guidance on

1 this, 40 pages of stuff to people to disagree with if
2 they want to. We have not had disagreements with the
3 fundamental principle; we have had disagreements about
4 some of the edges.

5 I didn't feel that Zeke described a middle
6 ground at all. I think he described what exactly our
7 position was. If you really believe that -- yeah, we
8 -- Susan and I talked about that considerably. We
9 didn't think -- it reads like E-10 to me. If you
10 really believe that not getting an anti-depressant is
11 going to be dangerous, if you have evidence to that,
12 then you can't study new antidepressants. Put it away.
13 We totally agree. The question is whether that is
14 true.

15 And if you look at, you know, thousands of
16 depression trials, you won't see an increased suicide
17 rate in the people who didn't get treated; you actually
18 see increased suicidality in the people who are
19 treated -- he didn't know that at the time he wrote
20 that; that's more recent news -- but if there is a
21 risk, even a low risk of something bad happening, then
22 you can't do it. We agree with that.

1 His example of severely emetogenic
2 chemotherapy, we have always been troubled by that and
3 thought that was at the edges. If it keeps you from
4 getting your chemotherapy, you have to either not do
5 it, design around it, or something like that.

6 And there are ways to make the period during
7 which a person is miserable and suffering shorter. You
8 can have your end point be the first sign of something,
9 instead of, you know, having to vomit for hours and
10 hours. You don't have to do that.

11 In the case of severely emetogenic
12 chemotherapy, actually, I'm quite sure you could do an
13 active control trial. But don't mistake that for
14 thinking that all studies work -- there has been a
15 review of studies of Ondansetron, which is the way you
16 prevent emesis. And in dozens and dozens and dozens of studies,
17 it failed to be placebo when it was being used
18 post-surgically. And the reason was simple. The
19 people didn't vomit, so you couldn't show an advantage.

20 So, in emetogenic chemotherapy, you probably
21 could use a non-inferiority study. There is a
22 legitimate question about whether people should be

1 exposed to this kind of misery. That's a perfectly
2 good question. There is -- we are -- I don't know what
3 the orthodoxy is. Everybody acknowledges that, so --

4 DR. GUTMANN: We are very pleased to --

5 DR. TEMPLE: I am comfortable with his
6 position.

7 DR. GUTMANN: We are very pleased to hear
8 that. We are not going to settle every scientific
9 dispute about particular studies, but if there is a
10 ground that the two of you agree on, that is an
11 important step forward.

12 So, let me call on Christine Grady.

13 DR. TEMPLE: I'll say one thing. I don't
14 think Ruth and I differ on very much. Probably the one
15 thing is the Surfactin case, where I'm not so sure that
16 is really wrong, and that deserves discussion. But I
17 realize most people don't agree with me. So I know
18 that.

19 DR. GUTMANN: Yeah. But there will be -- and
20 we could all agree on all the standards at a level of
21 specificity, and still disagree on particular cases
22 because of specifying the facts and the

1 counter-factuals.

2 So that is extremely important, what the two
3 of you have just said in response to my question. Let
4 me go on. Christine?

5 DR. GRADY: Thank you both. I think my
6 question follows a little bit on Amy's, in a certain
7 way, although I was thinking of it in a different way
8 before she started.

9 You both have been through the war, so to
10 speak, in terms of this controversy. And it sounded
11 like, from each of your presentations, that
12 with -- now, many years after the debates began, and
13 the changes to Helsinki, and the E-10, and the
14 literature that has been available to sort of carve
15 middle grounds, that actually, the disagreement between
16 you is hardly there at all.

17 And so, I guess the question that I would have
18 is, at this juncture in history, what do you think
19 needs to be done to sort of put this question to be, so
20 to speak? I mean what's still out there that is
21 troubling people, in terms of this question about
22 placebo control, or standard of care?

1 (No response.)

2 DR. GRADY: Or do you think we should put our
3 energy someone else? I guess that's part of the
4 question.

5 DR. MACKLIN: Well, I do think we should put
6 our energy someone else. But I think it doesn't help
7 to revisit the 076, that controversy, because people
8 are entrenched, and don't like to give up their
9 positions, whatever position they took. So that's not
10 helpful. New examples --

11 DR. GUTMANN: It's not helpful to go back to
12 those people who are entrenched, but that, if you ask a
13 lot of educated people who are following this debate,
14 that's where a lot of people think this is in this
15 debate, not where the two of you are now.

16 DR. MACKLIN: Well, I think what we have
17 to -- let me -- in order to answer the question, what
18 is the remaining disagreement between Bob and me?

19 Now, if it comes down to the Surfactin trial,
20 there was a -- later, an active control Surfactin trial
21 that was done, not a placebo-controlled trial. This is
22 not one of those cases of the symptomatic trial, of the

1 symptomatic situation.

2 So, the defense that Bob gave was fewer
3 babies -- yeah, some babies died that wouldn't
4 otherwise have died if the trial had been done. But
5 the question that arises is, "Why wasn't an active
6 control trial done? Why could it not have been done?
7 Would it not have yielded scientific information?" And
8 that's what I didn't hear. That, it seems to me --

9 DR. GUTMANN: So that's -- we're not going to
10 spend all our time on Surfactin --

11 DR. TEMPLE: No, but I will tell you we
12 concluded -- and whether this is right, in some sense,
13 doesn't matter -- but we concluded that showing
14 equivalence to the existing animal -- bovine-derived
15 surfactant would not be persuasive, because some of the
16 trials of the initial surfactant had not been
17 successful, even though we all know it's a wonderful
18 therapy, and it saves babies' lives.

19 What they eventually did was beat a synthetic
20 surfactant, which probably isn't as good as the actual
21 surfactant. So they were able to do a superiority
22 trial. A superiority trial would always have been

1 acceptable. No one would have ever doubted that. But
2 a non-inferiority trial to the bovine surfactant would
3 not have been interpretable.

4 Again, I am not all that knowledgeable about
5 the trial, so I don't know if that's true. All I would
6 say, though, is that if that is true, then you needed
7 to do a trial, show a difference.

8 By the way, they would never have done a
9 superiority trial in the Latin American countries, they
10 would have done it in the U.S. So that trial would
11 never have gone there, because, among other things, we
12 would have been less certain about the applicability to
13 the U.S. We worry about that.

14 So, it really is a case where the trial they
15 wanted to do could not have been done in the U.S.
16 Nobody disagrees about that. And it really focuses on
17 whether -- it really -- sort of depends on whether you
18 focus on the people in the trial, and how they are, or
19 how you feel about what it tells you about the world,
20 that you can do that trial there.

21 And I -- you know, I am into social justice,
22 but you've got to think about the people in the trial,

1 too. I think that's the tension.

2 DR. GUTMANN: John?

3 DR. ARRAS: Okay. So, Bob, I am detecting a
4 bit of a tension within your presentation, okay? So,
5 earlier in your presentation, you did make a
6 distinction that I think you thought was important
7 between studies that were done for the benefit of the
8 local population versus studies that are done simply
9 to, you know, get approval back here and market the
10 drug here. Right?

11 So -- but then, near the end -- and just now
12 -- you seemed to float a very different sort of
13 standard, which is what you might want to call a kind
14 of Pareto standard, you know. If people are made
15 better off, and nobody is made worse off, then it's
16 okay to do the study.

17 So, there is, I think, a tension between those
18 two sorts of standards, because you could say, well,
19 the fact that some people will benefit, you know, if
20 the trial is done, that's not a decisive reason if that
21 first principle is really paramount: namely, needed
22 within the local community, needed within that

1 country's public health structure.

2 So, could you discuss that a little bit? I
3 mean how do you reconcile those two? Because it could
4 be that you could just go with the second, right?

5 DR. TEMPLE: No.

6 DR. ARRAS: Okay.

7 DR. TEMPLE: The distinction is between what
8 the consequence of not getting the standard therapy is.
9 If it's a symptomatic condition, where the only
10 consequence of not getting the standard therapy is
11 you're symptomatic, I think that's okay anywhere you
12 want to do it.

13 And, for what it's worth -- I didn't mention
14 this -- the sorts of trials that people do of
15 depression in Eastern Europe and elsewhere are the very
16 same trials they do at home. So, everybody is treated
17 the same, and nobody comes to harm. I have no trouble
18 with any of those, wherever you do them.

19 There are people who are uncomfortable about
20 how many trials are being farmed out to poorer parts of
21 the world. Separate question. I have not been
22 addressing that.

1 This arises where there is clearly harm from
2 not getting the standard of care. And there I want to
3 make the distinction between -- this isn't necessarily
4 my position, but everyone is quite comfortable with the
5 idea that where doing the trial and not giving the
6 standard therapy is very much in the interest of the
7 country, because they will get a treatment for -- to
8 prevent HIV transmission that ain't the best, but it's
9 pretty good, or they'll treat malaria better than they
10 otherwise could have, even if it's not the best,
11 everybody, I thought, at WMA was very comfortable with
12 that.

13 What they're not comfortable with is my
14 thought that maybe it's okay to do a trial if everybody
15 in the trial is at least as well off as they otherwise
16 would be. People, in general, are not comfortable with
17 doing that in, say, Latin America for -- in order to
18 market a drug in the U.S. Okay?

19 And I think it's the social injustice. They
20 don't like the fact that you would have to do a trial
21 like -- that you could even get to do a trial like that
22 in those countries. They resent the disparity of

1 wealth, and things like that, all of which are
2 perfectly legitimate. I just think it's also important
3 to think about the people in the trial, because they
4 would have been better off.

5 DR. ARRAS: Well, yeah. And if you were a
6 parent of a child with that kind of lung condition, you
7 probably would want your child in that study.

8 DR. TEMPLE: I think you would. And they did.
9 That's why they wanted to do the trial.

10 DR. GUTMANN: Christine? Quickly, because we
11 have a hard stop.

12 DR. GRADY: I just wanted to follow up --

13 DR. GUTMANN: But I know Christine wanted to
14 follow up.

15 DR. GRADY: -- because it seemed like the
16 disagreement about Surfactin has to do more with what
17 some people call responsiveness or, you know, local
18 needs, than it does with the design of the trial, the
19 placebo.

20 So, is that right? I mean is the placebo
21 question settled, and we have to worry about these
22 other things, like whether or not responsiveness

1 matters? Or do we still have work to do on
2 what -- agreeing on when placebo is okay and not okay?

3 DR. TEMPLE: See, I think to approach the
4 ethical issue you should assume that you, in fact, did
5 need to do a placebo-controlled trial to get
6 information. I mean if you could do an equivalence
7 trial, then the issue doesn't arise. If you could find
8 a loser surfactant to beat, then the issue doesn't
9 arise, although you wouldn't do it in Latin America.

10 The issue arises where, for one reason or
11 another -- let's assume it's true -- you really can't
12 do an equivalence trial, and no one will let you do a
13 placebo-controlled trial where the drug is available,
14 because harm would come to people. You know, there is
15 a million drugs --

16 PARTICIPANT: Is there an example of that?

17 DR. TEMPLE: Oh, yeah. Suppose I want to know
18 whether a new -- okay, ACE inhibitors prevent death in
19 heart failure. Okay. How do I get a new ACE
20 inhibitor? How do I get that claim, if I'm a new ACE
21 inhibitor?

22 Well, I can't do an equivalence trial for a

1 variety of reasons, and the main reason is therapy has
2 marched on and now everybody gets a beta blocker and
3 Spironolactone, in addition to the ACE inhibitor. So I
4 don't know what the effect of the ACE inhibitor is. I
5 can't do the non-inferiority margin. So I can't do
6 that. But I could go to a country where there are no
7 ACE inhibitors, and show that the ACE inhibitor works,
8 compared to placebo.

9 Is that a good idea? Well, maybe if everybody
10 is better, and everybody gets a Spironolactone and a
11 beta blocker and a diuretic, and they're better off
12 than they currently are, and you compare added ACE
13 inhibitor with placebo, I'm not sure I'd object to that
14 trial.

15 But that's where the issue -- there is a
16 million things you can't study any more, because an
17 equivalence trial is uninformative, and you can't
18 deprive people of a known therapy that saves your life.

19 DR. GUTMANN: This has been enormously helpful
20 to us, and I think is an example of how bringing two
21 people who have sparred, but are very thoughtful and
22 responsive, can make a difference.

1 So, on behalf of the whole commission and
2 everybody present, we thank you very much.

3 (Applause.)

4