



Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

Commission Members

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James Wagner: Good point. So we are a rare situation of finishing a session ahead of schedule, so why don't we just move into—

Amy Gutmann: So we are going to move into our next discussion which is Study Design. Steve Hauser is going to introduce our thinking on this. Again, we will open it up for broader discussion of the Commission and our participants in the public.

Stephen Hauser: Thank you, Amy. Our subgroup has had numerous, very animated discussions that are still evolving and John has very ably led much of our thinking in the subgroup and Alex Garza is not here today but has also been quite active. Our discussions have centered on study design and we have focused around two general areas. The first is the science of study design, rigorous science as an ethical requirement. And the second, reviewing the tensions and possible ways forward between achieving scientific rigor, useful clinical information in some cases, while protecting patients.

To begin with the science behind study design considerations, it is clear that if the science is weak the ethics cannot be strong. These issues are particularly challenging in the new era of global trials. In addition to the myriad of clinical issues, there are scientific issues that are raised in new ways by global trials: genetic differences, disease differences, underlying heterogeneity, interaction effects because of environmental conditions, other drugs being used in some parts of the world, etc., and all leading to stratification responses. And it is very important that trials that are global take into account the stratification issues in different parts of the world so that we can understand if a study with one population is applicable for the other.

The second issue that spent actually most of our time on relates to what is probably the most contentious issue in this arena: the choice of comparison groups in trials. Our fundamental question was how to decide a path forward for determinations about comparative groups that are ethically acceptable. We, as others in the recent past, have moved towards a common ground for comparative groups. And the comparative group may either be placebo or, in some cases a choice of an active treatment that may arguably not represent the most effective treatment available.

We would propose that when the requirements of rigorous study design potentially conflict with the legitimate rights and interests of research subjects, that we embark upon this middle path that would protect subjects in this comparative group but only if certain conditions are met. We would propose six:

First, when the most effective treatment globally is not known to be the most effective treatment locally for a particular population because of genetics, the customary health behaviors, level of infrastructure or other considerations;

Second, when the choice of a particular comparator is required to advance a study that is responsive to the local host community;

Third, if potential harm or inconvenience to subjects is insignificant or extremely unlikely;

Fourth, there are weighty methodological issues behind the choice of that particular study design;

Fifth, subjects in the comparator group are not subjected to substantially increased risk of mortality or serious morbidity; and

Finally, whatever comparator arm is selected, IRBs need to carefully review and approve the scientific rationale and ethical justification for the study design. And IRBs should ensure that subjects at risk of harm from non-response are excluded, that the placebo or less effective comparator group is of limited duration, that subjects are carefully monitored, that rescue measures

are in place should symptoms develop, and that withdrawal criteria for subjects with adverse events are implemented.

Amy Gutmann: For people who weren't at our last session, I think it is important to remind everybody that we had a session in which we invited Ruth Macklin and Bob Temple who engaged in an ongoing debate about when placebo controlled trials are justified. There was a remarkable amount of convergence between the two, not just in our eyes but also in their eyes and said the actual science and the scientific consensus had moved forward and they outlined certain standard that they felt not only could they agree on but that scientists generally could agree on. But they admitted that there are a few people who still might have a raging debate but that there had been an enormous amount of convergence over recent years. This we put into the context, as Steve said, that this particular debate which has been raging is only one part of many issues of study design and one of the things that we will consider recommending, or at least finding, is that it is important for IRBs to look at the whole validity of the study design. This convergence, I think, have us all recognize that there has been some real progress here on how to apply ethical standards to actual trials in a way that "increases the light and reduces the heat" in this particular area.

Before opening this up for other people's questions and comments, I am just going to make a very general statement that we, as a Commission, made in putting forward our report on Guatemala. It frames what Steve has said on study design. There is no good ethics without good science because you should not conduct any human trials that don't have the promise of good science. And there is no good science without good ethics. So it is a two-way street here. So getting study design ethically right in general is a very important, and in this particular case, I think we can point to some real progress that is to the credit of both researchers and people that are doing ethics coming together and looking in great detail about how to best serve populations. Now it is up for any comments and questions. Raju?

Raju Kucherlapati: I think a couple of comments. One is that at the NIH, I don't know about other agencies, any research that involves foreign countries, it has to be justified as to why you cannot do such research in this country and why you need to go outside this country. Of course, any such research that is funded by the NIH and many other federally agencies are peer reviewed so any such applications for support require rationale for doing the study and include study design and so forth. So there are a number of different layers of protection to ensure the research is properly designed and that there is a rational reason for going outside.

For privately funded research, many of them are really related to getting a drug approved and that could be marketed in this country elsewhere and those are regulated by the Food and Drug Administration. And, again, the Food and Drug Administration ensures that all of the study design has absolutely is very clear cut and there is a very good rationale for it. And that it would lead to the kind of information the Agency would require for it to make a decision as to whether or not the drug is or is not going to be approved.

So the question that I have for all of us to think about is that, given the current set of rules and regulations and review procedures that we have, do we consider that they are not adequate? Or are we saying that there are additional things that we need to add in the types of recommendations that we have heard about that would strengthen them? A clarification of that would be very helpful.

John Arras: That's a good question, Raju. I think one of the purposes a commission of this sort is to try to bring consensus where that is possible on contentious issues. If we look at the history of

this particular issue, as Amy was suggesting, really dramatic progress towards consensus. At the beginning, as you'll recall, with regard to the perinatal AZT studies really the field was just split between two warring camps, one of which felt that placebo controls were acceptable and the other felt they were genocidal. Blood on your hands, right? So I think one thing we can do here is to try to nudge that emerging consensus along with the imprimatur of a Presidential Commission. So I think that is an important function that we can perform here. We are not saying that the system is broken. But we are saying that so long as the system adheres to the criteria that we set out, that it is a morally justified system. There is still some debate really about whether the good clinically practices approach is ethically acceptable. There are doubts out there, because it does not address the placebo issue, if I am not mistaken. And we can fill that gap.

Amy Gutmann: Dan?

Daniel Sulmasy: This may be a challenge or maybe you have already done this. But I think it might help if we could have an example of a study that would fit these criteria and one that would be excluded by these criteria. I think they are right and it would help us to be more reassured if we had some examples.

Stephen Hauser: I think, Dan, that is exactly right and that is our intention.

Amy Gutmann: And that actually should be easily doable because there are studies that have been done that don't fit this and there are many, many studies that do fit. So I think it would be good for us, when we get to the report to indicate that. And, of course, there are studies which are in the gray area because people don't agree about the facts of the study. As far as those studies that clearly do and clearly don't, there are more that clearly do than don't. And then there are a few where there is a raging debate, not about these criteria, but about whether the facts of the study fit them which is, of course, something that we as a Commission is something that we cannot settle.

John Arras: Just to follow up on that, Amy, I mention the AZT perinatal trials, that was the huge debate, and one of the crucial pressure points in that debate was really a kind of -- well to call it a factual question is really a bit misleading, but it was a question about methodology. And whether a placebo really was necessary because the opponents were saying you could do an active control trial here and get the information you need and others were saying, "No, you can't."

Amy Gutmann: And those we put in the gray area because we are not constituted -- and I don't know if anyone is -- constituted to settle that particular one.

John Arras: Yes, it is a very complicated scientific question.

Amy Gutmann: But what Dan is asking is eminently doable and I think it would be a good idea to include that in our report.

James Wagner: It would bring out those principles.

Amy Gutmann: Yes, it would highlight the importance of those principles. I saw Christine?

Christine Grady: I have two questions.

Amy Gutmann: Again, if anyone has any questions, please put them on a card, they will be sent up here.

Christine Grady: The first one has to do with I understand the working group already moved away from just placebo to larger questions of randomized controlled trials. But as I'm looking at this, I am wondering whether we even need comparator in there. Couldn't it be just choice of design in each of these criteria?

Stephen Hauser: We have been searching for the word.

Christine Grady: Because I think many of them, and I love Dan's suggestion of examples, but there may examples in which there is no comparator group. But these still apply.

Amy Gutmann: So we could say it applies more broadly. But, in fact, the comparator group was what stirred this huge debate and I think it is incumbent on us to try to indicate where there has actually been progress in reconciling good science and good ethics.

Christine Grady: I wonder if we could do both, though. Recognize where it came from and go further.

Amy Gutmann: No reason why we can't do both.

Christine Grady: The second question is very specific and Steve I think you mentioned this. Criteria number three that says "harms or inconvenienced" and I'm wondering how you are thinking about "inconvenienced" because that is a pretty undefined term in this context and "insignificant inconvenienced" might be pretty high bar. I don't know. I just don't know what you were thinking about when you put inconvenienced in there.

Stephen Hauser: Well .. John, I see you are moving your microphone.

John Arras: Just to be closer to thee. I've got a comment but if you want to go ahead Steve.

Stephen Hauser: What we wanted to do was to define the terms of minimally risky or dislocating studies where a person might be asked to do something that might not be comfortable or might take time doing something else. Somebody comes in and is asked to participate in a study that might be a very simple study in the course of a medical visit. That sort of minimally disruptive study is what was on my mind. John?

John Arras: Yes. Christine is raising a generic question that can be asked at just about any attempt at standard making. Here, the focus is on words on harm and inconvenience. These are meaningful words and they should act as some sort of a check. But there is always going to be a big question about inconvenience or harm according to who, right? And what degree of harm or inconvenience crosses the threshold? I think it is just unavoidable that someone at some lower level is going to have to provide definitive meaning to those abstract terms in practice.

Christine Grady: Could I follow up?

John Arras: Yes, sure.

Christine Grady: I just wonder if we really want to say inconvenience. I think protection from harm makes sense. Inconvenience is different for each person and they may agree or not agree, depending on how inconvenient it is for them.

John Arras: That makes sense. Yeah. The debate in Zeke Emmanuel's paper that we are leaning on here is over this drug to reduce vomiting after chemotherapy. There was a major debate between Bob Temple and Zeke on the issue on how severe does the vomiting have to be.

Amy Gutmann: What Christine is raising is really about the word. The idea was that it doesn't have to be a physical harm, it could be having your life really thrown upside down because you are nauseous all the time. It is not going to harm you in any way ultimately. But the word "inconvenient" doesn't convey that. So we need to broaden the notion of harm.

John Arras: Discomfort, maybe.

Amy Gutmann: John is absolutely right. It is not going to be the case that we can use a word that is immune from have the need for interpretation. But that wasn't Christine's point. It was really that inconvenient seems trivial.

John Arras: It is not the word.

Christine Grady: Too broad.

Amy Gutmann: I think it sound trivial.

Raju Kucherlapati: Can I give you two specific examples of what you are talking about? In cancer, for example, one of the drugs that is used is antiangiogenesis compounds and they are very effective. Yet one of the effects of that is hypertension. So that is a mechanism based adverse reaction. So you cannot get a benefit from the drug without having some degree of hypertension. Similarly with lung cancer, there is a drug that is used that is called [Inaudible] inhibitors. You treat them and people get a rash. Rash is an indicator that the drug is working. So you cannot have any kinds of adverse of reactions associated with this and that would be bad. So all of these are called mechanism based adverse reactions as opposed to other types of things and one has to be careful in defining what it is that we consider to be acceptable and what we don't consider to be acceptable.

Amy Gutmann: And no one is saying it is unacceptable to have trials that have side effects. That is not what—

John Arras: They just need to be compensated for by the benefits of the drug.

Amy Gutmann: It is the proportion of benefit argument. You are not going to say any side effects

are justified, right? We'll put you on the spot, Raju. You're not trying to say that we can't have standards that require that trials have —

Raju Kucherlapati: I'm saying that we cannot speak in absolutes. All of them have to be nuanced. That's all I'm saying.

Stephen Hauser: We agree.

Amy Gutmann: Other questions or issues from the audience on study design?

James Wagner: Nothing from the audience?

Amy Gutmann: We can actually break early because we are going to go on late. So nobody is going to be deprived of a full day of working. We will reconvene at 3:45 and we will go on until 6:00 because we have Ken Feinberg who is coming at 5:00 and he turned his schedule upside down to get here. So we will reconvene here at 3:45, where we are going to have a broad discussion of equivalent protections, community engagement and site selection. Then our final session of the day, we will have a discussion with Ken Feinberg on compensation for research related injuries. Okay, thank you all very much.

