P R O C E E D I N G S

OPENING REMARKS

DR. SHAPIRO: All right, colleagues, I am going to begin the meeting. We have other colleagues that will be joining us shortly, but we have not an overabundance of time, given our agenda, and I would like to get started.

First of all, I would like to welcome all commissioners -- at today's meeting, and I want to say a few words about the objective of our meetings, both today and tomorrow, are.

I will focus right now only on the International Report. We will deal with other aspects of our meeting, very important aspects of our meeting, dealing with our Oversight Project, which we will be dealing with later today and tomorrow, but I will deal with that sometime after lunch.

So I want to focus my remarks right now on what I would propose as a way of proceeding with the material that we have in front of us, that is, chapters 1 through 5.

First of all, I want to apologize to the commissioners for the late delivery of the drafts of 4 and 5, 5 especially, which probably most of you got last night as you arrived here in town, depending on

how efficient FedEx was to your area.

And chapter 4 was only -- preceded 5 by a few days. And so I am going to structure our meeting somewhat differently so that after a few introductory remarks and comments with respect to chapters 1 through 3, I want to really recess the meeting to give all commissioners here a chance to review chapter 4 for maybe a half-hour, 45 minutes, to see -- make sure you have had a chance to look at that carefully. And then we will reassemble and discuss chapter 4.

And then we will repeat that procedure for chapter 5, which is something which most of you probably have only just begun to look at.

The objective is that -- my objective is I want to send the report for public comment sometime in the next 10 days. So that, certainly, in chapter 5, there have to be some, in my judgment -- I am going to recommend at least -- some changes. There may be others that come up in the meeting, that may come up in the next few days, both because of our discussion and communication we may have through e-mail and so on.

But my objective is to really get it out for public comment within 10 days. That will be a 45-day public comment period, which will take us past our Salt

Lake City meeting. So that the Salt Lake City meeting will be focused primarily, if not exclusively, on the Oversight Project.

By that time, we will have quite a lot of information. We already have a lot of information and some preliminary drafts of the first chapter, some initial recommendations in chapter 2.

We will have a good deal -- and some very interesting, at least I think very interesting -- supporting papers that have been provided to us by various consultants. We will have more chance to discuss that later on today and tomorrow. And so the Salt Lake City meeting will be focused primarily on that.

I hope that we will be able, in fact, however, to issue the International Report, or at least maybe -- no later than our December meeting at the very latest. We may have to -- we may find it useful to call one or two special teleconference meetings in the interim in order to achieve that, depending on where we are. But if we -- if that is necessary, that is what we will do.

But I simply think that this report is close enough and ready, and we ought to get that out as expeditiously as possible.

So we will focus, as I said, most of today on

chapters 4 and 5, and I really don't want to focus on the editorial issues that surround 4 and 5 except as they are central to an argument, but only on the recommendations, the ones that are proposed, and maybe alternatives to them, additional ones. But we want to focus our discussion on those recommendations.

Now, we have had chapters 1 through 3 in your possession for really quite some time now, and I really want to thank many of the commissioners for their extensive feedback on some initial drafts, which played a big role in bringing these chapters together. And I really want to thank you for your attention to that.

The reason why 4 and 5 were somewhat delayed, that is, you didn't get them until so close to this meeting, is it did take me longer to restructure chapters 1 through 3 in ways that made some sense, or were helpful to me, at least. It took me somewhat longer than I expected, and therefore, 4 and 5 came a little later.

The general feedback we have gotten, and those of you who have been following e-mail, it has been positive, of course. There have been some very positive and useful suggestions. I am sure we will have some others. But I really don't propose that we

focus on those right now. The commissioners have had those in their hands for a long time.

If there are additional issues that you want to raise on chapters 1, 2, and 3, why don't you see me at the break, and we will arrange to focus on those. So I don't want to brush by them, but we have been through these recommendations. We have accommodated, I believe, all the issues that were brought up regarding our e-mail discussion, and so I think we are really in pretty good shape, not perfect, but pretty good shape.

So I really want to focus on the recommendations that are before you in 4 and 5. Now, each of you, in addition to the text of 4 and 5, have this sheet, which has all the recommendations on one sheet, one following the other.

As you can see in this sheet, in chapter 2, there are only three recommendations that come, the central one being 2.2, which is the one that we focused most of our attention on in previous meetings.

Chapter 3 has a much longer set of recommendations. However, the number of recommendations has little to do with the importance or the impact of what we are saying, I have discovered. Since I think probably the three recommendations in 2, in some sense, in one way of thinking about it, are at

least as important as whatever we have -- I think it is 15 of them so far -- in chapter 3.

And so I am going to just go by those right now. And so please let me know at the break, or any other time, if there are particular issues you want to get back to. We certainly will arrange to do so in a way that is effective.

But I wanted to go, as I said now two or three times, to chapter 4 and chapter 5. Now, chapter 4, in a sense, is like chapter 2, at least in one way. It only has a small number of recommendations. It has essentially two, probably the most important one being Recommendation 4.1. But it has two, 4.1 and 4.2.

And then 5, in some sense, has a longer series of recommendations. I have to say, however, that we articulated these recommendations in 5 just this last week-end, and there are some issues -- there are some parts of these recommendations I am not very satisfied with, and we will bring those up when we get to that discussion.

So let's begin with chapter 4. Now, my proposal had been that we recess for something like half-an-hour so that members of the commission who received this late really have a chance to read through chapter 4, at least to give it one careful scan.

And I know Bernie didn't get it until I think he walked in here this morning. I think that is right. And others may be in that same -- so if there is no objection, we will just take a half-hour, and see how a half-hour works, to go through chapter 4, and then we will begin the discussion of the recommendations.

Does that seem reasonable to people? Steve? Okay. All right. It is now a quarter to. Let's try to call the meeting together again, or call our discussion together, in roughly a half-an-hour. Okay. Thank you very much.

(Whereupon, at 8:45 a.m., a recess was taken.)

DR. SHAPIRO: Okay, colleagues, I would like to call the meeting to order again if you would reassemble. All right. As I mentioned before at the beginning of our meeting, we are going to focus now on recommendations coming out of chapter 4.

And I don't want to deal at the current time with any editorial issues. But we are very dependent on you to please give us your recommendations, hopefully, before you leave the meeting in that respect. Because there are obviously improvements that could be made, and we would very much like to get your views on that.

But I want to at least begin by looking at the

recommendations themselves. So let me just -- I will try to negotiate this, or referee the discussion in some sense, and let me turn to Eric to present these recommendations.

We will just do them one at a time. In then 4, as it currently stands, there are really only two recommendations, although that may change as a result of our discussion. Eric?

DR. MESLIN: Thanks, Harold. Just a point of background, as you probably surmised, chapters 4 and 5 have been reorganized in a way that divides up recommendations into different clusters.

The recommendations in chapter 4 are now limited exclusively to those pertaining to what possible or potential benefits should be available, to whom they should be available, and by whom, or on whose shoulders the obligation to provide those benefits lie.

The two recommendations, the first on page 12, and the second on page 29, of chapter 4, try to identify these aspects of post-trial obligation. Recommendation 4.1, which attempts to deal with the Commission's wishes regarding the limitation of benefits to participants and what remaining benefits to communities and countries through negotiation, is before you.

The text says: "After a clinical trial is concluded, sponsors should continue to provide the successful research intervention or other effective treatment provided during the research to the research participants if these participants would not otherwise have access to an established, effective treatment. The duration, extent, and financing of this objection should be explicitly negotiated among the relevant parties in advance."

And then we have suggested some cross-referencing with other recommendations. The other would be 4.2 and 3.1.

DR. SHAPIRO: Okay. Thank you. Let's see what comments the people have. Alex?

PROF. CAPRON: I have a suggestion just for wording. I don't know if you want that now.

DR. SHAPIRO: Yes. No, on the recommendations, any and all suggestions would be very helpful.

PROF. CAPRON: The reference to "the successful research intervention" without prior reference just doesn't strike me as correct.

I would say: "After a clinical trial is concluded, sponsors should continue to provide a research intervention which has proven successful,

along with other effective treatment that was provided to participants during the research, if these participants would not otherwise have access to an established, effective treatment."

DR. SHAPIRO: That sounds useful to me. Have you written that out?

PROF. CAPRON: I have written it out.

DR. SHAPIRO: Let's discuss it further, but if you could keep this written out, we could then give the material to Eric -- Larry.

DR. MIIKE: Well, I have to discuss 2 in reference to 1, but I will save my main discussion until later. I think parts (a) and (b) of Recommendation 2 properly belong under 1, where if you are going to include in the protocol itself, it should really be in reference to the research participants.

I would also on (b) just include the part about the IRB. And then I have a lot more to say about 4, 4.2, later on.

DR. SHAPIRO: Well, okay. We will come back to 4.2. Thank you very much. We will come back to 4.2, because I think there are some changes necessary there myself. Other comments on 4.1? Carol ?

DR. GREIDER: I think it was implicit in some of the language leading up to 4.1, but it isn't

directly stated there whether the research participants are the people in the entire trial or the people who receive the initial treatment. That is, are the control -- is the control group included?

And I understood from reading the material leading up that it would be. But that is not stated very clearly here.

DR. MESLIN: The answer to your question is, yes, it would be, and no, it wasn't explicit. So you would have to decide if you wanted to make it explicit, realizing that in some trials, the placebo arm may be present. So those individuals weren't at that point receiving the intervention as part of the trial.

DR. SHAPIRO: Let's just see how the Commission feels about it. Let's not worry about the exact -- and, that is, whether all participants in the trial, regardless of which arm they are in, should have this benefit, which is the question Carol raised.

And I would be interested to know what the Commission thinks about it. It is easy to write the recommendation either way. David?

DR. COX: Yes. Based on the logic of why it is participants in the trial as opposed to the general population -- I mean, it doesn't make a difference whether you are in the control group or the

experimental group. I mean, if you are participating, you should receive the benefit, at least that is as I read the logic.

DR. SHAPIRO: Other views?

DR. COX: I would like to raise one other issue.

DR. SHAPIRO: Let's stick with this one just for a few seconds. I will come right back to you, David. Is that largely agreed amongst the Commission? Okay. We will make sure it is written -- let's make sure that that is explicitly stated, and we will have to formulate something just a little later on. David?

DR. COX: So in reading this recommendation, I mean, it is hard not to be in favor of it overall. But what concerns me is the fact that there are very few interventions in life that by themselves really are -- provide this kind benefit to people.

So it is always a combination of things. It is very seldom that one drug or one treatment has a major effect on people, occasionally, but very seldom. Most of the time, it is a drug that has incremental improvement in something, and it only really works in conjunction with a whole bunch of other stuff.

Now, the research demonstrates that incremental improvement, maybe a 10 percent increase,

but in order for the people to really see the benefit, what they need is X, Y, and Z in addition to the drug you have given them.

High blood pressure is a very good example of this, where any particular drug that you give isn't really going to help, but it is in conjunction with all sorts of other aspects of lifestyle.

Now, very frequently, the clinical trial itself doesn't include those other factors. But if the people are really going to benefit from this, and if you give that type of a treatment, ensuring it by itself isn't really going to help these people at all.

So are we saying that what they really need are all the other things that go along with it? This is very different from some drug that, basically -- if you give an antibiotic and somebody has an infection, you know, it is going to kill the organism.

So, for me, I think the implementation of this recommendation is going to get very muddied by that issue, which is: How many other things need to go along? Now, the wording is very carefully done, and Alex, you just hit the nail on the head by your wording on this. Because it is not just the intervention treatment, but it is the other things that were provided at the time of the clinical trial.

But I just want to point out that, very frequently, the things that are provided at the clinical trial aren't in and of themselves sufficient to make this product really useful to people. This is a classic misconception, I believe, that most drugs are magic bullets and are basically going to cure disease. They are not.

So I just -- I am comfortable with this point, and I realize I am not being, as usual, I am not being very precise, but how to make this distinction in the wording. Maybe the wording is okay, but I wanted to raise the issue and see if people feel this posed a problem or it is like not a problem.

DR. SHAPIRO: Larry?

DR. MIIKE: I guess I am responding in two ways. One is that the other arm of this recommendation is that if there is not an otherwise established effective treatment. So it doesn't say it has to be superior or equal.

Second of all is that we talk about the successful research intervention. So I read that to mean that if you are going to be able to prove a benefit in a clinical trial, it may not be the drug itself, but those other factors, and that is what would be provided, in a negotiated way.

DR. SHAPIRO: That was my intent, but I -- there are, incidentally, I should mention, I think it is obvious to every commissioner, there are a whole set of practical, logistical type issues that will make this not an easy thing to find an operational solution always. That is, I think, a part of negotiations.

You know, what about trials -- preliminary trials -- leading the way -- there is a whole set of issues. It is very seldom a single trial that shows it. Right? You need 20 trials, or whatever you need, to show the effectiveness. So there is a series of those kinds of issues that are certainly involved. Alex?

PROF. CAPRON: You know, David, I obviously have to yield to you on the medical side, but I will say that, in reading the reports of trials of drugs, I have the impression very often the manufacturers, in testing drugs, do actually bundle their new intervention with what is considered state-of-art basic care.

And to give the example that you use, if they are testing a new blood pressure medication, they would provide both the controls, and those receiving the intervention, with the panoply of behavioral counseling and exercise that is known itself to be effective. The

controls would get a placebo, and the others would get the drug.

Because, very typically, with this, you will see a very favorable response rate among the controls. It is just where the drug makes a difference, a yet more significantly better response rate among those receiving the drug. And that is -- it struck me as the reason, as you correctly say, to emphasize the other interventions there that have been provided.

But I don't have the same sense that you do, or that you suggest, that in many cases, people are treating their drug in isolation with subjects who are otherwise left as naive as possible vis-a-vis other forms of therapy or surrounding medical care.

I don't think drug manufacturers would like the prospect that they’re taking a step back in treatment and only seeing if their drug is a magic bullet.

DR. SHAPIRO: David?

DR. COX: Well -- and I think that is a fair statement. As usual, I laid out an extreme position on one side, because I can see that being an argument for additional resources.

If we make it really clear that it is what was provided in the trial, whatever that was, then I am

really happy with this. But in the sense of it being at least precise and logical.

DR. SHAPIRO: Right. Well, that is certainly the intent here.

DR. COX: But how effective that is going to be, I think, will depend on the situation. But that people can't argue it both directions is what I am saying.

DR. SHAPIRO: Other comments on 4.1 before we move on to 4.2? Alta?

PROF. CHARO: It is not on the language of the recommendation, but on the justification for it, if that is permitted.

DR. SHAPIRO: Sure. Absolutely.

PROF. CHARO: And I think it applies to 4.2 just as strongly. I have circled in the document a number of places where the word "obligation" appears, and I have done it because I find that, in the discussion that leads up to this recommendation, there is a set of arguments about whether or not there is an ethical obligation to provide post-trial care to participants. And, similarly, in 4.2, post-trial access to successful developments.

And I feel like the discussion of obligation is weakening the conclusions that we are trying to

reach. Because it is easy to argue that there is, in fact, no obligation. In fact, the very discussion has taken place around this table at various meetings.

And what could be argued, I think, quite easily is that, whether or not there is an obligation, it would, nonetheless, be a decent thing to do.

Whether you give it the name virtue, ethics, or say, be a mensch, in family language, or find some other way of describing it, I think it captures the actual reasoning behind the international and other national guidelines that call for this extended provision of services.

It is not because of a rigorous argument that says, this is something governments must do, but simply something that governments ought to want to do. I think it also helps us around some of the places in the text where there are comparisons to what we do for research participants here in the United States.

Because in the comparisons, where we say we don't do certain things for people here, and so critics have said, why should we do there? But we find that unpersuasive. Why do we find it unpersuasive?

Well, part of it is because, although it would be a decent thing to do in both places, there are policy reasons why you might choose to do the decent

thing in one place and not in another. And it has to do with politics, and with diplomacy, and with a sense of different circumstances, etc.

And I think it would actually strengthen the recommendations when they get to the point of saying, we think it would be a good thing to do. We understand that there are political and economic and logistical obstacles that will make it impossible to do it all the time, but to the extent that we can, I think we ought to. And we are calling on your decency.

I think in some ways, weakening our justifications will strengthen our recommendations.

DR. SHAPIRO: I think I understand and appreciate the point you are making. I think something like that, whether it is that exact language or some other type language, might be helpful also in tying what we have to say to other parts of the literature in this area.

And we might actually be helpful by making that distinction. Because in the literature, that distinction is very often not made, and you are quite right. Because the ethical obligation we argue, we say ourselves, maybe it works this way. Maybe it doesn't. Because it is not absolutely compelling the way some arguments could be, at least not to everyone. It may

be to some.

So I think that it is an interesting observation.

PROF. CHARO: And, if I may, it would then, ideally, but not necessarily before we go out for public comment, but ideally, I think it would then require a couple of paragraphs on one other thing, which is having identified things that you think would be decent things to do, or whatever language we pick, how does one decide which ones government should take on? To actually address that.

Because there are many places where the government could be making an effort, and how we pick and choose it is something that is worth discussing.

DR. SHAPIRO: I should -- I wanted to make the remark in response to something you said before. We should recall that it is not only governments involved here. Right? It is a whole panoply of non-government organizations, for-profit and not-for-profit. If you just look at the data, there is just a lot of these people involved. Alex?

PROF. CAPRON: Well, we -- you know, I agree with Alta that this is an issue that we have to be a little clear about. And I thought in some of our previous discussion we had -- without using the notion

of aspirational -- in the first chapter, we say we want to say things that are not merely aspirational, that is to say, pie-in-the-sky aspirational.

There is a notion of saying that a certain state of affairs is a more just, fair, or ethical state of affairs than another and that if you can achieve that, you have done the right thing.

If you aren't able to achieve it, you haven't failed in an obligation in the sense of having breached something, but I think that is the way -- Alta is agreeing on this -- and so I think if we can convey that thought. I don't know exactly where it comes. Perhaps Bernie has a suggestion.

DR. SHAPIRO: Well, let me just make a comment. Jim will be next and then Bernie. I thought a lot about that, that is, at least I tried to think carefully about whether I could distinguish a more ethical from less ethical state of affairs as it impacts relationships between nations as opposed to just relationships between people.

And I think -- I found it very helpful, but also very difficult to pin down, that is, very difficult to mobilize the arguments in any particular case that we ---

PROF. CAPRON: Mr. Chairman, I think we have.

I will have to find it, but I think we have language like that in chapter 1.

DR. SHAPIRO: We do. We have language -- we do have language.

PROF. CAPRON: Don't we?

DR. SHAPIRO: Yes, we do.

PROF. CAPRON: So that is why I just thought it was really contrary ---

DR. SHAPIRO: No, no, I understand. The only point I am trying to make is that I think we -- my own thinking on it, in any case -- is that we have to be -- it is a general statement. It is a general aspiration and will carry us forward, and I think you made good arguments, but not necessarily the final, telling argument. I think you are just agreeing with what Alta said before.

But I want to give Jim and Bernie a chance also.

DR. CHILDRESS: I agree with the direction of the conversation that Alta and Alex have just had and think that if we think in terms of the state of affairs, and a more decent state of affairs, we can use a lot that is here in terms of reciprocity and the relationships between research and so forth as indicating that state of affairs.

But what -- focusing on what a decent state of affairs leaves open, obviously, is the question of who should be bringing it about. And that is one of the advantages of obligation language. If it is specific enough, it can target the person, or the entity, who ought to do it.

But I would very much agree with going this direction and seeing what we can work out. Let me use that as an occasion also to say that in our text, the way we currently present Recommendation 4 and then move to the who should provide, we are not as clear at that point.

We have already said in the recommendation that sponsors should continue to provide. We have already said that. But then we move to the who should provide, and it seems to me we are mixing up in the text in ways that I couldn't try to sort out right now, but I think could use a bit more attention, the relationship with the participant in the trial and the host country in terms of getting at the who should provide, the different agents who should be acting.

I think that if we move to the notion of decency and decent state of affairs and recognize the different potential contributors to that, we are also going to have to then ask whether we can -- how we draw

the distinction between the decent thing to do relative to the research participants and the decent thing to do relative to the host country.

And so we may need to rework some of the arguments here, but I think the overall direction that has been proposed is a good one.

DR. SHAPIRO: Bernie?

DR. LO: Well, I also could agree that this line of discussion that we have having, I think, is very useful and very fruitful. This has not been addressed in the current discussions, and I think we can make a real contribution.

In terms of the distinction between what is legally enforceable and required and what is ethically desirable, I think we can push that a little further, at least from the point of view of what do researchers -- what should researchers do as opposed to what should governments do?

I think physician researchers are very used to having sort of ethical obligations imposed as a matter of professional norms that are not legally enforceable. So no one can force you to do it, but sort of part of being, you know, a good researcher, an ethical researcher or physician, is to do things that go beyond the mere legal requirements.

So I would try and put some of that in. That, you know, we are not going to hold people to this as a legal obligation, but I think it is, as Alex was saying, more than a pie-in-the-sky aspiration. It is an expectation that a good researcher should do. So it is a little stronger.

In addition, I think it is very important, as we specify both the what kind of obligation and who has the obligation that we be a little clearer about what exactly we are asking researchers to do.

All too often, I think, researchers are put in the position of being asked to do things that aren't really under their control. For example, they really cannot, given their own resources, go out and provide all the things we would like have provided to participants after a trial.

However, I don't think it lets them totally off the hook to say, well, it is a sponsor's obligation. I would like to suggest that we have some discussion that researchers have a professional, ethical obligation to try and do what they can to persuade the sponsors to follow through with the sponsor's obligation.

So I think one of the things researchers do not always say -- are not always willing to take on is

their role of an advocate, in a sense, for the participants in the trial or the population of the host country that is being studied.

Many of them feel this on a gut level and want to do things as individuals. I think we heard testimony earlier how they set up free clinics and volunteer to do all kinds of health care that is not at all related to the study, but it is just that they want to do something for the people.

I think that is good, but I think what is probably more to the point is that part of their professional job should be, in all their negotiations with the sponsor and the federal agencies that oversee this and other bodies, Harold, that you were referring to, that they become advocates for making the interventions that are proven effective more widely available.

We saw this early on in the AIDS epidemic, where, at first, researchers said, I am just here to investigate, to do the clinical trials. I will prove whether or not the drug works under certain circumstances. It is up to everybody else to make the drug available.

The AIDS community very rightly says, no. We need more from you than that. That you have a voice

that is going to be heard beyond just the voices of sort of members of the population being studies and the governments. And that scientists, researchers, ought to view as part of their professional role the obligation to sort of speak up and sort of advocate for this.

It doesn't mean they actually have to produce the tangible product, but they need to sort of do what is reasonable. I think, for many scientists, this could be a way out of their dilemma that they would like to something, but they don't have the resources.

We are saying, use your sort of persuasive powers to try and get the resources, and you do the best job you can. You can't guarantee it, but we are all better off if you sort of try and make the best argument.

DR. SHAPIRO: Thank you. Alta?

PROF. CHARO: (Inaudible.)

DR. SHAPIRO: David?

DR. COX: So, I really agree with what Bernie just said, and I have a suggested vehicle to incorporate both the prior discussion that Alta started and Bernie's suggestion -- is that the -- and it is already in our recommendations.

That the researchers have to, when they submit

their research plan, have a plan for how this is going to be implemented too. So what that does, it is what the researchers do best. They think who these different stakeholders and the various components that are required for such an implementation to take place.

It is not in their control to control all of those, the sponsors, the host country, but they lay it out of what the plan would be. And that is, I think, a reasonable obligation to give the researchers, to think about it. Because they are the ones that set up the study design too.

So they can think about what a reasonable approach to do this would, to clearly identify who the stakeholders would be by their strategy that would be required to implement this.

Then they are not in control if one of those key stakeholders, a host country, the sponsoring agency, whoever it is, doesn't play. Then their plan doesn't work. But that doesn't mean that they didn't try. And that fits this idea that, you know, you don't get dinged if it is not successful.

But you at least have to put forward a plan to show that you thought about it and to identify the stakeholders, and I think simply by identifying with a particular plan who has to play in order for it to work

helps shine a light on who you try and politically convince.

DR. SHAPIRO: Okay. Trish?

PROF. BACKLAR: And actually, following on this discussion, which Alta started, Alex, Bernie and David, you actually have written an argument in here that you can use, and that is, using the language of obligation of the researcher to the subject, or to the participant, similar to the obligation of the clinician to the patient, not muddling up the therapeutic misconception. So it is somewhere in here that you have stated it.

DR. SHAPIRO: Okay. Thank you. Those are really very helpful comments, and I think will help us fashion some of this language. Bernie?

DR. LO: I wanted to sort of throw in one other thought, which I would suggest we try and include in the report. We put a lot of emphasis on negotiating prior agreements before you actually do research. There is no question you have a lot of leverage as the host country and the potential participants before you sort of sign up to do the study.

But, realistically, once the study is completed and something is shown to be -- effective, you can mobilize a lot more support for transmitting

resources to the country.

And I think that while it is right to put a lot of emphasis on doing what you can ahead of time, we need to say something that, realistically, you are also going to, at least as a researcher, have to do a lot more afterwards once the study is in to really become even more of an advocate.

I just think back to the original HIV perinatal prevention trial. Once you have -- you know, no matter what you thought of the original Thai study -- once that was on the record, there was a lot more forceful movement towards getting access to zidorudine, because you knew it worked. If it is still hypothetical, people are going to say, well, yeah, maybe, maybe not.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I am very supportive of the tact that started with Alta. Perhaps would want to offer a somewhat of a variation on it.

The language of obligation versus being a mensch very much focuses on the individual, and I think what is at stake here is a concept of the role and meaning of the researcher. And that the researcher who undertakes those obligations as his or her own, a community which undertakes research where those

obligations are in play, has a very different enterprise of research than one which doesn't.

And what we are advocating is that the world in which research is characterized by people who take on those obligations that many other positive things eventuate from it. There is less of an opportunity or at risk of exploitation. There is more of an inclination to make the benefit available.

Effectively, what you were pointing to, to Bernie, was the advocates were saying, you need to reconceive the role of the physician and that one who takes on the obligation of health advocate is a different kind of role. And that that is a better world. So taking up that level, I think, can help explicate why the language of obligation is in play.

DR. SHAPIRO: Bernie?

DR. LO: No. I think that is very helpful, Steve. It strikes me, as I was reading the supporting test leading up to these recommendations -- while I think our discussion of sort of what is the ethical basis for these obligations is a good one -- we need to do a lot more work on sort of sorting through what we mean by the researcher's role.

And we sort of make an analogy to the physician's role, but I think that argument needs to be

made much more carefully and much more fleshed out, with particular attention to how is the researcher's role to subjects different than a physician's role to patients.

I think there are a lot of things there that if we can clarify that will actually help with the ideas that Steve was saying.

DR. SHAPIRO: Alta?

PROF. CHARO: First, for the sake of the people writing the transcript, mensch is spelled m-e-n-s-c-h.

DR. SHAPIRO: In all languages?

PROF. CHARO: In all languages. I actually am very interested in the way we manage to characterize the obligations of governmental and corporate sponsors without trying to detract from Bernie's focus on the individual researcher.

It is going to be the governmental sponsor and the corporate sponsors that actually have the funds to make these wonderful plans real.

Now, government can take on such tasks for itself as a purely political matter. Government creates lots of benefit programs that it is not morally obligated to take on, simply because it finds that it is politic to do so, and there is nothing to stop our

government from doing the same.

A more interesting question arises with regard to the imposition by the government upon the corporate sponsor, a requirement that the corporate sponsor be a good corporate citizen.

And yet we actually do that already to some extent, because in the context of the drug approval process at FDA, we have said that the corporate sponsors have to test the drugs in accordance with certain kinds of rules, or their data simply won't be used. It is not because the data is invalid. It might be very excellent data, completely technically useful.

But we have decided that we will forego the usefulness of that data in order to expand the sphere of influence of the government when it chooses to try and create a situation in which people are treated better than they have to be.

And I think that we might want to 4.2, or somehow in the test leading to it, somehow spell out this way in which government can choose to impose the requirement of "mensch-hood" on the corporate sponsors. Because without that, there is the risk of a kind of an over-reaching.

You have to explain why it is that you can

reach out, because we are a government commission. We are not the moral arbiters of the United States. We are simply advisers to the federal government as to how it should behave. We have to be able to spell out the justification and the means by which it could do this.

And a lot of it will probably be through things like the FDA's treatment of foreign data, which is the primary mechanism by which we can extend these rules to those corporate sponsors.

PROF. CAPRON: Alta, it is "mensch-heit." And the question is: Can Eli Lilly also be a mensch?

DR. SHAPIRO: Well, we will leave linguistics to another part of this report. Other comments? This has been extremely helpful, and we will have -- but are there other comments on 4.1? Now, we are going to get to 4.2, which has a somewhat different focus, in a moment.

Okay. Let's go on then to see what comments -- Eric, do you want to introduce 4.2?

DR. MESLIN: I think we have -- I want to make sure we don't lose Larry's suggestion. Although we have left 4.1, I don't want to leave it lying.

Larry, were you suggesting, if I heard you correctly, what is now 4.2 (a) and (b) would be moved up to 4.1 in some way?

DR. MIIKE: Except that on (b), just the part about IRBs and I would delete the second sentence.

PROF. CAPRON: I think that the second sentence of the existing 4.1, in effect, addresses the issues that are addressed in 4.2, in the (a), (b), (c) sort of things. In other words, Larry, doesn't that second sentence already say: "The duration, extent, and financing of this obligation should ---"

DR. MIIKE: No, but in (a), it talks about -- it is in the protocol itself. You say it is a protocol and then an IRB review, all of those negotiations; whereas, the way that 4.1 is currently written, that can be outside, and there is really no IRB.

PROF. CAPRON: Well, if you wanted to go in the direction you are suggesting, and I see what you are trying to do, it would seem to me that it would be more sensible to have a Recommendation 4.3, which says that in fulfilling the requirements of the prior two recommendations, 4.1 and 4.2, researchers should include this in the plan. IRBs should review it, and so forth.

DR. MIIKE: Well, actually ---

PROF. CAPRON: Because it really applies to both.

DR. MIIKE: Our original justification was

that these are improper burdens to place on an IRB and the researchers on 4.2 about obligations or negotiations for the whole country. And so I would personally be happy to leave it the way 4.1 is. I just -- my initial impression was that 4.2 (a) and (b) do not belong in 4.2.

PROF. CAPRON: And you were just going to ---

DR. MIIKE: And that if there was going to be something as explicit as that, it more properly belonged in 4.1 rather than 4.2.

DR. SHAPIRO: Okay. Other comments? Because Larry has made a suggested change here.

PROF. CAPRON: Well, I do not -- I don't favor that change, of moving it to 4.1. I mean, I think it is a substantive, separate issue as to whether or not the kinds of obligations to include this in a protocol, how you are going to go about this in a protocol, would apply in any of these circumstances.

I don't have problems with it, but I guess I reached the opposite conclusion that Larry does. That to the extent that we want to say that you have to plan for this, it belongs in the protocol, for which both the sponsor and the researchers have some obligation, and it should be reviewed by the IRB. They should know that it is there. They should make it a point of

looking for it.

DR. SHAPIRO: David?

DR. COX: Yeah. In this situation really, I agree with Alex, because I think this is the way to implement the list of stakeholders. It is not to lay out what the discussion is going to be.

I mean, most researchers are clueless as to how to actually implement this kind of stuff. But what they can do, as Bernie pointed out, is that they are real advocates for getting it to happen. And they can be sort of the oil for this.

So if they identify, you know, the funding agency, they identify some of the other people that they see are involved. And to have that in the research protocol, I think, is a reasonable expectation on researchers. It is not a reasonable expectation to expect them to do the negotiation, to go out there and do international diplomacy. That is not reasonable.

But if somebody isn't the spearhead of this, it will never happen. And the researchers may not get the funding agencies to support it, but at least what they have done is they have put the plan forward. And the funding agencies see that from the get-go.

DR. SHAPIRO: Other comments? Larry?

DR. MIIKE: I think the discussion is getting

mixed up between 4.1 and 4.2. All I am simply saying is that -- let me start from the beginning again.

I do not think that (a) and (b) belongs -- I don't think you should burden the researchers and burden the IRB for doing a plan that applies to the whole country or the community. That was my basic point.

If we are going to make something as specific as that, it belonged in 4.1, where we do say there is an obligation to research -- the participants. And that if we are going to negotiate that in advance, it has to be some place. And I think, actually, Dave, in your previous discussion, I thought I heard you say it should be in a protocol.

DR. COX: Yes.

DR. MIIKE: Yes. Right. Okay.

DR. SHAPIRO: I am sorry. I didn't mean to --

DR. MIIKE: So that was my point. Whether or not we say -- state this explicitly in Recommendation 4.1 is neither here nor there for me. All my basic point was that it does not belong in 4.2.

I don't agree with Alex that we need another 4.3. Because if we are going to include this, it has to be a corollary to 4.1 and not applied to 4.2.

DR. SHAPIRO: Let me try to see if I can understand what is being said here maybe and at least help myself understand; 4.1, okay, deals with obligations to participants. It doesn't deal with any other aspect as far as I understand the language there.

So that is one of the things that distinguishes it from 4.1; 4.2 talks about knowledge -- resulting from research to host communities and countries. It is really a different matter, and if we want to -- I mean, I agree with part of what Larry -- I believe that Larry is saying.

That is, if we want -- with respect to obligations to participants now -- I am not talking -- if we want that to be in the protocol, and we want the IRBs to approve the plan for that, then we have to say so. Okay. Somehow as a part of 4.1.

That does not deal with what 4.2 is really focusing on; 4.2 focuses on the suggestion, or recommendation, that indeed there be another set of negotiations going on that don't impact directly the participants, but impact the plans for perhaps making successful products reasonably available, or some other language like that, to these communities.

They also talk about a negotiation. They are prescriptive. They don't say what will happen, how it

will happen, and so on. And it asks again for IRBs to review the plan for that discussion and so on.

So let me try to break this up in the following way. Does the Commission believe that with respect to obligations to participants, which I will call 4.1 now, that those plans should be in the protocol and approved by the IRB?

(Many "yeses.")

DR. SHAPIRO: Okay. So we make that -- in that way, Larry, I think, your comment that that should be part of 4.1 or otherwise make something that relates it to 4.1. Yes.

PROF. CAPRON: Couldn't we simply say, as the second sentence -- and a lot of what Larry says -- the research protocol should specify how the duration, extent will be explicitly negotiated among the parties in advance. Does that do it?

DR. SHAPIRO: In 4.1.

PROF. CAPRON: I am reading it on the separate sheet, and I don't have all the other -- here it is. "The research protocol should specify how the duration, extent, and financing of this obligation will be explicitly negotiated among the relevant parties in advance."

That puts -- and, obviously, the sponsor and

researcher are responsible for the protocol, and the IRB is responsible for reviewing it. And I don't think we have to say more.

DR. SHAPIRO: David?

DR. COX: But in the same sense, Harold, then -- I didn't get it, Larry -- now I get it -- but you don't want the IRB going and seeing if the negotiations were successful or not. Because that is not ---

DR. SHAPIRO: No, no ---

DR. COX: Because that is not the point.

DR. SHAPIRO: No, that is not -- that is right.

Excuse me. Alta?

PROF. CHARO: I think part of the reason why this might be confusing us is that in the reorganization of these materials, I think actually the text is not completely correlating with the recommendations.

If you look at page 9, for example, the sub-heading is "What Should Be Provided to Communities and Countries?" But you get then, three pages later, to the recommendation, and it is about -- the focus there is on participants as opposed to countries. I mean, the slicing is different.

Then the sub-head after 4.1 is "Who Should

Provide Post-Trial Benefits?" But that is actually something already covered in 4.1. I mean, basically, it seems to me -- in anticipation of what you were surveying people on, we might want to flip some of the internal organization of the text and divide it into two recommendations.

The first one deals with participants and has three elements. What are they going to get? By whom? And how is it implemented? And then the next one will be obligations to the general country -- generally, to the country. Again, what are we saying that they ought to be getting? Supplied by whom? And implemented how? And it may allow us to break it out more effectively.

DR. SHAPIRO: That sounds useful, and I think we have here -- I am not going to repeat all the language now -- I think we have agreement on what we want to say in 4.1. Okay. But I think your observation is correct regarding the placement of the recommendations and so on. So I think that is very helpful, and we will re-organize that.

But let's now go on to see what it is what we want to say under -- what recommendation we want to have

-- under what is now 4.2, and 4.2 deals with arrangements to make successful products, other

knowledge, and so on to host communities and countries. That is what dealing with here.

The recommendation, as currently written, to be modified, talks about this is an issue to be negotiated by the parties, and then (a), (b), (c) talks about aspects of that. So let's focus our attention on that. Now, we are dealing with hosts, communities, and countries. Alex.

PROF. CAPRON: Well, in the recommendation itself -- I don't know if you announced this before -- but we discovered that there is a ---

DR. SHAPIRO: I did not.

PROF. CAPRON: -- word missing toward the end of the third line, where it says "...benefits resulting from research..." You need a comma and then the word "available." So it says -- will say: "Researchers and sponsors should negotiate in advance with the relevant health authorities in the host country arrangements that make successful products, as well as other knowledge and benefits resulting from research, available to host communities and countries."

DR. SHAPIRO: No. That is right. That was a typo. I am glad you reminded me. So that is the comment on that one, I think. Alta, then Larry.

PROF. CHARO: Well, then following my own way

of trying to reduce things to their simplest of what, by whom, and how implemented, it seems like 4.2 really ought to be starting with saying that sponsors should strive to make any successful intervention reasonably available in the country following the conclusion of the research.

That identifies by what and by whom, and then you get to implementation, you say that this should be achieved by negotiation prior to the beginning of the trial. And documentation of that negotiation should be provided by the researcher to his or her IRB before the research commences.

DR. SHAPIRO: Let me ask you a question about that suggestion. I know Larry also wants to make a comment.

It is not always clear to me, and then maybe -- that we know that the obligation ought to fall on the shoulders of the sponsors. It is just not clear to me. Because there are too many different kinds of sponsors. As I said -- I am repeating what I said before

-- there are governments, and if we think of rich governments, it is easy to imagine what we might think, but then there are non-profit organizations. There are for-profit organizations, and so on.

So it seems to me not so easy to say in advance where that obligation lies. Is that is sort of sufficiently vague and obscure to not be understandable?

PROF. CHARO: Personally, I understand it completely, and that is a good point. Of course, to simply skate by it by either using passive tense or lumping everybody together and not making it clear who actually has to ask first is an unsatisfying resolution, of course.

DR. SHAPIRO: David and Larry. Excuse me. Larry is first, then David.

DR. MIIKE: I think this recommendation, as currently worded, does not reflect the discussion that goes on in the chapter, and I have had an off-the-record discussion with Alta on this. And I think we agree on the intent. We don't agree on what this thing says.

Number one is that the way I read it is that it is a negotiation that says you have to do this, and you are going to negotiate the terms and conditions. Alta reads that to say we are going to negotiate about whether or not you are going to do this. So I have some language there that would clarify that.

But then, of course, I do not agree that this

should be in the protocol and subject to IRB review before the research goes forward. I think that goes way beyond any reasonable expectation of what the research protocol should address.

We already addressed that for the participants of the study, and we have all agreed that that should be in the protocol. But to take it beyond that and to say this also has to be in a protocol, I don't agree at all.

And then the other thing is I don't know how we
-- just getting to the point that you just raised about you don't know which parties -- I don't think researchers should be involved in this. It goes way beyond any kind of obligational competence on their part, I believe.

And Bernie may disagree with me, because he was saying something different along that line. But I think we can make the point that Bernie makes without including them in the recommendation.

DR. SHAPIRO: Okay. A number of people want to speak. Larry has raised a sequence of issues that we have to come back to, but let's see if they come up in the comments. David, then Alta, then Steve.

DR. COX: So, my comments ar directly related

to what Larry just said. So, first of all, I agree -- I support his view that this negotiation in 4.2 shouldn't be in the protocol. I think that, again, it goes over what the researcher's expertise is. Furthermore, I agree with what you said, Harold, it is hard to know whether it should always be the sponsor.

But it doesn't have to be just one or the other. It is -- you know, everybody is in the car. It is just a question of who is doing the driving. So, in 4.1, the researcher is doing the driving. In 4.2, the sponsor is doing the driving. And that neither one is responsible for seeing that it happens, but you identify who is the driver.

Now, the only difference in my view is that in 4.2, the sponsor is the driver, but it is not in the research protocol. Because the research protocol is something about what the researcher does. So the researcher has a part in these negotiations.

There, I agree with Bernie. But that they are not the driver of it; the sponsor is the driver. They can't be responsible for it always happening. But it is a different set of -- you put the focus -- if you don't have somebody who is the target for getting things moving, nothing will happen.

And so 4.2 is a different issues than 4.1, and

I now understand that. And I think it is appropriate to have the sponsor be the target person, but they are not responsible for making it happen.

DR. SHAPIRO: Okay. Alta?

PROF. CHARO: I think the reason why we are discussing the IRB's review, or non-review, of this aspect of the research is because that represents one of several possible ways to implement and enforce these superogatory obligations that we are identifying tentatively on the part of sponsors, but potentially on the part of a wider body of people.

So the question then is: What would be the best implementation and enforcement structure? The role of the IRB has always been to throw a light on things, and by virtue of doing that and forcing a discussion to create some incentive to action. If that is considered to be cumbersome or ineffective, what would be the alternative? Right.

I mean, one alternative is the FDA's non-use of data, the kind of government blackmail -- don't do it this way. Don't actually make stuff available afterwards, and we won't use the data. It is unrealistic here, because we are talking about things that have been proven successful. So it is kind of too late.

Another is the carrot approach. Everything that you provide afterwards is considered a charitable donation to the country, and we will give you some tax advantages. But, I mean, I think we need to be thinking about why we want the IRB to be looking at it and see if there are alternatives that would serve our goals better.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Relates to Alta's, but it was a question to Larry. While I understand you believe the IRB is not the appropriate place for review of the plan, do you want even a check box, so to speak, where the IRB is asked to review whether or not, in fact, there is a plan, as opposed to the content? So it says: Have you provided for a plan working with the sponsor for the provision thereafter?

DR. SHAPIRO: Good question. Larry, what ---

DR. MIIKE: Yeah. Well, actually, my answer to Alta would have been the only thing an IRB could do was put a checklist. They could not evaluate the adequacy of that plan.

But I don't think they should be involved at all. I guess I should state more explicitly where I come from on this topic, which I have mentioned before.

I think that we have got to take -- I agree

with the direction we are going on this. But I think that we are not only heading in a direction. We are trying to force the issue in the way that we trying to craft this recommendation.

I provided language before that what I really -- my only hope in this area is that you put this -- a spotlight on this issue in the countries in which this research is going on. So that they start thinking about these kinds of issues rather than trying to force it down either side's throat.

And that is why I would be perfectly happy if that as part of the negotiations before clinical trials go on -- one of the issues that comes up all the time is what is going to happen if we have a successful product in this country. And that was what I was trying to rewrite this recommendation the last time around.

And I think that is a reasonable expectation. To force it beyond that, to make it an obligation, I think goes a little bit too far at this point in time.

DR. SHAPIRO: Steve? Oh, you are done. Okay. Arturo? Sorry. Forgot to cross your name off.

DR. BRITO: I agree with David, what he said earlier about the -- and others -- but the negotiation part should really be left out of the researcher, and

the sponsor should do that.

The only -- it gets a little cloudy here where I am thinking about the whole protocol, which includes the informed consent process, and one of the obligations of the researcher -- okay, we are talking about the individual researcher -- is to disclose in the informed consent process to the participants what they should expect before and after the trial.

So I am just having -- I think the confusing thing with this recommendation right from the get-go is that we are clumping together researchers and sponsors. So I agree that the sponsors should do the negotiation, the research sponsors, but the researchers themselves also have an obligation to disclose to the potential participants what was negotiated.

So somewhere in there, it has to be defined and in place. I don't know if it is going to require two different recommendations, one for the sponsors, one for the researchers themselves.

DR. SHAPIRO: I guess -- Alex -- before I make my comments -- (inaudible).

PROF. CAPRON: I agree with part of what Arturo just said, but I think that that actually -- disclosure belongs in 4.1. Because what has to be disclosed along the lines of our present requirement in

the United States about disclosing of compensation for injury is what will happen to the participants.

I don't think that this other matter, which is a matter really either of inter-governmental affairs or of the ministry of health, in effect, licensing, permitting a research sponsor to come in to conduct research in a country is a matter for disclosure to the participants, because it is not really what is going to happen to them. It is a matter of health policy in the country.

And for that reason, I would recommend that we drop the word "Researchers and..." at the beginning of Recommendation 4.2, and once having done that, Larry, I would have language similar to what we had put into 4.1 here.

Because I do think that we should be pressing the envelope a little. We should say that a protocol ought to specify how the sponsor will negotiate that issue. Again, I agree with you, Larry, it is not to the IRB to say that one outcome or another of that negotiation is or is not acceptable.

But we have had a lot of discussion about this, and we are, in effect, reflecting, I believe, a changing mentality on this subject within the larger international community around research.

That these kinds of obligations to the country, which relate to the ethical premise we state at the beginning of the report, that it is wrong not to have some prospect of benefit to the people with whom the research is conducted, and that means, it seems to me, the community in which it is conducted, not simply the individuals who happen, by random draw or whatever, to be the ones who are selected.

So I would say -- I would recommend that we drop the word "Researchers and..." and add language that would say, "The research protocol should specify how the responsibility and mechanisms for making the products available will be negotiated among the relevant parties."

And that is sort of equivalent, I think, Steve, to what you are saying. They check off to make sure it has been thought about and specified.

DR. SHAPIRO: Let me -- thank you -- these comments really are quite helpful. Let me just ask what is to me a somewhat simplifying question, but it may not capture the spirit of what has been discussed here in the last little while.

If you look at Recommendation 4.2, as it is currently written, with its various inadequacies, the key sentence, to me, is the last one before you get to

these (a), (b), (c)s, where it says: "The responsibility and mechanism for making products available should be a matter to be negotiated amongst the relevant parties."

This doesn't say who is going to do what. It just says somebody has to sit down and figure out what they want to do. It is, I think, equivalent to what Larry was trying to say, I believe, when he said he wanted to shine a spotlight on it.

DR. MIIKE: No, I don't agree that that is what this says. To me, I read this, and it says, you are going to do it. You are going to negotiate who is responsible for doing it and the mechanism.

DR. SHAPIRO: Okay. You may be right about that. We will have to go back and see how we interpret these words. But, in some sense, some of the issues that we have been discussing here come out -- I was just asking myself, what would happen if we dropped (a), (b), and (c) and either started again with whatever we meant or just left them?

We have taken parts of (a) and (b) and put them up for different purposes into 4.1, dealing only with the participant one, not with the countries. Larry, then Alta. Then Steve.

DR. MIIKE: Well, I disagree with Alex about

including it in the protocol. But I have very simple language on this. It reads as follows: "Sponsors must negotiate in advance with relevant health authorities in the host country whether or not successful products, as well as other knowledge and benefits, resulting from research will be available to host communities and countries."

DR. SHAPIRO: Okay. That clarifies the issues that you were concerned with. It does not take up the issue at all, I think, regarding the responsibility for this. It is just something to be talked about. I didn't get all your language, Larry.

I think that -- we may have not stated it right in the last sentence as it stands. It may be too prescriptive, as you said. But that is an issue which, it seems to me, ought to find some place in the language. Otherwise, the language sounds reasonable. Alta?

PROF. CHARO: Whether with Larry's language, or with your suggestion of dropping the sub-clauses, which, I think, actually is quite promising, we can certainly say sponsors or another appropriate stakeholder should negotiate, and that is fine.

But I think it still lacks two things. One is, in the text of the recommendation, a positive

statement that we think that the right thing to do would, in fact, be to make some provision in this direction. Next, sponsor or other appropriate party negotiates. And then, next, what is still missing is: How are we going to make it happen?

We have all been participating in lots of government committees and commissions that write wonderful reports that manage to hold up bookshelves all throughout Washington and the Federal Depository [sic]? Library System. The question is: What effect it is going to have without some kind of enforcement mechanism?

I would suggest it is likely to have very little. The governments that we are talking about here -- because we have now appropriately limited the scope of the report to biomedical research with rich governments and not-so-rich governments -- the fact of the matter is you do not have equal negotiating partners.

The fact of the matter is when Grace Malenga testified about the lack of mefluguine in Rwanda, one of the reasons that can happen is because Rwanda is not in a position to say, you can't do the research here unless you make a post-trial commitment.

Because that kind of malaria is present in

other parts of Africa, and anybody who wants to do that research could, in fact, go to another part of Africa if Rwanda's government got sticky about it. And they know that.

And the research offers so many other ancillary benefits in terms of bringing in money, expertise, tech transfer, and ancillary health services that it is very hard to turn down.

Those ministries of health are subject to 16 different donor-country health programs, each of which offers a different kind of set of benefits, and I have watched personally, in my limited experience, ministries of health turn themselves inside out so that they can take the French kind of anti-contraceptive program in sexual health and the American pro-contraceptive program in sexual health and implement both of them, because it gives them money.

Unless we have got some way to actually encourage the sponsor, or other appropriate party, to engage in this negotiation in a good faith fashion with an expectation that the outcome will be some degree of post-trial obligation for availability, I think that it will become aspirational only and will never actually achieve our goals of really beginning to change the way in which research is done on the ground.

PROF. CAPRON: Mr. Chair, could we divide these points and see if we have consensus on the language of the first sentence, as Larry read it to us. Sponsors must negotiate in advance -- and we can get to that. And then we get to the question, as Alta has posed it, well, how do we put some teeth into that?

And there are several ideas on the table. One is that the IRB should make sure that there is a process that is in place that will lead to negotiations. Another is that the FDA shouldn't license drugs that have come from trials in which that negotiation hasn't occurred. I mean, there may be other ideas.

Then we will decide: Do those belong in the recommendation, or do they belong in a separate recommendation, or in commentary language. But I agree with Alta; that is to say, when we get to that point, I will vote in favor of some means of checking to be sure that this step has been taken. Because otherwise I think it will just be language.

DR. SHAPIRO: Tom?

DR. MURRAY: Alta, just a clarifying point. You also said you wanted a firm prescriptive statement. Is 4.1 adequate to that cause? Or do you think we need to reiterate that or say something somewhat

different.

PROF. CHARO: I think 4.1 is on a slightly different topic. It is a prescriptive statement which regards the participants in the trial specifically.

DR. MURRAY: Right.

PROF. CHARO: I would love to see 4.2 begin with a prescriptive statement that says we think the right thing to do is to make some commitment to countrywide availability should this turn out to be a successful product.

DR. MURRAY: So we really then have three components of the Recommendation 4.1.

PROF. CHARO: Right. The prescription, which is not clearly identified, although it is implicit. Right. The who, which is what I think Harold was accurately moving towards simplifying, and then the enforcement mechanism, which we have yet to identify, which would work, both logistically and in terms of achieving our goals.

DR. SHAPIRO: It seems to me that the arguments that we have put forth in this chapter are consistent with recent demand that we say somehow that we believe that there is some benefit beyond the benefit to the participants.

The nature of that benefit, the size of it and

so on, is very hard to -- but I think that position, I think, is consistent -- or if it isn't, we need to rewrite it so that that comes out more clearly. That seems to be a fairly easy, to me, a very easy position to be in.

And if that hasn't been clear, and it is not clear how the Commission feels about this, we ought to settle that issues first. Because that -- everything here is built on that premise. So is there is any disagreement on that issue, quite aside from the way it is precisely expressed?

That we don't know what -- we are not saying exactly what level of commitment is, but it is something beyond what 4.1 deals with. All right. So we are agreed on that. So we have to make sure that whatever language we use in 4.2 reflects that to begin with. That is where it all starts.

What was the language you suggested, Larry? Do you still have that? Somebody have it?

DR. MIIKE: "Sponsors must negotiate in advance with relevant health authorities in the host country whether or not successful products, as well as other knowledge and benefits resulting from research, will be made available to the host communities and countries."

DR. SHAPIRO: Steve wants to make a comment. I just -- clarify what your own thinking is, Larry. That calls for a negotiation. It does not say anything about whether we expect something to come out of it. It just calls for people to talk about it. Is that right? Okay. Steve?

MR. HOLTZMAN: With Alex, I would like to push the edge of the envelope with respect to who is responsible, and so I am trying to deal with -- I agree the IRB and the research investigator are not the right parties to be negotiating the specifics.

And yet I think what we want to do is to say to everyone involved in the research enterprise. You have a stake in the ethics of the total enterprise, which, simplistically, I think of why are you doing the research? How are you doing it? And what do you do with the fruits of it?

It may not be that you have primary responsibility for, say, the last, but you have a responsibility to make sure it is attended to. And so I do think -- and I would like to see a role that there is an onus on the researcher and the IRB to know that these are being attended to.

With respect to the issue of what level of obligation? I am very strongly disposed towards

concepts of presumption. There is a presumption that there will be provision of the medication. That it will be available. That presumption can be overcome, given the particular facts of the case, but it should start as a presumption. All right?

Because if that presumption is not fulfilled, then you haven't fulfilled the basic idea of why did I choose this population for the study? There can be good reasons, all right, that overcome the presumption. But then that is where the negotiation -- so my problem with Larry's language is it fails to embody the presumption. All right.

DR. SHAPIRO: Now, I thought ---

DR. MIIKE: I have no problems with a statement about the presumption.

DR. SHAPIRO: Then the "whether or not" doesn't it in your language. It is a small point I want to make. The language doesn't work with "whether or not," because that dispenses with the presumption. But we can go ahead with the presumption, which I thought was our agreement just a few seconds ago.

So we need to craft this so that if we want to put it in the -- of a presumption, I have no problem with that. We have to realize, however, that it is not accidental that language like "available," or even

"reasonable" has generated so much controversy. Right.

Because that deals with who has the obligation to accomplish this, and that is not an easy matter to settle. And I think very hard to settle in advance actually. But we are to see if we can fashion a recommendation that at least pushes us -- or tries to push people in some direction.

Let me make a suggestion. I am going to suggest that we designate -- that we do two things now. One, it is a quarter to eleven. So we probably ought to take a break.

Two, that I am going to ask two or three people to sit down and try to recast 4.2 in light of the discussion we have. And, also, we want to allow some time for people who just got chapter 5 to read it. So this will cause us to recess probably for about three-quarters of an hour.

But for the people that I am going to ask, in a moment, their first job will be to try to work with Eric to put in the kind of -- I think it is a general sentiment that we are starting to move towards here, and we will try to articulate that a bit better.

And I think it is useful to drop (a), (b), and (c) as equivalent from here and just try to say it directly in the recommendation itself. So, Steve, will

you and Alta work with Eric on this, try to get us a new formulation of 4.2? Then we can look at it a little later on. Yes. Arturo?

DR. BRITO: I just want to ask you a question. Can you just summarize briefly what it is we did agree on? That when they formulate it -- because, in my mind's eye, what I am seeing is that the confusion is arising from "who," the "who." Okay. The sponsor and the researcher.

DR. SHAPIRO: I think that is right, and I think my own view is that we don't have, as is currently written, a sufficiently well articulated premise, first of all. The presumption is that something will happen is the way Steve put it, but there might be other language that works.

That is not in here, although the word "should" could be interpreted that way, I guess. But it is not in here in an adequate way, I think.

And then we are going to have to look for language that encourages, sponsors especially, but I don't myself know how you separate sponsors and researchers so easily. It seems to be currency around the table here. But I don't really understand that issue, since the initiatives sometimes come from one area, sometimes come from the other area. The

preliminary negotiations take place in all kinds of different ways.

I think it is very hard to separate these things in practice. Maybe "and/or" is a useful way. But we will have to think about that.

But I think we are going to have to see what they come up with regarding whether we can say anything more about where the obligation falls and -- what mechanism of enforcement to use. I think those are challenges. We haven't got those in our minds just yet. Yes. Bernie?

DR. LO: I don't think we are going to come up with those specifics, and that is why I think that the best that we can do is spotlight this issue and make it, as Steve says, the presumption.

DR. SHAPIRO: Well, that may be right. That may be right. Bernie?

DR. LO: I think these are challenges, and you know, middle ground may be to come up with considerations and options as opposed as prescriptive things.

But I think I would like to see us push toward some implementation of reasonably available, because that is such an ambiguous, elastic term, and we ought to have some discussion of, you know, is a licensing

agreement that the host country chooses not to pick up on sufficient? Or does the sponsor literally have to give the drug away at cost?

I mean, those are the issues that are real-life issues, and I think if we can shed some light on that, and how the particulars of the case would influence whether you think a particular option is justified or not, that would be great.

Similarly, I think the point we would come around to is how, procedurally, do you ensure that the discussions have taken place at the various checkpoints we have, which are really ---

You know, if you think about it, submission to an IRB, and submission of a grant to a funding agency, and submission of an IND to the FDA that are sort of the barriers through which these projects have to pass -- it seems to me that we are going to have to make use of those existing procedural reviews to address this issue here. But I am not -- this is a totally new area, and I think, again, rather than trying to solve it all here, maybe we should just say, we have got to reach that level of specificity. Here are the options. Here are some of the problems with each, the pros and cons of each one.

DR. SHAPIRO: I think one of the issues you

point to, Bernie, is: Can we say a license, for example, or anything else, I think, is going to be extremely difficult to resolve.

Let's see what we can do, but I think that determining these obligations, where they fall in some detail, is so context-dependent, as I think it through, that you might give examples, but I think that we are not going to be able to make a final recommendation that holds. It is just too contextual, I think.

DR. LO: I think I would agree with that, but I think examples with enough sort of detail to indicate why in one situation was the agreement at a much higher level than the other would be useful and to give the reader some indication whether or not we think the final arrangement, on the whole, is a fair one or not would be useful ---

DR. SHAPIRO: Okay. Last comment -- Alta.

PROF. CHARO: This is directly relevant to how we draft the thing. In light of what Bernie just said, and also keeping in mind Larry's comment about the difficulty of being too specific, I find myself wondering if a way that we can go is to have a recommendation that calls on specific (?) within the federal government to search for ways that they can actually create an effective incentive to good-faith

negotiation.

And we have already identified a few agencies that have the potential to do this in a limited fashion. We have been focusing on researchers, in part, because we have a choke-hold on them through the IRB system, but that identifies OHRP as a place.

The FDA is another. The Office of the Trade Rep, interestingly enough, is another, because of the issues around the licensing agreements. The State Department is another.

And if we can't identify the killer enforcement mechanism that we think accomplishes our goals at a reasonable political and logistic cost, a second-tier alternative is to identify the places within the federal government, where we push that task off on them.

DR. SHAPIRO: That is, you know, obviously, that is a plausible enough idea. Seems simpler. So it is very attractive and seductive. But let's see what we can come up with.

Okay. We will break now. Diane -- I am sorry. You haven't even spoken today yet. So, fine.

DR. SCOTT-JONES: I just wanted to ask a question about our omission of (c), sub-part (c), under Recommendation 4.2. Some of that language is in the

first recommendation for chapter 5. It has to do with capacity building, but there it is limited to capacity building for designing and conducting clinical trials.

I hope there is a way we can keep the idea of assisting developing countries with capacity building for negotiating these distribution plans.

DR. SHAPIRO: This will come up when we deal with 5. I think that is an important point and will come up again when we come to chapter 5.

DR. SCOTT-JONES: Okay.

DR. SHAPIRO: But, you know, then we will see. We can move back and forth later if you want to something back in here. Okay. We will try to reassemble around 11:30, and ask Eric to assemble the subcommittee. The rest of you ought to be focusing on chapter 5.

(Whereupon, at 10:53 a.m., a recess was taken.)

DR. SHAPIRO: The small group that was designated to prepare an alternate recommendation for 4.2 has put it on a disk and is currently being reproduced. And we will hand it out and review that effort in just a few moments.

Our proposal is that we will try to go through that, see if we can come to -- we may or may not be

able to come to agreement -- we will see if we can come to an agreement on that, and if we do so, maybe the incentive is, we will break for lunch, and then come back and deal with various recommendations in chapter 5 when you have had a chance to look at it a little.

I think most of you have now at least had an initial reading of chapter 5. So perhaps while we are waiting, is there anything we want to -- why -- it is really quite short. So why don't I have Eric read that, and maybe that is sufficient, and hopefully, the copies will be here very shortly.

DR. MESLIN: This is the revision to Recommendation 4.2. "A presumption exists that successful products, or other benefits from research, will be made reasonably available to host countries. Sponsors should collaborate with host countries and other appropriate parties to achieve this. Researchers should include in their research proposal to their IRB a description of these collaborative efforts. IRBs may take these efforts into account in their review of the research proposal."

PROF. CAPRON: Could you read the beginning of that again? Why is it that they are obliged to do?

DR. MESLIN: "A presumption exists that successful products, or other benefits from research,

will be made reasonably available to host countries. Sponsors should collaborate with host countries and other appropriate parties to achieve this..."

DR. MURRAY: And then you use the permissive verb "may" rather than "should." The IRBs may take that into account.

DR. MESLIN: Yes. That was in the second ---

DR. SHAPIRO: -- second part of this.

DR. MURRAY: I am sure that was a deliberate choice. Can you tell us why you chose that instead of "should" or "ought"?

DR. MESLIN: I can tell you what I -- yes, and others can too.

DR. SHAPIRO: Maybe different reasons ---

DR. MESLIN: Yeah, I will give you the reasons that I -- this was to first recognize that Larry had a concern about IRBs specifically reviewing the plan itself and making an evaluation of the plan. That is one reason.

And the second reason was that there may be a variety of parts of the proposals for which these plans apply, the risk/benefit assessment, the consent process, and we don't want to tell IRBs which parts of the proposals these plans apply to.

Steve or Alta, did you have any other reasons

for why we did that?

DR. SHAPIRO: Alex. Tom first, and then Alex, then Diane.

DR. MURRAY: Maybe I am parsing this too finely, but it seems to me there are -- two things are conjoined there. One is that there is a plan that is put before the IRB, namely, that a plan exists, or some judgment about what ought to be done by the sponsors and the hosts exists. That is number one. And the IRB should take that into account.

Number two is the specifics of the plan, and that may be more permissive. So it seems to me two things are being conjoined into one there, and I don't know if it would be of any value to separate them or not. I am torn there.

On the one hand, I think I would like to have that clarification; on the other, shorter is better.

DR. SHAPIRO: Okay. Alex.

PROF. CAPRON: Two points. The first follows up on Tom, and maybe we are all just at a disadvantage until we have the language in front of us.

The reason I asked you to re-read that was there are three things which, as I understand it, the IRB might look at: The fact that there will be negotiation, or as you put it, collaboration; the fact

that there will be something provided, or the details of what will be provided, and I think we are all in agreement that the latter, and the adequacy of the latter, is not an IRB judgment.

I had thought when I listened to you that what the IRB was supposed to do was to see that there was a plan of collaboration, which meant that people were sitting down and figuring out what to do, I thought. Do you mean rather to suggest that there is a plan of distribution or provision of benefits? That is my first question.

PROF. CHARO: I can't speak for what we intended. You could watch what was going on up there. But I ---

PROF. CAPRON: I don't go to the sausage factory. I didn't watch.

PROF. CHARO: It is ugly. I think that we probably want to give the IRBs, if that is going to be a place where we use an accountability technique to encourage enforcement, we want to give the IRBs some degree of flexibility. And one way we can achieve it is this way.

The researchers tell them what they can tell them. If the researchers say, we have a plan for how there is going to be a collaboration in the future to

figure all this out, that is what they will tell them. If there is already a plan, they will tell them. If there already are details, they will tell them that too.

Whatever they give is what the IRB can then use in their assessment of, among other things, the overall risk/benefit rations of the research. The more that there is a plan for post-trial distribution, the more benefit we can say is coming from the research and the more favorable is the risk/benefit ratio.

And if you only have a plan, then -- so it is some benefit. It is not as much as if you really know what is going to happen.

Similarly, with regard to Arturo's concern about the consent process, to the extent that the IRB wants its participants about not only what they are going to get personally, but what will come from the research more generally. The more the researcher happens to know at the time it is being submitted to the IRB, the better.

But as Harold has noted, these collaborations, discussions, whatever are likely to be going on both before and after the IRB reviews a protocol. So to say that they have to describe a plan, maybe describe less than already exists, to say they have to describe what

the availability will be is maybe unrealistic, because nobody knows yet.

Some language that is broad enough to say, give them what you have got and let them review it.

PROF. CAPRON: I guess I will wait and see what the language you have is. I understand now better what the intent is.

My second question was that you have language in there not only about the tested intervention, but other benefits from the research, sharing other benefits from the research? And I am not entirely clear what that encompasses.

One way of reading it, which I think would be beyond anything that we have discussed are sharing the intellectual property benefits, as it were, in the sense that we have developed a product, and we are going to make some money off of it. And we now have to send some of our profits to you, because we are making -- and that is not what is intended.

So what is intended, and is it described as carefully as it could be?

DR. MESLIN: Well, the only thing I will say there is that was an editing link between what was in the existing 4.2 -- the phrase was "...as well as other knowledge and benefits resulting from the research..."

In the chapter itself, it does not go in lengthy discussion, but it certainly wasn't intended to refer to the kind of intellectual property points you are raising. It was those collateral health benefits that may arise.

PROF. CAPRON: Well, I guess, I mean, if we are talking about making things available, if it is knowledge in the sense that besides this intervention, you discover that purification of the water is also a key link in improving health here, and you make that knowledge available, that is innocuous and, indeed, I would think, obligatory.

I guess, I think that at some point either in the commentary, we have to explicitly address, more explicitly address, what we mean. Otherwise, it suggests an obligation which an IRB might think was much more extensive.

DR. SHAPIRO: I don't know if there are any other comments now before we actually get this document, before it is -- Arturo.

DR. BRITO: I am not sure if it is -- we have omitted this, or if I read this and thought about it and some of the other comments about the phrase "reasonably available." And it sounds like you purposely put it in here to give, I guess, a little bit

of flexibility in here.

But it makes me a little bit uncomfortable. There may be too much flexibility in interpretation of what that means. So I don't know if there is a better -- if there is another phrase we can use in there, and I don't have an answer for that.

I just felt a little bit uncomfortable when you read that in that first sentence. Maybe -- I would like to hear a little bit about why purposely that phrase was chosen for here.

DR. SHAPIRO: Well, I think "reasonably available" and "available" suffer from the same problem. I mean, you point out that it is true that itself doesn't say who does it, who pays for it, who has the responsibility. Those issues are left unanswered by the use of this kind of language.

And I think it does leave things unanswered, and I think my own view is we can't answer all those issues. That is just my own view. Diane.

DR. SCOTT-JONES: In the previous version of Recommendation 4.2, we are suggesting that the sponsors negotiate in advance with the host country, and there is no language like that that I could remember in what you just read, Eric. And I am wondering, have we decided that in advance isn't an important aspect of

this to keep in?

DR. MESLIN: I would certainly say the omission was not intended to remove that at all. It was the description of the presumption, the collaboration. Maybe it should say "in advance" with host countries. That may have just been an omission in the reading. But, no, it was not intended, I don't think, to remove that. That was what negotiation has to be.

DR. SHAPIRO: Larry.

DR. MIIKE: I have problems with three things. One is that what Alex has raised about the benefits, and it seems to go way beyond what one can reasonably expect sponsors of trials to provide. Let's leave that to the State Department, according to Alta.

The other part is that since it is a presumption and not a -- it is a negotiation that one goes through with good faith on the presumption. I don't think we need the word "reasonable" in there. That is implicit in that kind of discussion. Because you are going to reach a practical solution on a reasonable basis.

The third part is, I guess, I am referring to the IRB's role in here is what Alta was looking for as a hook to make sure it goes on. I remain uncomfortable

with that. I really don't think the IRB is the one to deal with this issue. I can see them dealing with the issue of trial participants, but certainly not this issue.

DR. SHAPIRO: Yes, David.

DR. COX: So this is sort of between a rock and a hard place. For me, what I wouldn't like to see, and in fact, my interpretation of what happened with the Commission, was getting these two issues muddled in the beginning, which is that what you give to the research subjects as a result of them participating in the study, 4.1, and what you try and do for the whole country, 4.2.

And that I think whatever we do, we should really strive to make it clear that those are two separate things. By having the IRB basically be dealing with both of them, it does muddy the waters.

On the other hand, who besides the IRB is going to be able to see that somebody is dealing with 4.2? So that is what I mean. You are between a rock and a hard place.

But be crystal clear to the researchers and the funding agencies that these are two separate things. Because dealing with 4.2 is a very complicated problem. We are acknowledging that we would just like

to see people try it, but realistically, by the fact that we have given it to the IRB, it ain't going to happen.

But 4.1 absolutely has to happen, and they are not sort of equivalent in terms of their priorities. So my concern in this is that by trying to bring 4.2 in, we really dilute 4.1, and the people lose -- and since they can't keep track of what the important priorities are, they won't do anything.

DR. SHAPIRO: Steve.

MR. HOLTZMAN: I agree that the issue of what is owed to the participants versus a broader obligation, or presumption of obligation, are very, very distinct. But I think that they both need to be addressed. I think there is a role for the IRB in both of them.

When I conceive of the role of the IRB, it is there to ensure the ethical conduct of research. They will check for certain formal requirements, and they will also look for certain substantive requirements. Hence, for example, they will review the consent form for the substance of it.

I think it is perfectly reasonable to say that there are additional requirements of the ethical conduct of research with respect to which they may lack

the expertise to engage in the substantive investigation, e.g., will this distribution system work?

But, nevertheless, can see whether the formal requirement of a collaborative enterprise or discussion is being undertaken, and that is, I think, a limited, but appropriate, role for the IRB in its role as the body that sees whether or not the research is being conducted ethically.

The second point is whether an obligation of a presumption, or a presumptive obligation, is part of conducting research ethically, and I would say it is. I agree that in any given case, who, how, and what can be very difficult and very different. All right?

But what we really asking the question here is: Why is it the case that you are not using this population as a set of guinea pigs? And it is only the case if there is a presumption that the benefit of the research will accrue to that population.

In the absence of the fulfillment of that presumption, you need to make the case why it is, nevertheless, ethical to undertake that. And that, I believe, involves the engagement of those who can morally speak for, with authority, the subject population and say that this is morally okay.

That is what I think we are trying to embody in the different parts of this recommendation.

DR. SHAPIRO: Yes. Bill.

MR. OLDAKER: Well, I agree with the concept of what we are trying to do. I worry a little bit, since the presumption runs not to the negotiation, but to the outcome of the negotiation.

I worry that we may be creating basically unintended consequences in that large populated countries will be discriminated against, since the presumption is something that could be quite costly for that larger population, forcing researchers to go to much smaller population countries.

Now, you know, we certainly don't intend that. But knowing how human nature works, and how people basically live with in the application of rules, we could be causing that, and I think we should consider that.

The -- you know, whereas some of the larger countries may, in fact, want the research conducted there, but want other things other than to have the drug to be totally reasonably available there. I am not sure what they are.

The negotiation, I think, has to be done, and I think it should be on these issues. Now, presuming

the outcome, or forcing the outcome, I think, becomes a more difficult point in my mind. I think it would be nice if we could have that outcome in all situations. I don't know if we can.

DR. SHAPIRO: Let me suggest that we -- these are interesting points -- let me suggest that we wait until we have the language in front of us before we carry the discussion any further.

There is a very important point here, that is, that has just been talked about. Whether the negotiations that we are asking for, which is one way of going at it, or whether we want to say something more than that. We settled -- didn't settle on -- the suggestion was that it be a presumption, meaning it is rebuttable. It may occur in some cases.

So we are trying to find a line here that, I think, is sensitive to those issues, but states, in my mind at least, in a fairly strong way that we do have an obligation to make everyone here better off -- not everyone in every way -- but the country in some broad sense. I don't think it means every person in that country.

But those are difficult decisions that need to be negotiated. David.

DR. COX: I just want to make clear. Steve, I

agree with everything that you said.

DR. SHAPIRO: Do you want to put that on tape? We could replay it every month ---

DR. COX: On tape, and you can play it, and people can tape it. But that implementing what you said, since these are subtle points, is to try and get -- it is all in the language, Harold. Because -- so people know what it is that we are asking them to do.

And that is what I worry about most. Because, in my view, that is one of the hardest things for the IRBs, or for the researchers, right now is that they don't get the subtleties. And so they don't understand what is about. They think it is about a bunch of paper instead of what the concepts are.

And so that -- and these are subtle points. I mean, we ourselves are getting -- you know, it has taken us a while to figure them out. So that while -- first of all, do we agree with the principles? And that is still, you know, sort of -- we are having that discussion.

But even if we agree to get the language in a way so people understand what the hell we are talking about. And that -- the latter point was my point.

DR. SHAPIRO: It seems to me -- at least it seems to myself -- I feel strongly that at least there

is, I guess, what other people have called a rebuttable presumption. That is not the language, I think, that is used here. But that some benefit beyond -- that reaches beyond the participants in the trial is, in my view, very important.

Does that include everybody in the country? No, it doesn't have to include everybody in the country? Does it include everybody in the country that needs this medication? No, it doesn't have to do that either. It could be something else. It could be a community. It could be another pilot study. It could be another research project that they want to carry out.

There are a lot of things that could occur here that would mitigate, in my mind -- against the notion -- you stay out of a large country. You would have to provide everybody. I don't think -- in my mind, that is not what we are saying.

But what we are saying is that there has got to be some benefit -- small, large, we don't even mention
it -- beyond what falls strictly to the participants, which is an issue, I think, we have resolved in our minds.

And I think that is what we are going to try

to reflect in the recommendation, precisely because there are those issues that you mentioned. These unintended consequences can be very serious and usually are. So we want to mitigate against them.

All right. I am going to -- unless there -- it is now 12 o'clock. I had expected this language here back sooner than that, but we don't have it. So I think we should wait before discussing that further.

So let's break for lunch now and reassemble at one.

(Whereupon, at 12:02 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

DR. SHAPIRO: I want to look -- there is a revised 4.2, which we agreed to wait to look at language. You now have language in front of it. Indeed, now, there is another alternative to 4.2 about to be distributed, that is, in the next five minutes. We will wait until that gets here.

But I wanted to raise another probably smaller issue in the scheme of things here. But there has been some discussion amongst us this morning regarding whether sponsors should do this or researchers should do that.

I have to say that I understand the points

that were made; namely, that, you know, researchers don't have the capacity to provide certain kinds of benefits and so on and so forth. That is clearly correct.

However, when it comes to talking about the collaboration, or the negotiation, either the initiation of the negotiation, or the carrying on of the negotiation, I do have some problems separating researchers and sponsors, and I want to give some examples.

I will give -- I am on the board -- I will give you one example which I know about directly. I am on a foundation board which sponsored in the early days -- I think still some -- the IAVI initiative that you all know about. In fact, some of that described in here.

Well, the way that happened is some very really energetic researchers got the whole thing together, did all the negotiations, had everything arranged, and came to the foundation and said, we need money. We don't need your advice. We don't need anything else. We just need money, and here is what has happened.

And it has turned out in that case it worked out positively from their perspective. We gave them

money, but we never went to the site. We never saw any government officials. We never saw sick people. We never saw anything. We were just really at quite a distance from it.

So there is an example of where the researchers involved really carried the ball forward and concluded everything. Yes.

PROF. CAPRON: Wouldn't you, in that case, say that IAVI is the sponsor. You are a source of funds. I mean, Bill Gates is not now conducting AIDS research, but he is putting up a lot of money that makes products available.

DR. SHAPIRO: Well, that is not such an easy -- in my mind, it is not such an easy kind of position to make. For example, the U.S. government we call the sponsor of a lot of research, which it really has almost nothing to do with a government agency. It just sort of reviews and says, here it is. It is a good idea. Go do it. That happens, I believe, all the time.

It is really a more modest suggestion. It doesn't go to the heart of anything that we are really talking about except that I think we should realize, and our recommendations should realize, that when we are wondering who is going to carry on the actual

negotiation, it will be a mixture. We have to distinguish, in some cases, and not -- it is really a very small point.

PROF. CAPRON: I appreciate your point. Could we handle that by using an example like this, and then taking the next step of saying that even where the language here describes a sponsor, in many cases, in investigator-initiated work, the actual steps will be undertaken.

Wouldn't you say it would be fair that the Sloane -- I don't know if this is the Sloane ---

DR. SHAPIRO: It was in this case.

PROF. CAPRON: -- if the Sloane Foundation would have wanted to ensure that these issues that were addressed.

DR. SHAPIRO: Correct.

PROF. CAPRON: And all we are talking about here, I think, is that kind of assurance. Where we are talking about commercial sponsors, or the CDC, or some other government agency. Where the agency or commercial sponsor is more the active, organizing element, then it fits more easily.

I agree the example you cite, we have to be clear about who is going to undertake what obligations, and we might want to differentiate sponsor-initiated

versus researcher-initiated. The resources are not going to come out of the researcher's pocket.

DR. SHAPIRO: That is -- no, no -- I completely agree with that. Oh, I completely agree with that.

So let's go on. Because this will -- we can easily accommodate this in the language in some way. I just want to make -- so when you see other recommendations, you are going to see some changes.

So here, for example, if we look at 4.2 that we have in front of us, it says: "Sponsors should collaborate." Well, maybe they should, but somebody should, and it all depends on what we mean by sponsor and so on, as you point out. So we will have to find some --

Arturo and then Bernie.

DR. BRITO: Harold, I agree with you that there may be situations, especially when we are talking about

negotiating the -- it may be that the host countries, or not so much the host countries, but communities within those countries, may want to negotiate more with the researcher, and there may be more of a trusting relationship than going to the sponsor.

And I think, in the big picture though,

ultimately, the sponsor has the obligation to assure that some sort of negotiation is ---

DR. SHAPIRO: I agree with that. I agree.

DR. BRITO: So I thought about how to say this, and there is some question that I have about this revised 4.2, but I will have to wait for the next one. My question is: How does this fit in now with 4.1. What are we going to do with that? Because there seems to be overlap.

But the language on this ---

DR. SHAPIRO: Let's turn to 4.2 that you have in front of you.

DR. BRITO: Okay. Well, how about something -- I like the language if it was stronger, something on the order of: "Sponsors have an obligation to assure that negotiations with host countries and other appropriate parties are done in advance of the research..." And then somewhere in there where negotiations may be done by either the researcher or the sponsors with the host countries, something of that nature.

But I think that would capture -- I think the critical point here is to make sure that the negotiation is done in advance of the research. Whoever does the negotiations, I am not sure, is the

key. But then the sponsors ultimately have the responsibility for making sure they were done.

DR. SHAPIRO: So you would put that in place of the second sentence?

DR. BRITO: Right.

DR. SHAPIRO: Would you just repeat it once again? To just make sure it ---

DR. BRITO: "Sponsors have an obligation to assure that negotiations with host countries, and other appropriate parties, are completed in advance of the research protocol..."

DR. SHAPIRO: We understand the point. Other comments on 4.2, at least the version that is in front of us here?

PROF. CAPRON: The phrase that comes at the end, "...to achieve this" is, to me, ambiguous. The "this" in the previous sentence is a presumption. Perhaps the one reference would be a presumption. Another "this" is reasonable availability of products or other benefits. That -- are we saying to ensure that reasonable availability has been achieved? Is that what we are saying? I just want to be ---

DR. SHAPIRO: I understand.

PROF. CAPRON: I am not worried about the words, but I am trying to ---

DR. CHILDRESS: One possibility that struck me would be to achieve this "goal," because the "goal" is the reasonable availability.

PROF. CAPRON: But that is not stated in the previous sentence as a goal. It is stated as a presumption that it will occur.

PROF. CHARO: Alex, this is where -- yeah. Eric said, I don't like ending sentences with a preposition, and I said, okay. Well, you mean this state of affairs, because the previous suggested that it is a presumption, not a goal, an objective, no an aspiration. Right.

So "state of affairs" was the unspoken noun phrase that followed "this." Blame it on *Strunk and White*.

PROF. CAPRON: But I think one thing about diagramming sentences and so forth is that it points out where you haven't been clear about what you mean.

And so "this state of affairs," instead of saying that, why don't we say what we think the state of affairs is, the reasonable availability that -- and see I think that the other wording of the rest of the sentence would be better achieved if we put this phrase first.

And I was trying to do that, and then I realized I wasn't sure what I was putting there. "To

achieve reasonable availability, sponsors should ensure that collaboration with host countries and other appropriate parties occurs." Is that what we are saying?

Because we just got -- in the colloquy between Arturo and Harold just now, the idea was, we are moving away from saying that they should collaborate to make sure that the collaboration has occurred, whether it is themselves and their agents or the researchers or someone else.

And are we saying "to achieve reasonable availability"? Is that what we mean?

PROF. CHARO: Or to try to achieve it, since we can't make it an obligation or a guarantee.

PROF. CAPRON: So what is the "state of affairs"? That doesn't clear it up to me. The "state of affairs" is the attempt"?

PROF. CHARO: "...to try to achieve reasonable availability..."

PROF. CAPRON: "...to try to achieve reasonable availability..." But it is not an objective. It is a presumption. See, that is the hard thing.

DR. CHILDRESS: The presumption is that this goal or objective will be realized. It seems to me

that is the way one reads that.

DR. SHAPIRO: Steve and then Bernie.

DR. LO: I think we have some conceptual lack of clarity as well as our linguistic problems. There have been a number of things on the table for what we want sponsors to do.

One is to just make sure that negotiations happen before the research is conducted. One is to make sure that there is some sort of collaboration with the host country. Third is to make sure to use best efforts, reasonable efforts, to try and achieve -- and I would agree with Alex -- the object should be "such availability" or "reasonable availability." And a fourth is to actually achieve it.

I think we are not -- I don't know that we are in agreement as to what it is that we are trying to accomplish, and not in a linguistic sense, but are we holding people to saying, you had better do this unless there is a really compelling argument for why not? Or is it just, try to do it, which is much, much weaker than a presumption.

So I think the presumption language that I think, Steve, you originally proposed, to me, is, you are going to do unless, and that is much stronger to me than just trying or even making reasonable, you know,

efforts to try and do it.

DR. SHAPIRO: Well, I think I know what my own views of this area, although I don't know if anyone else's are.

It is my own view that it is an obligation of sponsors to ensure that some benefit related to the health condition being studied is delivered to the country in excess of what is owed to participants, or in addition to what is owed to participants.

That is the one thing I am sure of. I feel that that goes along with the premise of this whole approach that we have taken from the beginning that this has to be something that is related to the health needs of that country, or else what on earth are you doing there?

Now, so, I am convinced in my own mind that that obligation exists. However, I think what the problem is in it for me is the nature of that obligation is very contextually grounded, and I can't think of any rule that satisfies me in all cases.

Just to take some examples. If you are looking at a health need which exists only in that country and nowhere else in the world, the obligation, in my mind, of the sponsor to do additional things is different than, let's say, than the exist reverse to

it, whatever the opposite of that is. We wouldn't approve of the opposite. Or let's say where it is a case where the health condition exists everywhere. The health condition to take that case exists everywhere, and you have to ask yourself, what on earth are you doing there? You could be at home and just do it at home.

And so it seems to me that, consistent with the whole premise here, is that there must be some additional obligation that falls beyond what is owed to participants. However, once I get to that stage, it becomes so contextually grounded as to what I feel is a reasonable expectation I don't know what to do besides search for a procedural solution, where people are asked to recognize this responsibility and use their best efforts to negotiate some type of equitable agreement.

I understand that people have different bargains and so on and so forth, and I don't have a solution to that either. That is a problem, and that is going to continue to be a problem. I don't know how to provide for it in this kind of a context.

But I would feel, myself, very good if people conducting trials abroad in a host country, one, recognized they had an obligation, recognized they had

a serious obligation to carry on good-faith negotiations of some kind, and hopefully, reaching some type of agreement which would be beneficial.

Just what that would be sort of escapes me. I mean, I think it should be related to the health condition of that country. I would go -- that far seems clear to me. So sending a tank is not appropriate if you are studying -- as another benefit -- just to take an extreme case.

PROF. CAPRON: You can't wipe out mosquitoes with a tank?

DR. SHAPIRO: Well, maybe actually with a flamethrower of some kind. But, I mean, it should be related. So I can get that far. But the minute I try to get farther than that, to know just who should provide what, who should pay what, at what cost they should do it, and to how many people and so on, I just -- every example I think of gives me a different solution. Bernie.

DR. LO: Well, I think this is helpful, because you have just put out another possibility, which is either the therapy that has been shown to be effective or something else that relates to health -- I am wondering, I mean, we are having a lot of trouble with this.

And perhaps we are trying to do too much all at once, and maybe all we can do is call attention to the problem, but try and flesh it out with examples. I mean, we keep saying, it depends, it depends, it depends. Let's put out some examples of what it depends on.

Because, Harold, what bothers me about the way you left it is that a sponsor can say, look at what we did. We trained 10 host country scientists and 12 nurse-clinicians, who after we leave will be able to carry on the work. And that is a clear benefit to the country, because, you know, of the capacity building.

I would want to say, again depending on the context, that the example that I have are, for example, studies of new drugs for osteoporosis in China, where the drugs are going to be marketed in the U.S. and developing countries at very high prices -- blockbuster drugs.

To just train people -- you are going to do the work anyway -- and say that, well, that is our obligation
seems to me to set too low a threshold. So maybe what we can do is get some examples of cases where we think people have done it well, not just done the minimum, but sort of set an exemplar for the kinds of outcomes.

And, therefore, without specifying what needs to be on every case, at least, through our examples, point out that we mean this to be sort of a high aspiration, not just, you know, we had some conversations, and they were amicable, and they thought it was reasonable.

I would like to set the bar higher and, as you keep saying, leave open the actual implementation in a case, because it is going to be so contextual.

DR. SHAPIRO: I think that is helpful. We want this to be serious. We are not meaning this to be trivial, and I am putting perhaps more faith than is deserved, in the circumstances, really on the power of countries, to take China as an example, but take a less powerful country, to understand what their interests are and to protect them in some way.

So I think that we should not unnecessarily just presume here that these countries have no power to protect their own interests, and I don't want to take the sponsor's word for it. I agree with that. That is why I want the negotiations in advance.

And even though I know they are not always equal parties -- I am quite aware of all that -- that is something, and that is why I think letting an IRB at least look or -- the nature of that proposed plan or

set of negotiations has got some benefits too. It is just public exposure. That is what it is, and it leads to have some public accountability in an area where we have none right now.

Now, I haven't got the language to express all that even if everyone around this table would agree with me, which I am sure is not the case. Jim.

DR. CHILDRESS: Let me try my hand at an earlier part of that. Alex had indicated -- might begin with the second sentence rather than the first, and I am just wondering if we couldn't, given the difficulty we are having with presumption, with identifying the relevant parties and so forth, if we might try something like the following version.

"Sponsors should collaborate with host countries and other relevant parties to make successful products or other benefits from research reasonably available to the host countries." That has the advantage of being fairly simple and straightforward. And then we can move into the kind of advanced negotiation or something like that.

PROF. CAPRON: Harold?

DR. SHAPIRO: Yes. Alex, then Arturo and Will.

PROF. CAPRON: I like Jim's suggestion, but I

have an alternative to offer is a little stronger. It beings with you were saying a moment ago, Mr. Chairman.

What is we began with the statement: "Those who sponsor and conduct research abroad are ethically obligated to provide some benefit to the host country relevant to the condition being studies. From this obligation, a presumption arises that successful products..." And then we give some source for that presumption.

And then say, "Sponsors should ensure that negotiations occur with host country officials..." I don't like negotiating with "host countries" -- you have to say there is a person here -- "...and other appropriate parties prior to the initiation of the research about how this objective will be addressed."

That goes to the point that Diane raised before that we lost the timing aspect of this in the rewrite.

But I would begin with the statement of the ethical obligation and derive the presumption about successful products or other benefits from that. And then state the obligation to ensure that the prior negotiations have occurred.

DR. SHAPIRO: That sounds -- it sounds right to my ear. I don't know it has got everything in it.

If you could write it out, that would be helpful. Arturo.

DR. BRITO: Well, I will refrain from everything I was going to say, because I would like to see what Alex just said written. I would like to see a lot of things written down.

But I still want to go back to the point about who has the obligation to ensure these negotiations and the collaboration have occurred before. Because in the text, it is even mentioned on page 13, for instance: "In general, individual researchers do not have the resources or authority to directly provide post-trial benefits to participants."

So I really think that the negotiations and the collaboration should occur either between sponsors and/or researchers and the host countries and other appropriate parties.

But the obligation ultimately rests with the sponsor, because they have the means and the money. So the obligation to ensure that those negotiations, or collaboration, whatever word we use there, is their responsibility.

DR. SHAPIRO: In my mind, it is important to distinguish between the obligation to carry on the discussion and the obligation to fund the commitment

-- all right -- that if you have a post-trial commitment. Clearly, the researchers have no capacity in the latter. And many sponsors don't, incidentally. But some do. And that is what makes it, I think, everywhere you turn a complex ---

DR. BRITO: Exactly. But I am not hearing in any of the language where that obligation really lies. I don't hear it. I don't see it in any of the language, and I am just worried that what we are going to end up with

is ---

DR. SHAPIRO: The obligation for negotiation or the obligation for funding?

DR. BRITO: No. The obligation for negotiation.

DR. SHAPIRO: That we should clarify. I agree with you. Will.

MR. OLDAKER: I agree, Mr. Chairman, with you that it would be better, in my mind, and maybe this is not what you are saying, but if there were a list of things that were presumed to be negotiated, list of types of things, almost a cafeteria plan. One of them could be "reasonable available." But there could be a number of other things too.

And I think that negotiation has to occur

prior to commencement of anything, and my other point is that I think that negotiation has to come with someone that we identify like the minister of health. I think we would probably harm ourselves if we leave it too ambiguous about who that negotiation is with.

So by specifying, we empower whoever that official is with some authority to negotiate. Then if we set out the things, I think that would benefit the country. This is kind of 4.1 plus that says that you have to do more than 4.1, and here are five examples that would satisfy that.

I think that would work well, and that would empower the minister of health, or whoever else, to try and get one of those things. I realize bargaining is not always equal, but that would help.

DR. SHAPIRO: Thank you. David.

DR. COX: And so just following on those lines, I think one of the things you said from the get-go here, Harold, is that it is very difficult to separate the researcher and the sponsor in this. So somehow they are going to both be together in it. So you don't have to designate who is going to be the lead at any particular time.

But that they together have to do this. And then it is not ambiguous about who is putting it

together. You don't have to say who is the lead, but that they have to be linked at the hip doing it. And then if one person wants to take the lead, then, by definition, they talk to each other.

So then those are the two components. Then what they do is sort of what you were saying. But in terms of who it is, it is clear. It is the sponsor and the researcher together.

DR. SHAPIRO: Larry.

DR. MIIKE: Since people are asking for examples, I want to ask a practical question. We have NIH and CDC-funded research in Gambia. Who can make that promise and who can deliver on that promise?

DR. SHAPIRO: I can only answer for myself, and the answer is that that is something to be negotiated between CDC, or whoever, and the appropriate authorities there.

DR. MIIKE: But I don't see CDC as being in the position to be able to provide ---

DR. SHAPIRO: And they may not. They may not. They may say -- I am now talking only for myself -- they may say, this is what we can do. This is what we are willing to do. The country then has to decide whether that is a plus for them or not. That is my view.

DR. MIIKE: On another issues, which is -- someone had voiced the concern that -- well, I guess it was you -- that you don't want them to say, well, no, we trained 10 nurse-practitioners, etc. That is easily addressed in that we are talking about benefits beyond what was necessary to conduct the research.

DR. SHAPIRO: Right.

DR. MIIKE: I still say I would rather have a vague statement rather than one that tries to put a list together. You put a list together. It inhibits the creativity of coming up with other things other than that list.

People will tend to focus on that and say, well, we couldn't deliver these. You know, that is the end of it. And then who is to say we are going to be right in what is listed.

DR. SHAPIRO: Steve.

MR. HOLTZMAN: I, in general, agree with your approach, Harold, and I think it ties -- what Alex is providing is a very good way to do it. Because in my way of thinking, the obligation -- let's come back to what the obligation is in a moment -- is grounded in the conduct of research, the meaning of what you are doing as research as opposed to exploitation, and a reflection upon that.

And I have given Eric some language about thinking about when you provide blood, whether you get if from money or as a gift, how it changes the meaning of the act. And I think that is the source of the obligation to be provided a compensatory medical benefit.

That is, why did I undertake it in this population? Because they could benefit from it. They are not just guinea pigs. I think, to me, that creates the presumption that there is a plausible way in which the medicine, if successful, will become available to them, a presumption. But it is rebuttable.

And this is where then, as you get into the contextual elements of it, you allow scope for, as it were, the host country autonomy to assert itself, to rebut that presumption, or to figure out creative ways to have the appropriate kind of compensatory benefit.

With respect to whose responsibility it is to ensure that the research enterprise has that flavor and character, as distinct to whose responsibility it is to fund the provision of the drug, in my mind, it is everyone who is a participant in the research process.

And you don't need to say any particular person's role in that, but they all have a stake in that being on the table, in play, and ensuring it is in

play.

DR. SHAPIRO: I fully agree with that.

MR. HOLTZMAN: And that is why I am much more comfortable with your examples of who may be responsible for what particular piece, the researcher here, the sponsor, or the what-not.

I want to just go over the top with it and say, you are all responsible to examine the situation and figure out all of your responsibilities to ensure that the presumption is either fulfilled or rebutted, and if rebutted, what is the substitute?

DR. SHAPIRO: Alta.

PROF. CHARO: First, just a question. The draft language that was done over lunch, is that going to be available?

DR. MESLIN: We are waiting for it to come back.

PROF. CHARO: Great. Because it actually is very similar in spirit to what Alex had suggested, although it is considerably more telegraphic in its presentation.

But it adds one thing which, Steve, you would suggest we avoid, and I am still not comfortable avoiding, and that is, some degree of detailing in how we actually implement this collective responsibility.

What I fear is that although what you say is in the best possible spirit of how research culture is developed, I think, especially in an area in which we are trying to extend the notion of what is expected as part of research, it is very important to have a few very clear directions for a few very well-identified bodies or people, lest everybody just kind of push off their part of it to somebody else. And a collective responsibility becomes -- it dissipates into non-action.

MR. HOLTZMAN: And I agree with that. I mean, in the sense that I want everyone responsible -- as a corporate officer, I will typically be a sponsor. I want the clinical investigator in the companies actually basically take responsibility to say, have you done something about this, sponsor?

And I do believe that if there is a rubber hits the road issue here of you could locate it with the money, the sponsor, even if the sponsor is not the relevant party for the eventual provision of the drug. But before they let the trial go forward, a responsibility to ensure that, again, this has been taken on. Because they are the -- they hold the faucet.

DR. SHAPIRO: I think that I have two senses

here. One, I think there is rather more agreement here than would meet the eye. We are really all hovering around the same set of issues. We understand we are not going to discharge in some kind of formulaic way just who is going to pay for what, who is going to do what, in each various situation. We understand that.

We understand that there is a benefit -- there is an obligation here, which we all recognize. The question is: How does it get -- how does one deal with it? And the details are important.

We will look at the -- when we get it, we will look at some language that Alta put together over lunch. We want to look at that, and Alex has given me his language.

I think we may not be able to resolve 4.2 itself without some telephone conference, as we get to assimilate this a little bit and really work over these alternative suggestions very carefully. I just don't think we can get there with the amount of time we have today. So we are going to have to do that in that fashion as we go ahead.

Now, let me -- excuse me, Carol.

DR. GREIDER: If I could just raise a separate issue that maybe we could be thinking about in here, and this is something that goes back to what Larry

brought up. But it has to do with the process.

I am thinking about an investigator-initiated set of experimental protocols, and if I am correct, investigators have to go before an IRB before they necessarily have a sponsor on board. That is, the NIH has not signed off on this yet.

So how can the IRB make sure that the sponsor is behind this if it hasn't -- if there is no sponsor yet?

Right. We are asking the IRB to make sure that this process is in place. So I just don't understand the process.

DR. SHAPIRO: Well, there are a number of ways -- I don't want to -- that is an important issue. There are all kinds of details of that kind in here, and we are just going to have to think carefully about how we --- Whatever obligations we give to IRBs, we are going to have to articulate them pretty carefully. Because they are going to get to look at this at different points in time, and the sponsor may not be here. But you can still have plans of what you expect from your sponsor, or what you will do, and that could be presented to the IRB.

But there is a bunch of hands over here.

PROF. CHARO: Just a two-word answer:

continuing review. IRBs see these things more than once.

DR. : At a certain time ---

DR. SHAPIRO: He or she may not, and they may have plans for what they are going to expect of the sponsor or may not. But the review is going to have to continue either way. Okay.

I think what we will do right now is just wait until we get that other language. We want to proceed -- Alex has language here. When the other language comes in, maybe we can spend a little time comparing these two.

You have heard Alex's before, and he has now written it out carefully. And I want to thank him for that. Could we copy this? That would be very helpful actually.

Then maybe, Eric, we can get (?) started. We will jump over the rest of chapter 4 right now and get at least an initial start on chapter 5 and the recommendations that are associated with it.

DR. MESLIN: For those who are keeping score with the clock, we know that there are two people who have expressed an interest in giving public comments. And if there are more, we would like to know fairly soon. This will give us a bit of a sense of how far we

can go.

At this point, I am just going to suggest, Harold, that we can go until about 2:45, and then turn to the public comment for the last 15 minutes and still stay on schedule. And we will just adjust as we go along.

There is also the possibility that some time can be made available tomorrow morning. Dr. Speers and I did have a discussion about perhaps shortening slightly the discussion of chapter 1 that is scheduled for tomorrow morning. So we may be able to get a bit more discussion time on chapter 5 ---

DR. SHAPIRO: Chapter 4.

DR. MESLIN: -- on chapter 4, and what we may have not finished on 5.

Chapter 5 has, at this point, nine recommendations. There is nothing magical about why there are nine. Principally, these recommendations are supposed to do three ---

DR. SHAPIRO: There is; nine is my lucky number.

DR. MESLIN: So there is a reason, and you have just heard it.

DR. SHAPIRO: I am nine minutes older than my twin brother, which is the reason. I have even got a

good reason.

DR. MESLIN: Boy, is my face red. The recommendations are unevenly lumped. There is one recommendation, 5.1, which focuses on capacity building generally with respect to infrastructure, training, education, research-related capacity building.

There is a recommendation, 5.2, related to the specific aspect of capacity building related to research ethics review. In the rewrite, it was felt that these two components of capacity building needed to be flagged. This is an important topic, and they needed separate treatment.

The next several recommendations, 5.3, 5.4, 5.5, 5.6, and 5.7, are recommendations that are supposed to address the issues related to current research regulations and, specifically, the equivalent protection provision found in the current sub-part of 45 CFR 46.

The idea behind those several recommendations is to, first of all, as, that the new Office of Human Research Protection, would be able to provide policy guidance on this matter. That agencies would have input into this, and that determinations of other countries' guidelines regarding equivalent protection could be made in a clear and understandable way.

I won't go over each of them individually unless we can do that in order. There are some distinctions that are made between those countries that have their own guidelines, such as Canada or Australia or France versus those countries that do not have their own guidelines, but may wish to use international guidelines, such as CIOMS or Helsinki.

And the last recommendation, 5.9, really mirrors recommendations the Commission has made previously about having resources made available. In this case, Recommendation 5.9 is a recommendation related to the cost of complying with these regulations.

So those, in a nutshell, are what the recommendations were intending to do. Capacity building in two components and revisions to, and clarifications of, U.S. regulations as they are applicable overseas.

DR. SHAPIRO: Thank you. Let me make a few comments. We haven't actually devoted as much attention as I would have liked today to chapter 5, but we are -- since we obviously got to it last -- but let me do two things now, at least until we get the other material in here.

One, to talk about Recommendation 5.1 and 5.2,

which are capacity and see what kind of reaction you have to them. Regarding recommendations of the 5.3 and on, I have some, what are to me, significant issues I would like to raise, both with concerns I have about them and being uncertain where the Commission stands on them.

But let's just talk about 5.1 and 5.2 first to see whether the text in those recommendations have given you any cause for concern. You want changes or anything

-- Alex.

PROF. CAPRON: I wanted to come back to the point that Diane had raised and wonder whether, given the surrounding text, it would make more sense either to put a phrase at the end of the first sentence on 5.1 that would say: "...and for negotiating with sponsors regarding their post-trial obligations..."

Or if it would make more sense to have a Recommendation 5.3, although that would lead us towards a decalogue instead of a nanologue, and to have a separate statement, just as we have a separate one about the ethical review capacity.

But I think she is right to say that somewhere here we are talking about the development of capacity even if we have to make reference back to chapter 4 as

the basic source for that discussion. We have dropped it out of the process of Recommendation 4.2 (c) unless you put it in here somewhere -- (inaudible).

DR. SHAPIRO: Well, that seems reasonable to me. We will do something to that. Any other comments on 5.1?

PROF. CAPRON: Linguistically, it would seem to me that the second recommendation -- oh, I am sorry -- 5.1. This is on 5.2.

DR. SHAPIRO: Yeah. 5.1 or 5.2.

PROF. CAPRON: 5.2. I would recommend adding the article "the" before "capacity." "Assist in building the capacity to conduct," instead of "for conducting."

"...to conduct scientific and ethical review..."

DR. SHAPIRO: Okay. Let's go on then to Recommendation 5.3. First of all, it is my own judgment that I don't know what the last sentence is doing here, frankly, to start the discussion off.

The one that says that we recognize someone else's authority, since that is not our business in that sense. It doesn't seem to me to be dealing with the same issue, unless I misunderstand what was said here in the first part of 5.3.

What 5.3 obviously deals with wanting to find

some language that would ask OHRP to give more structure and transparency to the decisions regarding establishing equivalent protections. But what kind of comments ---

PROF. CAPRON: Mr. Chairman.

DR. SHAPIRO: Yes.

PROF. CAPRON: I think that -- I had nothing to do with the wording of this, so I am not trying to defend it -- but I understood it to say, sponsoring agencies should accept this determination, that is to say, the determination of OHRP and thereby recognize the authority to conduct the review without requiring a single project assurance from them.

In other words, once it has been done, OHRP is the lead agency and other U.S. agencies should accept their determination. But somewhat confusing to me is the relationship of that recommendation to 5.4.

And I must say that if I were looking for something that was opaque, it was 5.4. I didn't really understand who was deferring to whom about what and what they still had to be able to do, and so forth. I will love to have that explained.

DR. SHAPIRO: Okay. As we -- this gives me an appropriate point to raise a matter, an important matter of principle, as far as I am concerned.

And, that is, if we imagine a system which declares that the procedures, rules, regulations, and so on in some particular host country are equivalent, or provide equivalent protections, if that is determined, or certified somehow through some organization here, and let's suppose the U.S. is going to sponsor research in that country, the question is: Under those situations, how many reviews are required, should be required by the U.S. sponsor?

Would the host country review be sufficient? Would you need both our local IRBs and the host country IRBs. Or to complicate the issue a little further, if this was joint work between Canada, the U.S., and some other host country, all of whom had equivalent protections accreditation, how many IRB reviews would we consider necessary for an ethical point of view?

Obviously, these countries can do what they like. They can have as many different ones as they want. But that we would consider necessary. I am just saying that would help me understand how we should write these things.

PROF. CAPRON: Well, my understanding is if a researcher from USC does research in Princeton, collaborating with a researcher in Princeton, that both our IRBs have to review it. And that this simply says

that if the researcher is at the University of Eboden (?), the same requirement exists. Both have to review it.

But if it has been determined that the review body at Eboden operates under rules in that country which are equivalent to the U.S. requirements, that that organization, having once been determined to be within those, doesn't need to go through the process.

And this is particularly relevant where the body is actually located in the ministry of health or something of the country, and there has been this awkwardness of every time they do something having to come in as though they were some little contract IRB that nobody ever heard of operating on their own hook.

And this is an awkwardness between the countries and everything else. Furthermore, as we looked at the substantive point that is behind this, as we looked at the research rules in other countries, if anything, they seem to be more rigorous than ours, and it is odd to sort of have this, well, you are not equivalent attitude, which we have had.

DR. SHAPIRO: Steve and Alta.

MR. HOLTZMAN: I would like to understand what we are driving at with this specific example that we are living right now. It doesn't involve a developing

nation, but it is another nation, where because of what is considered standard treatment in the United States versus this other country, England ---

DR. SHAPIRO: Previously developing nation.

MR. HOLTZMAN: There is a trial we can undertake in England with our drug candidate which we cannot undertake in the United States. Because, basically, (?) does not reimburse for this drug; therefore, standardly, the alternative therapy is nothing versus in the United States, where there is a drug which is considered standard therapy.

So if you write the protocol as test versus placebo, it is an unacceptable protocol in the United States. And someone who knows the regs can explain this better. I think under one interpretation, sure, we can go over to England and do the trial. But the FDA will not accept that finding, because it was unethical and therefore didn't meet the standards.

There is one reading here that says we find -- or someone designates that England has equivalent protections, and therefore, if they are happy with the study, and have blessed it as ethical, then FDA ought accept the findings. There is only one review necessary, and we have blessed a system as overall equivalent.

Is that what we intend? Or do we intend something different?

DR. SHAPIRO: I will try to answer that in a second. But Alta.

PROF. CHARO: Actually, it is completely responsive to this. So, a fortunate ordering of hands going up.

As I read through this, although I agree that it can be confusing, it does yield itself upon parsing. I thought it would be easier to follow if it were ordered differently and if an analogy were kept in mind that would help to answer Steve's question.

And that has to do with in the world of law, comity and the recognition of foreign judgments, that is, the recognition of the acts of the courts and legislatures, etc., of other states and nations.

In that world, in that analogy, step one is an observation of what the other entities are. There are other states within the United States. There are other nations that are recognized as nations by some international consensus or body. And here there is a step laid out as well.

And the next is -- the equivalent step here would be the recognition that there is a national body of some other country that functions as a kind of

central repository of guidance and authority in the area of human subjects protection. By the way, a test that we would be hard pressed to pass.

Second, that there is kind of a generalized acknowledgement that we will recognize as valid the discretionary decisions made by that body when it is acting according to its procedures.

So that, for example, in Wisconsin, if somebody comes in having been married in New York, we don't ask whether or not the judge that married them in New York actually was the same kind of judge we would have used in Wisconsin.

We ask whether that person was duly authorized by New York State, and if so, it is enough, because we have acknowledged that New York State satisfies our requirements for a functioning state that set up marriage rules.

But you can have reservations on a substantive level. So it is generally a procedural kind of approach that will incorporate a kind of respect for the substantive decisions that are achieved by the discretionary acts of those governments.

But you can have reservations, and you will find reservations, for example, on things that seem to cut very close to fundamental values, core values of

your own society. It might be age of marriage, or it might be certain kinds of employment contracts that are viewed in some societies as being equivalent to involuntary servitude.

So that although you have a general respect for the substantive judgments arrived at, you can make reservations. And in your example, the question would be not whether we would recognize the English procedures for protection of human subjects, because, invariably, I think we would conclude we do.

It would be whether the use of a placebo in this context falls under one of the reservations we might have made. Earlier in the report where we talked about placebo controlled trials, where the justification for the placebo is that in that country there is no good, effective alternative, but in this country, there is.

And we have to go back to our earlier chapters and our earlier recommendations to see how those two things would dovetail.

We have a similar kind of reservation earlier on in terms of truth telling, where duly constituted and quite adequate bodies in other countries might come to the conclusion that locally telling people the truth about a terminal diagnosis is not necessary and

actually is not in accord with local custom.

But we have made a reservation earlier on this report saying, it doesn't matter. On that score, we won't yield on this core value, although we will yield lots on how you actually go about telling people.

I think, kept in mind that way, with that kind of order of events, the whole things begins to fall into place a little bit more clearly.

DR. SHAPIRO: Steve, is that responsive to your question?

MR. HOLTZMAN: I think it is 99.9 percent responsive in that I think that the logical way of thinking it through is absolutely correct.

When I come to my specific case, if I describe the trial as experimental versus standard therapy -- all right -- we have exactly the same rules.

When I describe it as what is the standard therapy, and there is a deviation, I have a difference in the two societies. There it is placebo or nothing is the standard.

And so -- and you are making this point that says, we recognize any state's authority that is duly competent and constituted; provided, however, if they say marriages can be effected at nine years old, it is beyond the pale.

So, now, how are we -- where are we going to determine what is beyond the pale, and how is that mechanism -- because you pointed to one case -- but there are lots of cases.

DR. SHAPIRO: Alex.

PROF. CAPRON: Steve, I really think the issue you are raising is not the issue which these recommendation speak to.

What I understand these recommendations speak to is the situation in which -- since you are governed by FDA rather than NIH -- let's assume -- I don't know if you get any federal funding for your research, but assume that your research is what you sponsor yourself.

If you were to go to New York University Medical Center to conduct a trial, the only IRB you would have to go to is New York University Medical Center, which has a Multi-Project Assurance, we can assume.

Now, if you go to a foreign IRB, what this would say is if that IRB operates under national standards which have been established to be equivalent to U.S. standards, then it would have a similar standing as the IRB at New York University would have.

The substantive issue of whether the IRB then approves a project, and its own approval somehow did

not meet requirements is, I think, what Alta says you begin with the presumption that they are operating correctly. If someone says, wait a second, they allowed a project to go forward, and their standard was women don't have to give consent, or husbands will consent for them, and that is not what U.S. requirements are, then it turns out that their approval doesn't give you data which you can use with the FDA.

But it is not because they had to go through a process of establishing themselves as an IRB, as though there were no process in their own country to establish them according to standards that are equivalent to ours.

So I want to take out the substantive question you are asking -- and we do address that elsewhere in the report -- the procedural question is all that this addresses.

And the part that I didn't understand about this, Alta, was the relationship between U.S. agencies other than OHRP, and it is really 5.4. And we may want to still defer to 5.4 for a moment. But that is what I found confusing.

Here, as I understand it, we are simply saying, OHRP ought to be the lead agency, just the way

they are in all the regulations. They ought to go through a process. If a country says, here are our regulations. We have a list of approved IRBs.

In effect, they have gone through whatever process we require for them to be recognized as an approved IRB. If OHRP says, right, your rules are equivalent, your IRBs are hereby suitable for review, Mr. Chairman, whether there is one review or two reviews depends on where the researchers come from.

If they come from a university, their own university, as a matter of employing them, is going to say, we need to review what you are doing abroad. Steve is in a situation with a private company, where they may not have that requirement internally, and their only requirement is with the IRB at the site where the research will be conducted.

DR. SHAPIRO: Now, let me ask a question about 5.3, and I really want to ask this about people who know more about these agencies relate to each other on issues like this. And it does make a lot of sense to have OHRP perform the function that is indicated here in the first sentence of 5.3.

And then the question is: What role do the other agencies have? And what authority does OHRP have? Or are we intending them to have here? Alta.

PROF. CHARO: We run into a difficulty here that now overlaps with the Oversight Report we are going to discuss tomorrow.

OHRP does not have any direct line authority over agencies from other cabinet departments, and therefore, it is very difficult to set it up as the single office that is going to oversee all the other departments' activities, which is why I think in 5.4, Alex, the goal there -- I think I have discerned it -- was to say that each agency that has this kind of research going on is going to operate with the same text that will have been arrived at by a joint effort, as outlined in 5.3.

They will each apply that text, but where interpretations begin to deviate in their application, OHRP is going to be the one whose interpretation should be respected. Now, I think I understood the intent of 5.4 that way.

But in terms of creating line authority, we have a dilemma. It would be much easier if in the Oversight Report we wound up suggesting that there would be something outside the current departmental structures. We are all familiar with some of the drawbacks in terms of the political insulation that that provides.

Otherwise, it becomes a matter of what we now have, which is a matter of comity and cooperation among department secretaries and leadership from the White House to those department secretaries to defer on something, which, occasionally, could be terribly touchy.

PROF. CAPRON: If Alta is correct, then I am with the chairman, I think, in suggesting that the last sentence in 5.3 needs to have the active voice. Who is making this determination? I had read it to be once -- OHRP. But you are saying that that is not the case, Alta. That each individual agency would make the determination according to what we are calling policy guidance?

PROF. CHARO: No, no, excuse me, Alex. I am sorry. That wasn't what I intended to say. It says in 5.3 that it is OHRP that comes up a guidance about equivalent protection, which is supposed come ---

PROF. CAPRON: -- in collaboration with -- right.

PROF. CHARO: In collaboration with the others. And in the last sentence, there is no hint as to who makes a definitive determination. I think probably the instinct had been that if OHRP finds the case to be -- that some agency in another country meets

these criteria -- that everybody will defer to that. But it is not said at all.

PROF. CAPRON: But suppose the ---

PROF. CHARO: And separate from 5.4, which is about the application of that on a case-by-case basis.

PROF. CAPRON: Yeah. I don't see how to separate what is in that last sentence from what is in 5.4 now. I guess that is where I get lost.

PROF. CHARO: I don't think we should worry about the language here, because it is likely to change a little bit.

PROF. CAPRON: But I think we should think through what we want it to say. And I mean, it seems to me that the first part of this is clear, which is when we question OPRR about what guidance they use in determining whether there is a equivalence, which was sort of a way of saying, how is it you have never found an equivalence?

You have a set of criteria. They said, no, we really don't. So we are saying, OHRP and other agencies that do work in this field should sit down together and come up with the standards which will be used.

Now, we come to a question. Is the first agency that happens to have an application -- USAID has

an application for research in Uganda. So they apply the standards, and they make a determination.

Once that determination has been made, other sponsoring agencies should recognize the authority. Is that what we mean to say? Whoever acts first? That sounds like an invitation to chaos to me.

Wouldn't it be more sensible to suggest that just as we have said, OHRP should take the lead in collaboration with others? That they should also, as part of that, develop a process for a determination to be made, and this would be an active voice saying that process, led by OHRP, will have made the determination.

And once they have done that, then sponsoring agencies should recognize ---

PROF. CHARO: Is the Interagency Task Force capable of doing that?

DR. MESLIN: Making the determination? I will have to ask the incoming director of OHRP what his plans are for -- (inaudible) -- I expect the answer is no. They can't.

DR. SHAPIRO: I want to just make sure -- I want to make sure that I understand this, because I still don't like the way 5.3 is put together. I understand the first two sentences. I think they have

to be rewritten, but I understand them.

And that is -- and Alex has just summarized it -- I won't go through that again. That we want this guidance somehow and, hopefully, in cooperation with OHRP and the other agencies, and they will all agree it. That we would recommend.

The second sentence that starts, "...Once a determination is made..." that has to do with whether you go through an SPA process or not, I think. I think that is what that has to do with, which is an important point, but I don't know what it is doing, in my view, in here with 5.3. That is just another point. We can put it where it is appropriate. That is how I interpret that.

PROF. CAPRON: But isn't this the alternative? If you established -- again, take Uganda -- that Uganda has standards and they have a way of determining that the University of Whatever has an IRB that meets those standards, this process, following the guidance that is here, would determine, yes, Uganda has such standard, and they apply them appropriately.

So their IRBs at that point have, in effect, negotiated with Uganda their assurances, and they don't have to negotiate with us.

DR. SHAPIRO: I agree.

PROF. CAPRON: But that doesn't seem to be separate, Mr. Chairman, from that. It is the conclusion
-- maybe what it needs is a separate heading.

DR. SHAPIRO: That is all I am saying. It is related to it. I understand that. And it is directly related to it.

But the 5.3, the first two sentences, or what is going to replace them, is a big issue. That will not be easy to achieve. I think it is important. I think we should recommend it.

And I just want to separate out the second part, although it could come right after it, because it is related, just as you have said. It is directly related to it. Steve.

MR. HOLTZMAN: I, for one, would find it helpful to get up to about 5,000 feet on this issue as opposed to the intricacies of the OHRP versus intra-agency task force, etc., and just try to understand what it is we ought to think should happen and the consequences.

One reading of it was along the way that, I think, Alta was going. That we have said there are other countries in the world who have responsible, ethical institutions for research just like we.

They may implement somewhat differently in any given case. But we don't want to, for pragmatic reasons, but also to avoid a certain kind of ethical imperialism, we want to put in place, I thought -- we want to put in place a process where someone, e.g., OHRP, says, we have examined their practices, their institutions. It is fine. You conduct research there. If they say it is okay, it is okay.

Now, I don't think that is a difference. The FDA's accepting my result is the moral equivalent of your local IRB saying, it is okay. And a conflict is: What if there would be two different conclusions.

Are we saying that we will defer, or that we will not defer? What trumps -- I think that is the first question, and Alta, you said, it trumps but for certain kinds of cases. All right? And maybe that is what we have to articulate.

We can then get into a whole bunch of other -- but are we agreeing on that? Is that the fundamental thing we agree on?

We want this government to figure out a way to look over the nations of the world and say, these are places in which you can go under their rules, and it is essentially the same as ours, even if particular cases may come out differently. And, therefore, you won't be

in violation of our rules if you defer.

DR. SHAPIRO: You is who in this case, Steve? You will not be ---

MR. HOLTZMAN: You, the investigator, who is seeking federal funding or looking to support an FDA application.

PROF. CAPRON: Steve, I don't think we go quite as far as you say. After all, an IRB at a university can approve a project, and then the FDA investigators come around, and they go through the paper records, and they say, whoops, there was no consent process here. Or the information that was given to people was totally inadequate. This is not ethical research.

Now, then they look at other projects, and they say, well, this seems to be the only problem. The IRB itself isn't incompetent. We don't have to throw out everything from this IRB. They goofed on this project.

And although they approved it, it did not have the information that was necessary, and they can then take whatever steps they think is appropriate vis-a-vis how those data are treated.

We are not doing anything more here. We are simply -- as I understand it, we are talking about the

system of review, not necessarily the outcome of every particular review.

And we are saying that the system in other countries can be equivalent to ours, and they don't have to come on bended knee to OHRP and say, will you approve us?

Now, if they are in a country that doesn't have a system, they will have to do that.

DR. SHAPIRO: Steve.

MR. HOLTZMAN: I believe -- someone who knows the answer -- isn't it the case that right now in U.S. regs, it says that for an informed consent to be valid, there has to be a signed informed consent?

PROF. CHARO: Incorrect.

MR. HOLTZMAN: Incorrect. Okay. Bad example. But ---

PROF. CHARO: It differs between FDA and NIH, and with NIH, there are waiver rules for that.

MR. HOLTZMAN: Okay. My point being -- Alex, I don't know if we are really disagreeing. Right now, there are what we call the procedural elements in certain places which are embedded into our regs, where unless you fulfill those, you will be considered not to have fulfilled them, and therefore, it won't be valid. You will be in violation.

And one of the gists of this report, I believe, is to say that as long as there is substantive compliance, we shouldn't get hung up in that. Right? So maybe that is a better example just to focus the discussion around. So it should be possible to say, with respect to Nation X, okay, they are in substantially the same ethical space as we are, albeit they have different ways of effecting it, and that different ways themselves should not be disqualified.

DR. SHAPIRO: Diane.

DR. SCOTT-JONES: I looked back in the text to try to figure out how this Recommendation 5.3 relates to the text. And it seems to me that this recommendation arises from two points that are made in our text.

The first is that 45CFR46, one of the sub-parts, already allows for the substitution of foreign procedures for our own procedural requirements. And then later in the test, we make the point that OPRR and its successor agency have not established what constitutes equivalent protections and have never made that determination of what is an equivalent protection.

So it seemed to me that Recommendation 5.3 was only asserting that these agencies -- that OPRR, or what it is now called -- should collaborate with

agencies to establish what does, in fact, constitute equivalence. It is saying that and nothing more.

It seems that the discussion has included -- right -- a lot that is not really intended here. It is a fairly simple thing. We asserted that something has not yet been done. That the equivalence that is allowed in existing regulations has never yet been established. And this is simply saying that it should be done, isn't it?

DR. SHAPIRO: Alta.

PROF. CHARO: Yes, it is saying it should be done. I do think that in the chapter already and in the ultimate rewrite, there is room for additional direction as to how to accomplish that.

Because I think, Steve, the degree to which you see regulatory and ethical issues intertwined is both a commonly shared difficulty and one of the reasons why the finding of substantial equivalence has been difficult to achieve to date.

I think that the goal I have for this chapter and for our recommendations is that we put an end to the regulatory imperialism, or procedural imperialism, in which the number of bodies, the makeup of their disciplinary array, those kinds of things, and that would include the signature at the end of the consent

form, as an additional procedural matter, all would be considered to be up for grabs in the sense that other countries might do it a -- different way to achieve the same substantive outcome, which is a review that satisfies our goal of adequate protection of human subjects.

On the issue, however, of the ethical standards that are used, by whatever procedures, I think there we want -- we have, in fact, adopted a qualified ethical imperialism. We have identified in earlier chapters a limited list of issues on which we will not compromise.

And if American researcher, subject to these regulations we are proposing for the U.S. wants to do research abroad, there are certain rules that can't be broken. One of those rules is that every individual who is an adult and is competent has to give consent for himself or herself. That substantive rule is unbreakable.

We have got a short list of those.

And if another country has different ethical standards, do not break those rules, there would be no obstacle to recognizing substantial equivalence.

DR. SHAPIRO: Diane.

DR. SCOTT-JONES: I think the recommendation

should refer to the 45CFR, to the regulation from which it arises, and should capture more of what is in the text. So that when the recommendations are read in isolation, as we are doing them now, it reflects more of the discussion in the text and gives the person reading it more a sense of why we even need to make these statements. I think it is a little bit out of context right now.

DR. SHAPIRO: As I understood it, in reading this myself, it was that this procedure, if accomplished, that is, the first couple of sentences in 5.3, however they are put together, would simplify the SPA process. That was its practical outcome, as I understood it.

Now, are there other practical outcomes of this that anybody else has in mind that I have missed, or misunderstood, or somehow not focused on?

Steve's problem is a problem no matter what happens. The problem is just a problem. This does not deal with that problem. It remains a problem, as far as I can tell. If we want to deal with it, we would have to do something else. Trish.

PROF. BACKLAR: I think it is worth rereading on page 19 what Bernard Dickens wrote. I am not going to read it out loud, but it really addresses this issue

in very nice language.

DR. SHAPIRO: Any other comments? We will have to rewrite 5.3. I am not satisfied with it as it currently stands. Yes.

MR. HOLTZMAN: Just to be clear, the case I raised, we do address it. It is a problem only in the sense that the Commission finds that we would recommend that that trial not be undertaken. Right?

DR. SHAPIRO: Well, that is right ---

MR. HOLTZMAN: And to the extent that you go ahead and do so, we would recommend that you not be able to submit the data.

DR. SHAPIRO: That is exactly right. Correct. Exactly right. Exactly right. Okay. Eric, do you want to go 5.4?

DR. MESLIN: I think Alta and Diane or others had commented on this. If there is agreement on the general picture of there being a clear idea of what the equivalent protection criterion standards are, then agencies should be provided with sufficient information to do that.

But that, ultimately, the decision as to whether the interpretation is correct or dispositive should rest with a body. In this recommendation, that body would be OHRP.

PROF. CHARO: Eric, just in the rewrite, and following on Harold's comment about practical implications, I think what would really help the most for sponsors, governmental and otherwise, that work in these countries would be if the mechanism within 5.4 and 5.3, etc., was not just to make it easier to get SPAs, but were to actually essentially grant MPAs, or whatever those will eventually be called.

The idea is essentially to grant England an MPA -- right -- as well as Nepal and recognize that its government has the ability to review and critique its own internal institution to decide which ones are capable of conducting research in accordance with Nepalese or English rules. And we will defer to the judgment of those governments as to the capacity of their institutions within those countries.

I mean, in a sense, this is the same problem that we have in all collaborative research. You know, University of Wisconsin, Madison, the UW hospital IRB, has a hard time trusting the Meriter Hospital, which is less than half-a-mile away.

So, I mean, I don't discount the difficulty of trusting the Nepalese IRB half-a-world away. But it is the same problem.

DR. SHAPIRO: Bernie.

DR. MIIKE: Just a practical question. Is 5.4 necessary? It seems implicit in everything else that goes before. I am trying to get it down to eight from nine.

DR. SHAPIRO: That was my initial view, but -- when I read this over -- that 5.4 was not necessary. But 5.4 apparently sets up, I think it was claimed, sets up who is the arbiter now that these guidance documents or procedures have been decided on. When there are issues, who decides whether -- who makes decisions on it? Who disposes of cases that come up?

And this thing, which, in my view, is not easily understandable the way it is written, says that OHRP ought to be the arbiter, not left to each agency to make those decisions on its own. That is how I understand 5.4.

DR. MIIKE: Well, then I will ask a follow-up question. Is that the current situation with research conducted in this country? Are we going to have a standard for overseas that we don't apply in this country?

DR. SHAPIRO: Could have. Yeah. Eric.

DR. MESLIN: Just as a point of information, Ellen Gadbois from our staff just reminded me that the regs do provide, or allow for, agencies themselves to

make the determination that another policy provides equivalent protection.

So the discussion you have having here is to change what they are already permitted to do, but don't appear to be doing, with probably the exception of USAID, to another system, where another body, for example, OHRP, would have that authority and perhaps only that authority.

And we have the regs here if anyone wants to see them. Bernie.

DR. LO: I may just be doing my post-red eye fade-out, but I am having a really hard time with these recommendations. I think there is a real forest and trees problem.

You know, this seems to me to be missing the big picture, which is we think that current way of getting SPAs is so cumbersome that it is a detriment to research, and although the regs allow for this equivalent protection determination, it hasn't happened.

We want to facilitate that happening, and so what we have here is a bunch of procedural things, who can do what, and who trumps whom, and we are missing the point that no one is doing it even though they are allowed to.

I am just wondering if the thrust of our recommendation is get on the ball, guys. There are other countries out there that we ought to recognize and, as Alta says, give MPAs to countries that have a procedure and policy in place. Then everything else just seems to be secondary.

That we ought explain -- have a process for how we decide it in this country. We ought to have clear guidance.

DR. SHAPIRO: David.

DR. COX: Yes, so, I concur with that, since I was on a red-eye too. And I understand the complexities of the different agencies, but if we don't have one focus in the United States that makes this determination in terms of equivalent protection, I think we are in trouble.

And so that to make that, you know, OPRR seems to make a lot of sense to me. But I guess I am arguing in favor of a single, you know, process in the United States that says, for this country, it is equivalent.

Because what is going to happen is, guess what, folks, the standards in the country are going to change over time. And then who decides? So if you don't have one place that is constantly in a position to, you know, assess that, it is going to be a

nightmare.

So what we are really saying is, listen, if we want to do business and research with different countries, then there has to be something equivalent, and there are some fundamental rules that, you know -- we are not telling the countries what to do -- but if they don't play by these rules, we are not going to basically do research there.

So there has to be something in this country that looks at that and says, yup, looks okay, or no, it doesn't. I mean, that -- Bernie, I am trying to come to your big picture thing. So there has to be some, you know, detailed mechanism for how you do that, but right now, I don't get that out of the regs. Maybe that is not -- maybe, you know, that is what people didn't agree to.

DR. SHAPIRO: Steven, than Alta.

MR. HOLTZMAN: I don't mean to be insensitive that if you start having to rewrite regs to effect our recommendations, it makes it more difficult. But isn't there a way we could do this that certainly uses the existing structure.

And following on what I hear to be the sentiment about getting it on with it is we would request that an agency, namely, OHRP, go out and do the

study on a repetitive basis, on a periodic basis, of who is and who is not equivalent; provide the list, all right; and each of the agencies, I guess for whom they have the right to make the determination, embrace it.

DR. SHAPIRO: Well, I think -- let's get bogged down into whether these agencies can really cooperate, can be made to cooperate or not. It really is a very generally difficult problem, given the way the authority

-- where the authority of these agencies come from, how they are governed through the Congress, and so on. It is a really a tough, tough issue, which we don't want to really focus on.

But I think we can make a recommendation. We have aspirations. This will be another aspiration, you know, and let someone else figure how to solve the problem. That it is a very difficult thing to go with. That kind of pluralistic approach to this makes it really quite difficult. There are often common sponsors and so on. Alta.

PROF. CHARO: Yes, in fact, quite consistent with that, I have got to say this. As a lawyer, I usually love working on trees, leaves, capillaries, you know, stoma on the leaves. But in this case, I actually like the idea of going up a level of

abstraction with two things.

First, to list the goals very cleanly and direct it actually at -- excuse me, Rachel -- the Office of Science and Technology Policy -- is supposed to be acting as a coordinator of science and technology policy across departments -- right -- where the goal is that there be a single place that can actually review and assess the adequacy of the procedural safeguards in other countries.

And that there be a single place that can apply a single set of substantive guidelines that define what constitutes substantive equivalence with regard to the ethical standards that will be applied.

And then just to give them a break, I think it would be appropriate as an ethics commission perhaps to list what those substantive guidelines ought to be, and by that, I mean to go back to chapters 1, 2, and 3 and draw out of it those things where we found we needed to list our reservations.

That you have to have individualized consent, which has followed upon complete information and disclosure; that men and women are treated the same way in the way in which they are recruited and enrolled; and all the other things that caused us to write special recommendations and then bump it to somebody

else to actually force agencies and departments to figure out a way to accomplish it.

And in the text, we can certainly write that in the interim, it might make good sense for the OHRP to try to accomplish as much of this as it possibly can on its own. But there is a little bit of a danger of us trying to prescribe the precise way OHRP would go about doing this.

Number one, it presumes OHRP is the right place to do it, but we are only working with a biomedical model here, and once you begin to realize that all of the non-biomedical research has the same dilemma, and it is the same agencies that are ---

USAID is doing social science research. CDC is doing social science research. We risk having inadvertently created a biomedical monster that will gobble all social science research into the same set of procedures.

And the second is that OHRP simply doesn't have the legal authority to force its solution onto others, which is why it took, what, how many years for the Common Rule to get adopted? And they have also got a lot of stuff on their plate right now anyway.

DR. SHAPIRO: Okay. I think we have discussed this long enough to kind of redraft a set of

recommendations along with text here in 5. We may get it back tomorrow, but I would like now to return -- maybe, Eric, you can take us through -- we have got a couple of options going back to 4 that are before us for inspiration, guidance, and so on.

You have the so-called revised 4.2. You have two options, which Alta provided, and one which Alex provided. Eric, do you want to just take us through this?

DR. MESLIN: I think they are probably self-evident. You have already been over the revised 4.2. Maybe since it went in this order, Alta, do you want to do your two options, just very quickly? Just maybe show how they are different.

PROF. CHARO: Actually, I think, substantively, I may be presuming upon you, Alex, but I think, substantively, I think we independently came to the same approach. Mine is far more telegraphic.

DR. SHAPIRO: What do you mean by "telegraphic"?

PROF. CHARO: Short.

DR. SHAPIRO: Oh, short. What's wrong with short?

PROF. CHARO: Mine is short perhaps to the point of being incomprehensible, as opposed to Alex's,

which spells it out in more detail.

But it very deliberately uses, in Option A, the language "reasonably related to the health needs of a country," because it copies language from earlier in the report and so tries to use an earlier recommendation that we have all agreed to as the premise that leads to a conclusion about what it means for something to be reasonably related, and therefore, what it takes to actually have major research related.

And it does includes -- and I anticipate opposition from Larry on this -- continued mention of the IRB, simply because it is the only so far identified choke point that has any hope of giving some teeth to this thing.

The second option I wrote, which is identical, except that it drops the language about "reasonably related" and simply substitutes "ordinarily yields benefits." Because David over here thought that "reasonably related" was lingo and that I was now creating lingo about lingo.

DR. SHAPIRO: Still think that, David?

DR. COX: It is better.

DR. SHAPIRO: Alex.

PROF. CAPRON: My entrant in this beauty contest is an attempt to, as Alta says, perhaps spell

it out a little bit more fully.

One difference is that I actually am more telegraphic on the last provision by combining into one fairly succinct sentence the notion of protocols including a description of the plans and IRBs taking that into account.

I don't think we have to put the emphasis on the researcher. Usually, of course, the researcher will draft that portion, but somebody else may draft it. The question is: Is it in the protocol, not who put it into the protocol?

But if you can read my writing, I don't have much to add to what I was trying to say.

DR. MESLIN: I do want to point out one point that both Alex and Alta share, but slightly in error, to make sure that you are agreeing or disagreeing for the right reason.

Alta used the phrase "reasonably related to the health needs of a country" in Option A. The language we used in the text "responsive to the health needs of the country." So I am sure that is an easy one.

Alex's, however, is slightly more different. Alex's says "relevant to the condition being studied," which is more narrow than "responsive to the health

needs" or "reasonably responsive." So if you are going dispute, it should be at least about that phrase or ---

PROF. CAPRON: No, I don't want to dispute about that at all. I actually was guided by the chair's discussion on this in the first sentence, and I think whether we say "relevant to the condition" or "responsive to the health needs of the country," the point is -- I think, the difference is that this is stated as an initial ethical obligation from which other things follow.

And I don't quite understand the sentence with or without that language about responsive. Where you are saying "because successful research ordinarily yields benefits to all or part of the general population," that is a descriptive statement ---

PROF. CHARO: That is why actually I preferred Option A myself.

DR. : It is Option A.

PROF. CHARO: No, that was Option B. Because "successful research that fulfills" -- that is why it is put in quotes -- that, in fact, is reasonably responsive to the health needs of a country. The definition of "reasonably responsive" embodies in it the notion that you are going to actually have -- (inaudible) -- coming out of it.

PROF. CAPRON: But when you say "ordinarily yields benefits," there are two kinds of benefits. One, the finding that something would be beneficial, if available, and the second is the making it available. I mean, I just understand ---

PROF. CHARO: It is fine. I really couldn't -- I don't care about which language ---

PROF. CAPRON: It is A or B.

PROF. CHARO: I think the goal was to actually create a structured argument and on that we absolutely agreed. Whether my language achieves it or not is not important, but -- maybe we are thinking like lawyers -- we both had the same instinct about the ordering of the argumentation to yield the conclusion.

DR. SHAPIRO: Okay. Larry, then David.

DR. MIIKE: I like Alex's better. I think that there is good reason to distinguish between his first sentence and the second one. Because the ethical obligation is to conduct research is relevant to the condition in that country.

But if you are going to talk about expanded -- of benefits to the population, one does not necessarily have to be limited to that. So I am okay with his statement. I mean, we are only quarreling about a dozen words more or so.

I still am troubled by -- although I see Alex has made an attempt to make this a softer IRB review, where the IRB may -- I assume, Alex, that was intentional on your part. Right?

But I still am troubled by putting another burden on an IRB, where I think, at best, all they are going to be able to do is to check a box that says whether some kind of plan was put forth. I don't think they will be in any position to make a really good assessment of that plan.

PROF. CAPRON: I think, initially, you were right.

DR. SHAPIRO: David.

PROF. CAPRON: The question is, in time, as this becomes a more familiar part of the research enterprise, will some IRBs helpful to investigators and sponsors as to what that process ought to look like just out of experience they have had. But it is a soft requirement, I agree with you, starting off.

DR. SHAPIRO: David.

DR. COX: So, by reading the two, I find more context in what Alex wrote, and it is easier for me to understand why we are doing what we want to do. And that although, Larry, I originally felt this about the IRB, too, I think that I have been convinced that the

IRB is the only place where we are reasonably going to have teeth to do this. I mean, I like Alex's -- as it stands.

DR. CHILDRESS: I am inclined to go in the direction of Alex's as well with the modification in the first sentence, and I am not quite sure how we wanted to do that.

But something like "ethically obligated to make that research responsive to the health needs of the host country." Is that where we are going? And "from that objection, presumption arises..."

PROF. CAPRON: I thought that in light of what Eric reminded us of, maybe the languages are "ethically obligated to provide some benefit responsive to the health needs of the country." And then you can drop "relevant to the condition being studied."

And I don't think we have to put it in quotes. I mean, it is a phrase that we have used in reporting here. It is a recommendation, and we are repeating that language.

DR. SHAPIRO: Any other questions here? It seems to me that we have -- I want to have a chance to review this in the context of reading the whole set of arguments that -- but I think we have something which we can structure which may be all right just as it

stands. But I wanted a chance to review in the context of all the text.

Okay. Thank you. I think we now ought to go to Public Comment, because we have kept those who want to speak to us waiting at least 15 minutes longer than we had promised, and so we want to go to that right now. Eric, have you got the list?

DR. MESLIN: I have a partial list. I understand Dr. Lee Zwanziger is here from IOM.

DR. SHAPIRO: I just want to remind all public participants that the rules that the Commission has adopted is we ask you to try to keep your remarks within five minutes. I will let you know when five minutes is up. We don't go to the exact second, but try to be responsive to that. And then there may or may not be questions from the Commission. But welcome. It is very nice to have you here.

PUBLIC COMMENT

DR. ZWANZIGER: Thank you.

DR. SHAPIRO: Does she have anything to distribute?

DR. ZWANZIGER: Yeah. Actually, I was going to hand it out at the end, but I can certainly do it now, if you would like.

DR. SHAPIRO: That would be helpful.

DR. ZWANZIGER: Thank you, ladies and gentlemen. I appreciate the opportunity to address the Commission. As Dr. Shapiro or Dr. Shapiro said, I am Lee Zwanziger. I am here from the Institute of Medicine National Academies.

I wanted to inform the Commission that the National Academies, Institute of Medicine, has recently released a report that may be of interest to you called, "Protecting Data Privacy in Health Services Research."

In this report, the expert committee suggests some ways that we believe we can both enhance the protection of data privacy, particularly in secondary uses of large databases and can facilitate at the same time the production of good-quality health services research.

We are passing around some executive summaries. I really wish I could have brought enough for anyone in the audience who might light one. Unfortunately, we are out of copies. We are nearing the impression limit. But the entire thing is on our web site.

Outside, anyone who is interested will find a flyer that I have left that gives the web site and gives my contact information. I would be happy to hear

from anyone who has questions.

And before I leave, I want to acknowledge, first of all, the chair that we had of this committee, Dr. Bernard Lo. We were very fortunate, and this would not have happened without his leadership and his insight. I also wanted to thank the Commission itself. I have been to many of the meetings and received very good insights from every one I have attended.

Finally, the Commission staff, as I am sure you all know very well, are very supportive, and I particularly wanted to thank Dr. Meslin and Dr. Speers and Dr. Gadbois.

Finally, let me just tell you that this, of course, would not have happened without the insight of our sponsors, the Agency for Health Care Research and Quality and the assistant secretary for planning and evaluation.

Can I answer any questions?

DR. SHAPIRO: First of all, let me thank you for coming here today and to relay our thanks and gratitude to the Institute of Medicine for addressing this. And none of us are surprised that both either our staff or Dr. Lo helped you in this matter. But let's see if there are questions from the commissioners. Yes, Alex.

PROF. CAPRON: Without having read your report, this is a question no lawyer should ask, because I don't know the answer.

But were our deliberations or conclusions regarding the use of data from the examination of human biological materials a factor in any way?

Because when we were writing that report, we were aware of potential tensions between the direction that leading analysts of data privacy, thinking of data as written documents, were going compared to some of the concerns we had about the data that would be derived from the examination of human biological materials.

And I wondered, did this arise during the discussions? And if you are familiar with our conclusions, how concurrent or different are yours on what you are calling data privacy?

DR. ZWANZIGER: Well, I would like to encourage Dr. Lo to add to whatever I have to say on this.

I found the meeting quite helpful. And we recognized that there certainly are a lot of similarities in the questions. The committee and the IOM staff felt that it was very important to keep very strictly within our mandate on this very short project.

We explicitly announced, which you couldn't know without reading the whole report yet, that we would not consider data derived from tissue samples just because that was not strictly within our charge. But we do expect that many of the kinds of suggestions we made would be helpful in tissue and DNA and several other kinds of secondary data research like surveys that might require recontacting patients at a later date.

DR. SHAPIRO: Thank you. Any other questions from members of the Commission? Alta. I am sorry. Alta, then Diane.

PROF. CHARO: I guess, just expansion on that or from Bernie. One of the things we talked about in our Biological Materials Report had to do with the value of keeping the rules governing research on medical records consistent with the rules governing research on tissue samples to the extent possible, so that everybody understands what the rules are, and since the two are often used in conjunction with one another, everybody can apply the same rules within their own research.

Since your Recommendation 3.1 specifically takes no stand on an interpretation of key terms that we actually looked at with regard to the materials

report, is there any place in your report where you even address the interplay between medical records research and other forms of research that were beyond the scope of your report with regard to coordinating the rules that govern the various kinds of research?

This does cover medical records research. Right? I mean, that is what a lot of this is.

DR. ZWANZIGER: Yeah. Again, I would encourage you to add anything that you feel like, Dr. Lo. We --

primarily, we are calling for advance considerations of terms that the committee heard testimony -- well, let me go back.

The committee heard testimony suggesting that several of these key terms were interpreted in significantly different ways by different investigators or at different institutions.

So our suggestion was that an IRB and an institution and the investigators, and finally, the patients, would benefit from advance consideration and agreement on how they would interpret terms like "privacy" and "confidentiality" and "risk" and applying them to non-physical risks.

So without addressing specifically tissue research in that, we are trying to suggest where the

system right now is allowing variations that is helpful in certain ways at the local level, but at the same time, is allowing perhaps very -- a lot of variability from one decision to the next.

DR. SHAPIRO: Excuse me. Diane, Bernie, Trish, and then I have some questions.

DR. SCOTT-JONES: I a question about any of your recommendations or any of your discussions that may have had to do with the special situation of children.

I noticed that you had a developmental psychologist, Ross Thompson, write a report on the special issues related to minors, and I was very interested in what the outcome was of your discussions in that regard. Because there are many issues, such as parents consenting for children, and then children later as adults having information about them that they didn't get any consent to.

DR. ZWANZIGER: And when you get a chance to look at Dr. Thompson's paper, I think he does give a very nice consideration of the special issues that can arise with consent for minors and what happens to those when the minors then become adults and how that affects other people that may not have been intended to be affected.

In terms of what the committee considered in our report, this was one of several cases in which the committee emphasized that IRBs need to have access to individuals either on the committee or on a consultant basis that have specific expertise, and sometimes specific sensitivity, to the special issues that might arise with minors.

For instance, might be concerned with developmental issues about differential exposure to psycho-social risks, such as embarrassment, or feeling of dependence, or need for more independence, the many changes as a person ages. In fact, we considered that some of those risks might actually increase with age rather than other kinds of risks can decrease with age.

And so we specifically -- the committee -- I am sorry -- I get very attached to these reports -- the committee specifically emphasized that IRBs should take care to take extra steps to beef up their expertise, where needed, in areas of special concern, one of them being studies involving data on minors.

DR. SHAPIRO: Thank you. Bernie.

DR. LO: Yeah. I just wanted to follow up on some of the points that previous speakers have raised.

In many ways, this report covers a very

restricted type of research. One of the things I think we are doing under Marjorie's direction is being mindful of how different types of research differ from clinical trials in the biomedical model.

And so in answer to Alex and Alta, I would say it is almost like sort of overlapping circles. There were some issues that we focused on that overlapped with the Human Biological Materials Report, but for instance, we spent a lot of time trying to distinguish what is research and what is not research.

It is a real issue for IRBs. People say, well, I am not really doing research, because it is really sort of more like quality assurance.

The other issue -- you know, rather doing the sort of conceptual analysis of minimal risk that NBAC did in the HBM report, we were much more practical.

We said, in the IOM report, that there are many things that investigators can do to protect the data, ranging from the way it is coded, the way you sort of round off certain categories, the way you combine data sets, that really reduce the likelihood that you could identify an individual subject, either directly or by inference.

And that if you do these things in an appropriate way, and also have strong organizational

protection of confidentiality, you can really make this minimal risk. And so without grappling with the definitional, conceptual problems, we said, if you do all this, most people are going to agree it is minimal risk, and very few people are doing this consistent ---

I think another thing that I would just like to highlight is that NBAC has done a lot to sort of advance the notion that all subjects of research should have similar protections regardless of whether it is technically falling under the ambit of the Common Rule.

And the IOM report really follows along that line of thinking by saying, if your personal health information is being used in a large data set using the methods of health services research, you should have similar protections, whether or not it is technically called research or something else like quality assurance, or quality improvement, or disease management.

And it should have protections whether or not the organization you are working under, that is conducting the research, has a multiple project assurance or not. So even if it is privately funded research, we suggested that similar safeguards should be in place, including some sort of IRB-like review.

So I think, in many ways, we pick up very

similar themes that NBAC has been articulating, but really looking at it from the point of view of one very special kind of research.

DR. SHAPIRO: Trish.

DR. BACKLAR: You have a paragraph here that says: "Put in place comprehensive policies that include strong and enforceable sanctions against breeches of confidentiality."

And I am interested to know, did you think through what those sanctions might be and how you would go about doing it? Do you have a section looking at that in this report?

DR. ZWANZIGER: You are asking me?

DR. BACKLAR: Both of you.

DR. ZWANZIGER: Okay. What that refers to is the -- we were very fortunate in hearing testimony from both private and public sector practitioners of various types in the field, lawyers, IRB chairs, researchers.

And the committee was very persuaded that organizations that had in place comprehensive policies and procedures and examples of enacting those procedures to both encourage good behavior and show that bad behavior was taken seriously and would be punished had a lot less trouble. And that employees and other participants knew what to do.

We did not -- the committee did not try and identify what type of sanctions should be in place, assuming, I believe, that that would vary quite a bit with the particular organization.

DR. SHAPIRO: Thank you. One, a number of things. One, I want to thank you very much for coming today. I want to thank you and Bernie and others who participated in this, because this is not an area we looked at directly, but it came up often indirectly in our discussions, when people would say, well, what about health services research, quality assurance, and so on.

And so sit is really very -- I am very pleased to see that IOM has done this. I have not had a chance to read the report in any detail, obviously, since I have just received it for the first time.

So I just will pass on observations. Maybe we could talk about it another time. The executive summary talks about strong, enforceable sanctions against breeches of confidentiality and carries an affect with it -- that kind of language carries an affect of sternness, I might say, not inappropriately.

On the other hand, I noticed a number of the recommendations use the word "adequately" a lot in trying to say, we give adequate protection. And maybe

when I read the text, I will understand a little bit more about what that means.

I don't want to delay us this afternoon, because there are other people, but I would be really interested in that, but I will get a chance to speak to you, or maybe I will catch Bernie over on the side later on. But, mainly, I want to just thank you very much and everyone who worked with you for doing this study, and thank you for being here today.

DR. ZWANZIGER: Thank you and let me again say, anyone who picks up a flyer is more than welcome to contact me if you have any questions, or you have difficulty finding the report, I will be happy to help you. Thanks very much.

DR. SHAPIRO: Thank you. The next person who would like to speak today is Francis Crawley from the European Forum for Good Clinical Practice. Mr. Crawley is here. I saw him this morning. Yes, here he is.

DR. CRAWLEY: Thank you, Mr. Chairman. My name is Francis Crawley. I am the chairperson of the Ethics Working Party of the European Forum for Good Clinical Practice, and I am also a member of the UNAIDS Ethical Review Committee.

Perhaps more specifically, in relationship to your work here, I believe you received this morning a

silver booklet, entitled, "Operational Guidelines for Ethics Committees that Review Biomedical Research."

I was very happily the chairperson that works with the international partners that put together that guideline, and now we are involved at the WHO in a project of capacity building and that of ethical review in Asia, Africa, Latin America, the Caribbean, the Mediterranean, Russia, and the Baltic States.

So I wanted to just give a few remarks. The first thing I wanted to say was really to thank you for both the report, the papers that I received today -- I have received some pieces before and had an opportunity, thanks to Dr. Meslin, to participant in a small part of the comparison chart that you put together, the comparative analysis there.

But I am happy to see the report. I find in the report a very good discussion, at least from what I can understand, of the current problematics that we have and the current real concerns we have with international research. And it is really laid out well, especially with regards to AIDS. It comes across very clearly what those problematics are and how they are understood.

And then I found today, listening to your discussion, was very much more enriching than the

report itself. I found it was a real complement to the report that I have read so far. I still have to read it in more detail, but at least I felt much better from the discussion as well.

You perhaps know that in Europe we have, at the Council of Europe, we have a working group putting together a protocol on biomedical research, and I was -- I wanted to say it is something similar to this, a little bit, the work you are doing, although it is more focused just on Europe.

I just wanted to say one thing. Please, from my point of view, bear in mind the importance of research. We are doing the same thing in Europe sometimes. We are setting up protections for research, but research itself, that is so important to people in developing countries like Belgium, where I come from, or Italy, or Uganda, or Thailand.

We find that it is very important to have research if we want to have health. And we need to stimulate that research. It is an ethical responsibility to stimulate the research, and also to stimulate research in all of its varieties and complexities.

Please be careful in adopting the language of inaudible. A host country and a sponsor country are

very difficult to identify or even to say they exist today. I do not know what is the sponsor country of Glaxo-Wellcome. I know that most of the protocols that I see for international biomedical research have a complex sponsorship.

For example, the sponsor might be -- one protocol would be a pharmaceutical company supplying the product. The Institute of Tropical Medicine is in Antwerp, and in Belgium, as providing the infrastructure, and UNAIDS providing funding. Now, I do not know who the sponsor company is there, and I do not know either for that protocol who the sponsor country is, since it is a multinational, multicenter trial.

So we have to be careful. It is very complex, and you cannot just say the sponsor is responsible, nor that the researcher is responsible. That doesn't make sense in that situation.

Please -- you were going towards that in your discussion today. I like this idea of negotiation, of discussion. Okay. And if that much we can get, we have achieved a great deal.

Also, your discussion coming up this afternoon, where you will be talking about the assurances for protections. I think it is related to

this, and you need to make that relationship, because that relationship is made in U.S. law. And that law impacts on international research, as has already been pointed out to you today.

When you talk about the duties for IRBs, please do read that gray, silver booklet there from the BRHL. Please do not ask for too much more than is there. We worked very closely with Melody Lin here, who is the interim director of the OPRR, OPHR, here.

I think this is in good conformity with U.S. regulations. It exceeds U.S. regulations. It exceeds any practice I know of in the world as far as ethical review concerns. If you add anything on top of that as a requirement, you will do severe damage to some countries, many countries, for example, Belgium.

So please be careful doing that. That was worked on in Africa and in Asia primarily, by those countries there, but with a real international team, and those were people from ethics committees. Don't ask more than they can do.

Finally, I would just want to say that what I would hope to hear, from my point of view, would be, from this committee, more that this committee would give guidance regarding the principles of international research and not overly emphasize obligations or

regulations in a situation that is enormously complex and enormously vulnerable, as it is today.

Mr. Chairman, thank you very much.

DR. SHAPIRO: Well, thank you very much. It has been nice to have you here today. I do want to point out to the commissioners who all have this booklet -- I think we passed it around earlier this morning.

That with respect to some of the issues we were discussing today, there is a section in here called the Informed Consent Process, and I am just going to read two -- a number of issues which need to be covered in informed consent -- I just want to read two of them, because they relate directly to what we talked about today.

And it is: "A description..." -- this is what should happen in the informed consent process -- "...of the availability and affordability of any successful study product to the concerned communities concerning research."

And followed by another provision: "The manner in which the results of the research will be made available to the research participants and the concerned communities."

Is actually very useful language, I find, and

I hope -- I only had a chance to look at it today. I apologize. But I think it will be very helpful to us, and I want to second your recommendation that those of us interested really look at this document, which seems to have been very carefully put together.

Thank you. Are there any questions from any other members of the Commission? Alex.

PROF. CAPRON: I echo, Francis, the chair's thanks to you, and I think the reminder to us of the complexity of the organization is in line with what he described. And I do think the next draft of our report should cite relevant examples that convey that.

Just one point of clarification, since the chair raised it. The issue of communicating the results of the research, as I understand it, refers not to anything about the products of the research, but is how the scientific findings, as such, will be made available to any of the subjects who want to be aware of them at any level of detail. Is that correct?

DR. CRAWLEY: That is correct. If you want, I could provide an example. I was involved in a study where, as an ethicist on a committee for a study, which had to do with a vaginal microbicide, and the study was -- the DSMV decided that the study should be stopped.

At that time, there was a discussion within

the committee to say -- there was an international agency that was the sponsor of that study -- and that agency said, we are going to publish those results immediately. The investigators on the committee said, you cannot do that. We have to inform the participants first.

Now, I thought that discussion was late. That should have been had earlier. And I think the people writing those guidelines had that idea in mind.

DR. SHAPIRO: Thank you. Bernie.

DR. LO: I wanted to also thank you for coming. Thank you for providing this. I guess, first, to encourage you -- that you know we are going to submit a draft of our report for public comment -- and hope that you and your commission will provide us your thoughts.

As I was looking at the section that Dr. Shapiro alluded to, I noticed that 6.232 talks about the need to make clear to participants any plans to withdraw or withhold standard therapies for the purpose of research. One of the issues that we have been grappling with is whether subjects in a control group must be given what we have called effective therapies. And I know this issue of withholding care that is considered standard care in a developed

country, but is practically not available in the country where the research is being conducted, is a very contentious one.

Could you give us a quick summary of sort of what your committee was thinking? It seemed to be allowing such type -- such withholding of established therapies, provided that it is reviewed by the IRB and explained in a consent form. Is that correct?

DR. CRAWLEY: I think that the persons -- and there is a list of -- a partial list anyway -- of persons who worked on that at the end of the guideline -- I think that we did not want to take a position on this argument, or this discussion, on standard of care. That is not a position we are interested ---

We did think, though -- and what we were concerned with is that the IRBs themselves be independent, and that the IRBs are able to make -- my own prejudice here would be that this is the kind of thing that goes to an IRB, and the IRB makes a decision on.

We thought -- whatever the international consensus might be, whatever the project might be, that in specific protocols, those activities should be communicated to the IRB. I think that is all that is wanted to be said there.

DR. SHAPIRO: Okay. Larry. Or Alta, excuse me.

Last question here. Because we have another person. We are running short of time.

PROF. CHARO: Thanks. Dr. Crawley, I am going through it quickly, so I can't find it if it is here. But is there consideration here about what the consequences should be for failure to abide by these particular guidelines.

That is, if research is proposed to an ethics review committee without this documentation, what should the committee do? If a committee fails to follow these guidelines in its actual review, what should happen to the committee, or to the research, or to the institution?

I am trying to figure out what happens.

DR. CRAWLEY: At the time we wrote the guidelines, which they were published in March of this year -- so it is very recent -- we were aware -- we had to make two choices in writing, of course, and one of the choices is, do we try to write a guideline that reflects the actual situation? If we do that, then that is impossible.

You spoke about equivalencies in human subject protections. I cannot think of two countries in the

world -- Belgium and Germany, Germany and France, France and the Netherlands -- they are not equivalent. There is no way to think of them as being legally or ethically equivalent. I don't see it. And Belgium and Uganda, or something like that, that is even more difficult.

So that is not -- what we thought was we wanted to write a guideline that was really something useful and that could help ethics committees. So we thought, what would it be if I was putting together an ethics committee, or I was working on an ethics committee, what would be helpful to me? What were the kinds of things I might think about?

I think we made a mistake by not putting a disclaimer in that guideline saying that this is not a standard in the sense of a standard of care or a standard of practice.

But rather these are helpful guidelines, and what we wanted from the guidelines would be that when different countries are making laws regarding ethical review, or hospital ethics committees, or national ethics committees are considering their own standard operating procedures that they could use this as a reference.

And, in fact, I can say to you that that is

what happening today. That is being used as a reference in many countries around the world, and it is going into many different languages as well.

DR. SHAPIRO: Once again, thank you very much. It was a great pleasure to have you here, and thank you and your colleagues for the work you continue to do.

Our last public comment today is -- Steve Peckman is associate director of human subjects research at UCLA. We will hear from Mr. Peckman later during the regular part of our meeting, but he wanted to address the Committee at this time as well.

MR. PECKMAN: Thank you. I wasn't planning on saying anything this early, but the discussion on Section 4.2 made me very curious about some issues.

In the discussion this morning, there was a lot of talk about the IRB's role in Section 4.2 regarding the reviewing and the distribution of benefits to the host population of a study. I think that we should be careful not to miss the IRB's role in the review and assessment of the application of the ethical principle of beneficence, specifically as it relates to societal benefits.

The IRB is required to review both the benefits to the individuals, the population that the

research is targeted at, and the benefits to society. I would posit it that it may be very difficult for an IRB to ultimately approve a protocol without knowledge of an adequate plan for making successful products, as it was noted this morning, available to the appropriate population.

For example, some IRBs in this country, during the regular review of domestically conducted research, such as Phase III trials, require that if any effectiveness is demonstrated, the investigator or the sponsor provide the drug at least to the control group for a reasonable period of time, such as until it is FDA approved.

The process ensures some form of benefit to a group that was on placebo or on another form of control. Just as we would -- just as an IRB would withhold ultimate approval of an investigational drug protocol without an IND, I would suggest that an IRB should not ultimately approve a protocol of international research until some plan is negotiated and the IRB is informed of that plan.

I would encourage the Commission to include the IRB in the informational loop and predicating ultimate approval on the closure of this negotiation. Otherwise, it is very difficult to weigh the benefits

to society, especially to the host population.

DR. SHAPIRO: Thank you very much. Yes, Larry.

DR. MIIKE: As you know, I have been arguing in this Commission to the contrary. It seems to me that when we talk about benefits to society, that is a different issue from the very specific operational issue of how one provides, in practice, benefits to that society, which is what we have been talking about.

One can look at to society about what is the risk and the benefit not only to the patient, but for advancement in treatments in certain areas. What is the importance of the problem being addressed, etc.?

So I don't see it, and I don't buy your argument that it naturally follows that the IRB must take a look at distributional issues once the drug is -- for example, once the drug is approved.

MR. PECKMAN: Well, I would respectfully disagree that I think that the importance of the societal benefit makes the justification for the research, fundamentally -- is that we have a group that is not going to benefit at all, say, through placebo, we will recognize that there -- if we will discount the placebo effect -- then there has to be some benefit to society.

And the society is the society of the host population, and that I think it does come within the purview of the IRB to at least discuss that and be made aware of what negotiation and plan has been decided in order to make an adequate decision regarding the protection of all subjects.

DR. SHAPIRO: Well, Larry, it looks like we won't satisfy everybody.

DR. MIIKE: Well, I guess we are sitting here just discussing what is the interpretation of benefit to society. Because that also has -- in our basic assumption is that any research that is going to be happening in another country -- that research must be relevant to the needs of the country.

That is a separate question altogether. Once you do that, then one must find some means in which to provide those benefits to the country spelled out, and I guess that is where we differ. And that is where I am differing with the rest of the Commission.

DR. SHAPIRO: Okay. Other questions? Alex.

PROF. CAPRON: Well, I actually take Mr. Peckman's remarks as a reminder to us that there is an "I" in IRBs, and individual institutions may choose to insist that research protocols which will be carried on at that institution, or by its investigators, meets

certain standards even if we don't end up saying that every IRB has to be satisfied on that interpretation.

The other thing is if Mr. Peckman has an original copy of the paper he wrote for us, it would be good to have the first page that isn't half-blank. It may have been pointed out to you it was difficult to read with the page obliterated for some reason.

MR. PECKMAN: (Inaudible.)

PROF. CAPRON: Maybe you can give those to the staff, and they can give us a corrected first page. I would like to get a chance to read it.

DR. SHAPIRO: Again, thank you very much, and we look forward to talking to you later on.

Well, we are running about 15 minutes behind time, but we do need a break. So why don't we take a 10-minute break and try to assemble. And my apologies to those who are waiting.

(Whereupon, at 3:20 p.m., a brief recess was taken.)

DR. SHAPIRO: Okay. I just want to ask Marjorie to give us a brief update on the program. That will just take a few moments. Then we will go directly to our guest, who is here to speak to us. Marjorie.

OVERVIEW OF WORK TO DATE

DR. SPEERS: Good afternoon. Let me just give a brief update, so that I can perhaps help us catch up a bit on the time.

Very quickly, during the time since our last Commission meeting, we held our final town meeting in Portland, Oregon, and we were very fortunate to have two commissioners present at the town meeting. Both Trish and Larry were at the meeting, and let me just ask them very quickly if either one of them wanted to make a comment about the town meeting.

DR. BACKLAR: Not right now.

DR. SPEERS: Okay. Great. There is a summary of other Portland Town Meeting in your briefing book, and we will be providing you with an analytic summary of all of the town meetings that we conducted before the October meeting.

We have also received several additional letters from IRBs and other organizations with their comments about the Oversight Project, and we will include those in your briefing book for October as well, because we will be talking more about the local IRB system at the October meeting.

Just to give you an update on the survey of the federal agencies, Kathi Hanna has provided us with a final draft of the survey -- of the report -- I am

sorry, and we are in the process of reviewing it.

We plan to share it with the federal agencies to make sure that we have not misinterpreted any of the information in it. And following the feedback from the federal agencies, then we will share it with commissioners.

We will probably send it to you before the October meeting, and then it will be available at the October meeting for you.

Regarding the Oversight Report, we are making progress on writing the report, and in fact, as you look at the agenda for this September meeting, I would call this a transition meeting, meaning that we both have on the agenda discussion related to particular topics, as well as, for tomorrow morning, a discussion of the first chapter.

We have called this chapter 1, because it is the chapter that is laying out the rationale and justification for this report.

When you look at this chapter, and when we discuss it tomorrow, what I will be most interested in hearing from would be whether you feel that this chapter captures the problem, the problem that we are trying to address, and whether it has the appropriate balance that you are looking for, specifically with

respect to protecting individuals who participate in research, as well as enhancing the research.

If you go back to thinking about the testimony that we heard from Jonathan Moreno and Harold Vanderpool and David Magnus, when we talked about objectives of an oversight system, we talked about it having multiple purposes, and we have tried to capture in this chapter.

I am not going to go over the agenda with you the way that I normally do, since we are short on time. But I think what I will do at this point is turn it over to Dr. Shapiro to introduce our first speaker today.

DR. SHAPIRO: Thank you very much. It is a great pleasure to welcome Dr. Koski here. Welcome. It is a great honor for us to have you here.

He is, of course, director of the Office of Human Research Protection of the Office of the Secretary, and the first director of that revitalized, reorganized -- I don't know what other adjectives we want to use -- but it is certainly a new time, and we are very pleased to have you here.

Dr. Koski was a professor of anesthesia and critical care medicine at Massachusetts General Hospital, and in many other ways, has had a lot of

experience in ethical and regulatory oversight of human investigation
-- or human subjects, human participants research.

One, we welcome you both to your new set of responsibilities, which will be central, I am sure, to everything we do here in this country regarding the issues of concern, and we are very, very pleased to have you here today. Thank you for coming.

NEW DIRECTIONS FOR THE OFFICE FOR THE OFFICE FOR HUMAN RESEARCH PROTECTIONS

DR. KOSKI: We will try again. Mr. Chairman and members of the Commission, thank you very much for this opportunity. I have to thank you in particular, Dr. Shapiro, because as I think back to the first press account of my appointment, I think I was cast as an assistant professor.

More recently, I have been an associate professor, and having just been appointed a full professor by the president of Princeton University, I am indeed honored. So thank you very much.

DR. SHAPIRO: Happy to be of any assistance I can.

PROF. CAPRON: If only they had a medical school, Greg.

DR. KOSKI: Having just met with the Ethics

Division yesterday, I think I should consult with them before I accept the appointment, but again, thank you.

Obviously, we, and when I saw we, I mean the big we. There are many of us who are anxiously awaiting the report that will come forth from NBAC after its deliberation on the issue of protection of human subjects.

I can only say that in being here today, it does seem somewhat presumptuous that I should be coming to speak to this Commission, since, in fact, I should probably be coming to listen; but nevertheless, I am also cognizant of the fact that there are many, many of those in particular who are seated behind me at this point, as well as those here on the Commission, who are quite anxious to hear what I have to say.

And recognizing that, despite that this is day 2 on the job, I will try to say something that is both relevant and meaningful.

Much of what I will say is certainly not new. I think what is really new and what should be emphasized in this discussion is the opportunity that has been given to us and, of course, the incredible challenge and responsibility that has been thrust upon us. And here again, when I say us, that is the big us, because that responsibility is not solely on my

shoulders. It is the responsibility that we all share.

Now, to begin, I will restate the obvious, and that is, that the American people love research. There is no doubt about it. The American people love research. However, just as society wants the benefits of research, and indeed, society does benefit from research, there is an essential need that we not lose sight of the fact that the benefits of this research do not come without risk, without a cost, and in much of the research that has been done, those risks have been borne not by society, but indeed, they fall upon the individuals who are participants in the research.

I emphasize this point, because we are about to enter, or are entering, a new age, and indeed, the research agenda of the next millennium is one that changes that former equation in that now there are very real risks, not only to individuals, but to large groups of individuals, and indeed, all of society from some of the research that has been proposed.

And so there is a heightened need to pay close attention to all of our policies and procedures with respect not only protection of individual interests, but also society's interest in the conduct of this research.

To a very large extent, the ethical principles upon which human research has been conducted for the last couple of decades, as stated in the Belmont Report, were cast primarily with the protection of individual research subjects in mind. The emphasis on autonomy and on informed consent are clearly evidence of this.

But over the years, we have found that the principles in the Belmont Report, in fact, have a broader application, and indeed, some of these principles have proven to be mutable.

A good example of that is the one-time exclusion of women from participation in clinical trials, which was viewed as a act of beneficence, is now viewed as being both disrespectful and unjust.

So, clearly, we need to continue to evaluate in an ongoing fashion the ethical framework in which we conduct human research, as well as paying close attention to the operational details in which we apply the procedures for protection of human subjects.

The current system for protection of human subjects is, in my mind, a somewhat dysfunctional one. I know others share that view, but I would like to state specifically some of the reasons that go beyond simply the workload placed on the IRBs and the shortage

of resources that are frequently cited.

In my mind, the system that has currently been serving us, and not in most instances terribly, is a system that has basically missed one important component of the overall protections process. And I will explain that.

On the one hand, the protections that have fallen under the auspices of the former Office for Protection of Research Risks, which have overseen most federally funded research, are processes that have focused on the front end, the up-front assurance of institutions that they would abide according to the regulations, and so on.

On the other end, the activities of the Food and Drug Administration, in exercising its own authorities under its own regulatory requirements, have focused largely on post hoc audits of the research process, which in themselves cannot do much to actually protect the research subjects during the actual conduct of the research.

The consequence of this is a gaping hole in the process, that is, the actual conduct of the research in which investigators and research subjects are actually taking part in the studies, which is the area, of course, where we could most effectively

protect human subjects.

So one of our great challenges is going to be find a way to bridge this important gap. Now, Henry Beecher pointed out three decades ago that the investigator is perhaps the single individual best positioned to protect the interests of the research subjects.

Unfortunately, the investigator is also the individual who is best positioned to harm the interests of the research subjects, which leads to the concept of what I have called Beecher's paradox in some of my own writing, and it is a problem that we certainly find an answer to.

The view that Beecher put forth, I think, reflects, to a large extent, though, the somewhat paternalistic attitude of medicine and research as it existed in the mid-1960s, and I would submit to you that, in fact, the individual participants in the research should also be well positioned to protect their own interests, their own well being, as well as to serve as advocates for research. Indeed, it is the subjects who often hope to benefit from the research as well.

Furthermore, the rise in consumerism over the last three decades has fostered a development of a

different sort of modality within the practice of medicine. There is the formation of what has been called the therapeutic alliance or patient/doctor partnership.

It may well be that a similar alliance between researcher and research participant may also be a step toward helping to improve the actual protections for subjects during the conduct of research.

The mainstays of the system, as it has currently been operating, have clearly been the IRB process and informed consent.

As I pointed out previously, I do not believe that the Institutional Review Boards, as they are currently structured or configured, are particularly well positioned for actually protecting research subjects, because, indeed, they have little, if any, contact with the research subjects or the investigators during the conduct of the research. This is a problem that has to be fixed.

Similarly, the informed consent process, as it is now practiced, does not achieve the goals for which it is intended. The process is one that is too form focused. It is not sufficiently process oriented, and its complexity is daunting, not only to the subjects and to the investigators, but to the IRBs as well.

So for many reasons, I believe that the calls within the OIG Report, as well as from the public, for a re-engineering of the current model are very appropriate. I believe that the current model is one that is largely confrontational in its foundation. It is a model that is focused primarily on compliance, and I don't believe that it is well suited to meet the challenges we are going to face in the next two decades of research.

Unfortunately, the OIG, in that office's report, actually stated that the IRBs are the only bodies whose primary mission is to the protection of research subjects. I submit to you that that is one of the fundamental flaws in the entire process that we are considering here today. And indeed, one of the points that we have to address is the fact that the IRBs are frequently caught in the middle of a process where they are basically mediating a confrontation between investigators and sponsors and research institutions, on the one hand, and the research participants, on the other.

This obviously leads to a oftentimes bad feeling, cries that the IRB process is there to constitute an impediment to research, and this is clearly not serving the best interests of anyone.

So I submit that a new model will serve us better. I call this model a subject-focused, collaborative model. It is a performance-based model that recognizes that every party to the research process bears as his or her primary responsibility the protection of the research subjects.

This model removes from the middle the Institutional Review Boards and, instead, places in the central focus of everyone the research subjects' interests and well-being.

And it allows us to create a collaborative environment that rather than focusing on confrontation focuses on the ways to conduct research in an efficient and effective manner to achieve the results that all of us want without ever hurting anyone in the process.

Now, to implement this new approach, I believe that we must add to the principles stated in the Belmont Report two additional principles. Those are responsibility and caring.

When I speak of responsibility, I mean the willingness of individuals to exercise their personal initiative to do the right thing even when it is difficult or not in their interests, because it is simply the right thing to do.

By caring, caring is that part of our

compassionate human makeup that allows us to subjugate our own interests to protect the interests of another individual.

By incorporating responsibility and caring into the broader paradigm for the protection of human subjects, I believe we can begin to see a road map toward creating a new model that will enable us to achieve the goals that I have stated above.

Even as I say that, however, I recognize that it is certainly idealistic in at least one dimension, and so we cannot lose sight of the fact that oversight is critically important, and indeed, oversight must be expanded in order to achieve the level of accountability that is necessary to make this process work. And there must be accountability at every level.

We must recognize that every party to the research has a responsibility to have proper education and training for the tasks that they intend to do within the research or within the process of oversight of that research.

They furthermore should recognize that their activities should be limited to those things that they are properly trained to do, and that they should not do those things that they do not understand or are not

properly prepared to do.

I further believe that they should attest to their commitment to fulfilling their responsibilities and that certification, through independent, verifiable processes, of individuals' knowledge and training is an appropriate step forward.

I believe that there need to be clearly established standards that are uniform for all Institutional Review Boards. These standards should be recognized nationally.

They should be accepted and developed with the input of all of the stakeholders so that they can serve as universal guidance for what the Institutional Review Boards should be doing. And the application of these standards should be subject to performance-based evaluations through a process of accreditation.

I believe that is also critically important that individual entities, such as research institutions, research sites, corporate sponsors, furthermore demonstrate their willingness to work within this framework by again giving assurances to the public that they will bring their resources and their efforts to bear to ensure that standards are upheld.

Finally, as I mentioned earlier, I believe it is critical that the public be more engaged in this

process and that they be better informed. It is important that the public fully understand the nature of the research process. That they understand that there are both risks and benefits.

And I would urge that we work toward a system that actually encourages broader participation in the research process, so that the benefits that are derived from medical research are truly ones that are due to all of society rather than carrying the burden on the back of a few.

I believe that the principles that I have set forth here are translatable to policies and procedures and programs that will begin to move us towards this goal. It is certainly not practical to simply to abandon the current system and leave a void.

We cannot allow research to come to a halt, but in the meantime, we must move swiftly and diligently to implement the steps that we can do immediately, and those that require longer-term solutions, we need to set the wheels in motion to bring them about.

It will be possible, on the one hand, to pursue these initiatives through guidance. There are others that will require the promulgation of new rules and perhaps still others that would require new

legislation. Our goal is to use the most efficient and effective means possible to re-engineer the current system to achieve this broad goals.

The Office for Human Research Protections has been created and positioned specifically to enable it to exercise broad leadership in these areas and to try to catalyze the important cooperative efforts that will be necessary to make it happen.

I want to assure everyone on the Commission, as well as everyone in the public, that I and the members of our new office take this responsibility very seriously, and we expect others to do the same.

I also believe that those who are unwilling to accept their responsibilities should recognize the cost that everyone else pays through their negligence and that their involvement in the process should be curtailed.

As I enter what is clearly going to be a challenging period ahead, I have had many come to me and give me congratulations, and then they say, you have a big job ahead.

Well, in fact, that doesn't really disturb me too much, because I simply remind them that, in fact, it is not my job. It is our job. It is something in which we all share responsibility, and if we can

approach it in that shared manner, I believe that we will succeed.

Thank you.

DR. SHAPIRO: Thank you very much. Let's see if there -- if you don't mind -- if you have time -- we would like to leave some time for questions from commissioners. Alex and Diane. Jim.

PROF. CAPRON: Dr. Koski, I appreciate your being here, and I applaud the framework that you set out, with which you began with the emphasis of the value of research to society and society's interest in seeing the ethical issues properly addressed.

And I am likewise very pleased to see your emphasis on the notion of a performance-based process. I say that not only as a member of the Joint Commission with obvious attachment to the notion of accreditation, but thinking back to the 1983 report of the President's Commission, which set forth its own test demonstration of the value of a peer-based process of accreditation. And, unfortunately, for the last 17 years, nothing has come of that.

We are in a situation were, although you were named to the job quite some time ago, you point out you have only taken it on and assumed it in the last 24 hours. And in the normal course, I think we would like

our relationship to develop more slowly.

But I think you are in a situation where you are, in effect, on a first date with someone who may have a terminal illness, and so I am going to be very forward and, in particular, on two points.

You spoke of assuming what you called broad leadership, which you described as a catalytic role. One of the other things that the President's Commission had reported in this area in 1981 was the value of having a Common Rule. As you know, it took a decade for that to occur.

Throughout our deliberations, as recently as today, discussing the whole equivalent protection issue, we have come up to the point of saying, well, there really ought to be some change in the regulations on this point. And then saying, well, but we can't recommend that, because we know that any recommendation of that sort will be futile.

So the first question I would like to ask you is: Whether in your process of assuming the job, in the terms of the assurances that were provided, or your own vision of the way that research regulations should occur, you see us moving beyond a situation in which an agency merely has to operate by providing leadership.

And we could have some centralization of

certain aspects, not the application of every rule, but certain aspects of the rule, so the process is not so cumbersome.

And let me put out the second issue. You have already indicated your interest in the conflicts of interest question, primarily within the context of academic research, where there is a pattern developing of even academic researchers who receive federal funds also having equity interest in companies that sponsoring research and the potential harm of that.

I think many of us are also concerned, and I have discussed this today with a number of commissioners, in areas that fall within, I suppose, more of the FDA's concern, but I think spill over, and that is, research conducted on a contract basis by organizations where the payment may be contingent upon eventual success in the approval of the drug.

And I wondered if, again, you have any views on how that issue ought to be addressed. So that the two issues, the issue of continued reliance on sort of coordinating inter-agency task force versus strong leadership that would provide a way of cutting through the interminable delays on some of these things and, secondly, this conflict of interest issue.

I am sorry to be so blunt and hope that we can

begin to get some real discussion here.

DR. KOSKI: Well, I have always tried to be polite on first dates. But let me do what I can to answer that. Forgive me if I don't repeat the question.

With respect to the leadership issue, clearly, as I mentioned, the Office for Human Research Protections has been set up specifically to carry out that leadership role, and through strong leadership, I believe that there is much that can be accomplished.

It has been positioned, as I said, to bring together all of the agencies within HHS to establish a level playing field with uniform guidance that will resolve some of the issues of conflict that have been cited between interpretations or application of the separate regulatory authorities for either NIH or the FDA.

We will be working very diligently with David Lepay and the crew at the FDA, as well as those at the -- individuals at NIH and any other agencies within HHS, to ensure that we actually have uniform standards across the board. That is what this office was set up to do, and I believe that that is what the Secretary's intent is in moving the new office to her locale.

So I think the answer there is that, yes, we

intend to do that. Undoubtedly, there will be certain issues that arise that in order to provide the necessary regulatory authority that would be exercised either by FDA or another agency, we may need to have specific new rules and regulations.

And when we identify those, we will, again, provide the necessary leadership to see that those are carried forward in a timely manner. I am much less of a naysayer than many. I don't want to use the difficulties of trying to change the Common Rule as an excuse for not doing what needs to be done, which I believe has been one of the stumbling blocks that we have run into.

I believe I pointed out at the Conflicts of Interest Conference that if people believe things are impossible, they usually are, and I think that if we can approach these things with an attitude of finding what we can do rather than finding excuses to say that we can't do it, we will be far ahead of the game.

With respect to the conflicts of interest, the situation that you describe, without going into any specific details, in my mind, would also constitute a conflict of interest.

When there are specific situations that would encourage an individual investigator to do things that

may not be in either the interests of the science or in the interests of the research subject, that is a conflict of interest.

And there needs to be an appropriate way for either eliminating the conflict, whenever possible, or managing that conflict when it is essential to allow it to exist in order to meet both the goals of the research and the well-being of the research subjects.

So it is important to have special protections, and I believe that is a very important role for the Institutional Review Boards in defining exactly what those special protections should be.

PROF. CAPRON: May I just ask a quick follow-up? You mentioned the HHS-wide authority. Is there, in your omission of any discussion of such authority vis-a-vis the other agencies, the implication that the office doesn't carry with it, in your understanding, any greater authority there than OPRR had in the Inter-Agency Task Force? As to other departments.

DR. KOSKI: No. I think that, clearly, when OPRR was positioned at NIH, it was an NIH agency, and of course, it was conflicted in its positioning there.

The intent of moving this office, creating a new office actually, and I think that would probably benefit all of us to not talk about moving OPRR to the

level of Secretary, but I think we need to recognize that this is a new office with a new mandate that will, I believe, for the first time, enable us to take the important steps that are required to meet these goals.

DR. SHAPIRO: Thank you. Diane.

DR. SCOTT-JONES: It is very helpful to hear you talk about your views, especially as we are working on our Oversight Report. And I understood you to say that we have sort of an adversarial relationship between researchers and the research enterprise on one hand and the participants and research on the other hand.

You said also that that relationship might better be replaced by one of trust between researchers and those who participate in research.

I would be interested in hearing your views at how we arrived at the situation in which there is this adversarial relationship and how might we productively recast the relationships, so that there is more trust between researchers and those with whom the research is conducted.

DR. KOSKI: I think it would be important to just mention that the relationship between investigator and research subject must embody far more than trust. I think that it clearly needs to be stronger than that.

It really needs to be something that is a participatory interaction that is also subject to outside scrutiny and oversight in order to give an adequate degree of accountability for protection of human subjects.

So I don't want there to be any misinterpretation of my comment. Trust is essential in order to do this right, but that trust has to be founded on appropriate practices within that relationship as well.

The second question -- I think, in order to, you know -- how did we get to the confrontational or adversarial type of relationship?

It is just seems to me inherent in any process where there are a set of regulations that are going to govern what one group of individuals are going to do, you know, with another that is subject to an oversight process. That oversight process is going to be one that is stuck in the middle and will invariably be seen as an adversarial type process.

That, I believe, is destructive to the overall process, and that is why I said that if we can manage to get the IRBs out of the middle and instead incorporate everyone into a collaborative, cooperative

process that focuses on protection of human subjects, we will be better of.

So I don't know how to go into that in greater detail than what I have already described in my formal remarks, and so I am probably not giving you a good answer to your question. But I think once formal programs are being announced and initiatives are being announced, those will probably answer your questions more directly.

DR. SCOTT-JONES: So, then, would you envision some other process other than IRB review that might be better than IRB review as we now engage in it?

DR. KOSKI: Well, certainly, the openness that comes to a process like this, bringing a collective wisdom together with various parties being represented, I think, is a valuable process.

I cannot personally, right now, envision that being replaced by having an individual research czar, for instance, make a decision as to whether or not a particular project should or should not be done. I don't think that would serve the public interest well, and I don't think anyone would find it acceptable.

You may have other models in mind that I would be happy to comment on. But, you know, I think that

the current structure of Institutional Review Boards, the way they are configured and positioned, is probably not optimal for doing this job.

As your colleague to your right mentioned earlier, we really need to get the "I" out of IRBs. This has been a slogan that I have used on numerous occasions. The placement of these review boards at institutions clearly brings up a potential conflict of interest, which, in many instances, is a very real conflict of interest.

So that moving to a different model that would have greater public participation in the review process, as well as moving it so that an institution's interests are not brought into conflict with the committee, the review committee's interest would be valuable in the long run.

So I think that many of the things that we will be trying to do as we move forward will address those issues head-on.

DR. SHAPIRO: Thank you. Jim.

DR. CHILDRESS: Greg, thanks very much for joining us today, and I really do appreciate the vision, powerful vision and model, you articulated.

Pursuing that vision and model will obviously require several different steps on several different

levels over a long period of time. And the first question raised some issues about sort of long-term how one might change issues related to the Common Rule and so forth.

What I would like to ask if you have any thoughts at this point about the immediate, concrete steps you might take in moving toward this vision and this collaborative model. What kind of things might your office undertake fairly quickly? Any thoughts you have along those lines would be helpful.

DR. KOSKI: Jim, we certainly have several things that we have been talking about and exploring in detail. I have only been on the job 24 hours, and I have only worked 18 of those.

So I think rather than lay out a full, you know, table for you, if you would give us the -- just have patience to wait a bit longer.

The reason, quite frankly, is that the Secretary is currently in Sydney for the Olympic games, and I think out of respect for her I would like to meet with her to discuss everything before we lay out a full timetable and so on.

So, clearly, the remarks I have made lay out, you know, I think what any reasonable observer could begin to translate into specific initiatives. Those

initiatives will be forthcoming in a timely fashion, and I will be happy to come here and talk to you again about the details of any of those on an early occasion.

DR. SHAPIRO: Thank you. Bernie.

DR. LO: I also want to thank you very much for coming and sharing your thoughts on your second day at work.

As we go about our report on protection of human subjects, it might be helpful for us to hear from you what kinds of issues would you like to see some analysis or recommendations on? What sort of level of analysis are you interested in? Are you interested more in principles, suggestions for new approaches to IRBs, new mechanisms.

I mean, you could help direct us towards the kinds of things that you would find useful as you go about your task in this collaborative fashion. It may help us as we write our report.

DR. KOSKI: I suspect that you won't surprise you to hear me to say that I would find the principle guidance and recommendations to be of greatest value, in part, because specific procedural or, you know, operational recommendations can sometime be very confining in try to move forward in a very complex environment in which we are going to have to pursue

some of these things.

So, you know, ethics is an area that has always been based on principles, and I think those will be extremely valuable. We will, of course, have to take the principles and translate those into specific operational details to develop and implement new programs, and I think that those are something that we can probably talk about in one of our future discussions.

DR. SHAPIRO: Thank you. Alta.

PROF. CHARO: Dr. Koski, one of the criticisms of the current system correlates well with your own criticisms at the outset, and that is, that the up-front emphasis of the IRBs has correlated with a sanction that basically consists of the withdrawal of an MPA. And with the FDA, it is the refusal to use data based on retrospective analysis.

Many people have suggested that we need a better bag of tricks for both inducing ethical behavior in the conduct of research and in providing some kind of sanction when it fails.

Have you had occasion to think about the kinds of things that might belong in that larger bag of tricks that would be consistent with the framework you are beginning to lay out?

DR. KOSKI: Absolutely. You know, it has often been said that the measure of a man's character is demonstrated by what he would do if he thought no one would ever find out. Saying that, we can also recognize that, you know, we also have value in looking to see what people are doing.

So that I think that it is very important that we take seriously the recommendations of the Office of the Inspector General in its report that we look with great attention at the continuing review process.

We simply can no longer have a process whereby research is approved and then conducted without some form of ongoing oversight of the activities on a regular basis during the actual conduct.

And various combinations of activities, whether they be, you know, educational tools, whether they be self-evaluation tools, random as well as site-directed inspections, all of which are done not by the FDA or the Office for Human Research Protections, but by individuals who are based locally.

And they don't need to be IRB members, but perhaps members of a larger human subjects protection process that embody quality assurance initiatives, quality improvement initiatives.

I have found in my previous life at another

institution that the application of quality improvement processes on a continuous basis through the conduct of the research process can be very valuable, particularly if they are coupled with educational initiatives and recognition of those individuals who are truly making the effort to do it right.

If there is a reward for doing the right thing and appropriate sanctions and penalties for doing the wrong thing, or failing to accept responsibility, it becomes a very powerful combination.

So I think that there are tools there that can be further developed, and if there is a laundry list of those that comes out of the NBAC report, I certainly would be happy to see those.

DR. SHAPIRO: Thank you. Larry.

DR. MIIKE: A related question to the last one.

We hear a lot about the inadequacy of the office in terms of being the primary organization responsible for auditing what goes on in institutions and Institutional Review Boards.

And then what happens in recent experience is that one prominent institution gets slammed, and then there is a sort of going out to other prominent institutions, and they are inevitably getting slammed.

That combined with the criticism that the review process is so overwhelmingly paper oriented that you really don't know what is going on, and it is most often an issue of documentation.

What are your thoughts about changing how your office might change that situation so that we have real audits looking at real problems and also getting away from this paper-intensive system?

DR. KOSKI: Well, I think it would be unreasonable and undesirable to create a new human research police force within the Office of Human Research Protections to go around and do spot visits everywhere.

I think what we really need to do is to build that capability into the local processes through the appropriate application of resources to basically create, if you will, deputized outposts of the human research protections efforts at institutions and performance sites across the country.

One of the key elements in achieving this, I believe, is establishing standards that would basically lay out what the expectations would be with respect to site visits, participation of a patient advocate within certain forms of high-risk research, and other examples that we could probably draw on.

By laying out those standards and giving people a set of goals to aspire to, and you know, I believe we can begin to get the level playing field that is necessary.

I think it is unfair to say that all IRBs, as they currently are configured across the country, are failing and not doing their jobs well. Indeed, you know, I have been on an IRB for along time, and chaired one, and I know the dedication, as well as the expertise, that people bring to that process.

What we need to do is, through education, and through again bringing the additional resources that are necessary to enable people to do their jobs properly, we need to improve that process and then work on reconfiguring it in such a way that will better enable it to achieve its goals. So there is certainly a lot of work that we can do there.

DR. SHAPIRO: Okay. Last question. Trish.

DR. BACKLAR: Dr. Koski, thank you very much, but you actually answered the question, which was, how were you going to -- answered it somewhat -- bridge the gap between the beginning and the end. Alta addressed that.

DR. KOSKI: Thank you. May I just add one last comment here, since I have talked about resources

many times. The human subjects protection process is something that is absolutely fundamental to the responsible conduct of research, and it simply cannot be viewed as sort of an afterthought, a necessary evil, any longer.

It has to be viewed, embraced, as something that contributes value to the process. And I think if you look at the comments that have come, not just from institutions, but from PhRMA and BIO and others, I believe we have reached the point where everyone recognizes the value of this process and the need to do it properly.

I have had discussions already with officials at NIH, who are working diligently to try to find new ways to bring additional resources through their funding mechanisms to help institutions meet their obligations for these processes and look forward to continuing working with them to do that.

So we have a lot to do, clearly, and again, I look forward to your support and tackling these challenges together.

DR. SHAPIRO: Well, let me thank you very, very much for being here. I didn't realize myself that you had just taken a day ago -- taken on the job in practice. So I doubly appreciate your willingness to

come and spend time here, and I look forward to many conversations.

You said a number of things which are very provocative and certainly made me to think a little bit on certain things. And I look forward to future conversations with you. Thank you very much for coming.

DR. KOSKI: Thank you all very much.

DR. SHAPIRO: Marjorie, why don't we just go directly -- why don't you go ahead?

PANEL I: ALTERNATIVES/SUPPLEMENTS TO LOCAL IRB REVIEW

DR. SPEERS: We will begin with our first panel, which is going to discuss local IRB review, and I would ask the panelists to come to the table.

Just as a reminder to commissioners, we commissioned two papers to be written regarding local IRB review. We asked that Mr. Peckman, who is the associate director for human subject research at UCLA, to write a paper that would basically argue in favor of the local IRB review system and point out the strengths of that system.

We asked Professor Soren Holm from the University of Manchester to write a paper that would describe an alternative model to the local IRB system. We specifically wanted to have someone who was

familiar with a system that was different from the system that we used in our country. And so Professor Holm described, and will describe today, the Danish system, which is a regional system.

And then, recently, it was announced that the Office for Human Research Protections had approved a health alliance among five academic medical centers to try to streamline the IRB review process, and Dr. Daniel Schuster, who is a member, and represents that health alliance, is here to discuss that one example that we have in our country.

And I assume we will just go in order as to how you are listed here on the agenda. So we would like to begin with a brief presentation from Mr. Peckman.

MR. PECKMAN: Thank you for inviting me here today to speak with you. I would specifically like to thank Marjorie Speers for her patience in the tardiness of my paper and Jody Crank for her assistance.

It has been an honor and privilege to write about Institutional Review Boards for this illustrious body.

My paper provides commentary on the importance of local IRB review and the local institution's ability to create an institutional culture that promotes and

upholds the highest ethical standards in the conduct of human research to provide for education and mentoring of the research community and provision of sufficient resources and staff to support the educational mandate of the IRB to involve all interested parties in the review process, including open communication and interaction with the community, which includes the source of potential research subjects, to provide oversight of the research, and to assess local resources and standards that may impact proposed research.

This afternoon, though, during my allotted time, I will briefly discuss two of the five points described in my paper. An institutionally based IRB, or local IRB, is ideally situated to help create a local culture based on trust and shared responsibility for the ethical conduct of biomedical or social behavioral research by encouraging direct institutional responsibility for, and community involvement in, the conduct of research.

I actually have an overhead if someone could put it up on the projector for me.

(Slide.)

The actions of the local IRB are governed by ethical codes of conduct, federal regulations, local

law, and institutional policy. Ultimately, a local human subjects protection program functions within a system of self-regulation and oversight on the part of the institution, the investigators, and the IRB.

A system of self-regulation and oversight requires a highly evolved sense of trust ---

DR. SHAPIRO: Would you just hold on a second, please. Let's get the right set of -- is that the one you want?

MR. PECKMAN: That is the one.

DR. SHAPIRO: Okay. Thank you.

(Slide.)

MR. PECKMAN: A system of self-regulation and oversight requires a highly evolved sense of trust and responsibility from all participants. Could I have a room light? Thank you.

A discussion of local IRB review, ethical scientific conduct, and the ability to protect the rights and welfare of human subjects requires that we address the ideas of trust and responsibility as essential components of research.

Successful IRB review balances the interests of three distinct but inter-related social and political entities: one, scientists; two, society; and three, the individual human subjects.

The IRB, however, does not balance these interests alone. The IRB functions in a dynamic relationship with federal agencies, research sponsors, institutions hosting research, investigators, and the public.

The dynamic relationship balances the competing interests of all parties and facilitates the continued conduct of human experimentation in an ethical and collegial environment.

As a result, the local IRB is not the sole party responsible for the protection of the rights and welfare of human research subject; therefore, an effective system of protections is a collective responsibility that requires a collaborative effort from all the previously mentioned parties.

When all parties acknowledge their shared ethical responsibilities at both the local and national level, and the balance of interests is met, they create a culture of trust that allows for their effective collaboration with the public and the research subjects.

An institution's Multiple Project Assurance, or MPA, outlines the responsibilities of the institutional administration, the IRB, and scientists and allows an institution to demonstrate responsibility

for the ethical conduct of research by creating a culture that respects and endorses the imperative of IRB review, approval, and oversight.

Additionally, the regulations and the ethical principles outlined in the Belmont Report that are respect for persons, beneficence, and justice ---

In spite of past and recent problems in the conduct of human subject research, society continues to allow investigators to engage in human research, because specific parameters are in place to ensure the protection of the participants.

The system of assurances for local IRB review is based on trust. The public, and this goes with the circle, the public has entrusted the federal government with its well-being as it relates to subjects research, human subjects research.

The federal government trusts the research institution, through the assurance of compliance, to empanel an appropriate IRB to review its own research. The trust is based on the acknowledged institutional responsibility for instituting effective mechanisms and culture for the protection of human research subjects.

The IRB is entrusted to review research responsibly, according to the federal regulations, community standards, and ethical guidelines in order to

maximize the protection of the public and collegially negotiate the conditions of approval with the scientists.

The local IRB review engages the scientists in a dialogue that ensures that the conduct of the research is in compliance with the federal regulations and ethical guidelines and is performed according to agreed-upon IRB conditions of approval.

The subject entrusts the investigator with the protection of his or her rights and welfare beyond any research objectives, and the investigator trusts the subject to be truthful.

The collective trust is built through institutional support of local IRB review and compliance with federal regulations. Without the many levels of trust working together, the systems of human subject research and protection fall apart.

I call this the Belmont Circle. By creating a circle that links all parties equally, and by dedicating ourselves individually and collectively through education and cooperation to upholding human dignity, we create an environment that ensures the protection of human subjects, as well as the advancement of science.

The 1978 National Commission Report and

Recommendations -- Institutional Review Boards outlined steps necessary to ensure the protection of the dignity and welfare of all research subjects. The report defined local IRB review as the cornerstone of the national system for protections, and it highlighted the importance of local IRB review.

They observed that local IRBs, as opposed to regional or central committees, have multiple advantages, including greater familiarity with the actual conditions surrounding the conduct of the research; the ability to work closely with scientists to ensure the protection of the rights and welfare of the subjects; to ensure the application of policies as fair to investigators; to contribute to the education of the research community and to the public regarding the ethical conduct of research; act as resource centers for information regarding ethical standards and federal requirements; and to act as the liaison with other local committees and the federal government.

Ultimately, the federal government achieves sophisticated goals through this process. Predicating a research institution's receipt of research funding on a commitment to ensure both the ethical design of the research and the ethical conduct of its faculty through local IRB review.

Such requirements hold an institution's proverbial feet to the fire regarding responsibility for the review and the ethical conduct of the research. The requirement of local IRB review encourages the institution to promote an environment that supports the highest ethical standards for the review and conduct of research performed under its auspices.

Some commentators have noted that the intellectual and ethical climate of the institution is more important than any single consideration in protecting the willing patient from unwise, inexpert, or ill-advised therapeutic innovation.

The imprimatur of the institution makes the local IRB an agent of the highest ethical standards embraced by the institution itself rather than an alien and disembodied review process, an agent of the government, or an adversary of research. As noted by the National Commission, such an environment demystifies the review process and builds the trust of the research community and the public.

How is an institutional culture created? As I previously noted, it begins with the assurance of compliance. The assurance encourages the institutional official to use his or her moral and academic authority to require the highest ethical conduct from the faculty

and staff, implement local policies and procedures that reflect the ethical principles of the Belmont Report and the federal regulations to create an internal standard of acceptable behavior.

Institutional policies and procedures translate into a demonstration of philosophical and practical support for the autonomy and authority of the IRB, while facilitating a fair and timely and collegial review of proposed research.

An institutional ethos that highlights the importance of ethical principles insists upon well-conceived and properly executed research. The requirements should be evident in written institutional policies and the actions and communications of institutional officials and the IRB.

Research that is designed or conducted so poorly as to be unethical or invalid exposes subjects and institutions to unnecessary risks. The institutional standard for well-conceived and properly conducted research minimizes the potential for conflicts between the IRB and the research community. It facilitates local review and ensures the protection of the rights and welfare of the subjects.

The creation of an IRB with respected membership, reflecting the highest level of scientific

expertise and community participation and support underscores the importance of review and facilitates ethical research.

An IRB that has the respect of the research community is better able to fulfill its principal charge, as outlined by the National Commission, and that is, education of the research community.

The responsibility of local review obliges all institutional parties to acknowledge a collective responsibility for the creation of a culture of participation, mentoring, and accountability.

Additionally, the institutional official recognizes that the board can only carry out its regulatory, education, and ethical functions when there are sufficient resources and high-level support staff to communicate effectively with the research community and to ensure adequate protections of subjects through oversight, including continuing review and monitoring of approved research.

The local system of review is most effective when the institutional official sets the highest ethical standards for the research community and insists upon an institutional culture that demonstrates support for the charge of the IRB, namely, respect for human dignity.

The local IRB, however, may struggle under overt or covert institutional pressure to approve research. The OPRR warned that the IRB must be, and must be perceived to be, fair and impartial, immune from pressure either by the institution's administration, the investigators whose protocols are brought before it, or other professional and non-professional sources.

The selection of the institutional official is crucial to the success of a local IRB program and to its ability to address internal and external pressures, as well as the protection of the rights and welfare of the human subjects.

The OPRR guidelines describe the institutional official as a person who has the legal authority to act and speak for the institution and should be someone who can ensure that the institutional will effectively fulfill its research oversight function.

The official, however, may delegate the authority to the director of research and development, a dean or assistant dean, or hospital administrator.

Bell and Associates in their recent NIH-commissioned report on IRBs noted that 35 percent of IRBs reported directly to a provost or vice president for research with only 7 percent reporting to the

highest-level official, such as the president, or the next highest level official, such as an executive vice chancellor.

Yet reasoned consideration of the concerns expressed by federal agencies, professional groups, and other critics requires one to question whether an individual who is directly involved and responsible for research funding, such a director of research and development, is immunized against financial pressures and whether an assistant dean or hospital administrator had sufficient authority to avoid institutional conflicts and to ensure that an IRB is given the necessary respect and authority.

An institution that successfully addresses such conflicts and supports the charge of the IRB can avoid the common systemic problems found by OPRR between 1998 and 2000.

For example, OPRR expressed concern that "placement of the IRB at a relatively low institutional level contributes to the diminished status and support of the system for the protection of human subjects." The office recommended elevation of the IRB to a higher level within the institutional hierarchy in order to demonstrate a greater institutional commitment to human subject projects.

The Bell Report indicates that IRBs continue to try to do their jobs without institutional support, staffing, resources, and education. In spite of the perceived conflicts and pressures on local IRBs, though, the Bell Report reports that local IRBs are not approving research without due consideration of scientific and human protection issues.

The Bell Report also found findings are consistent with OPRR site visit letters, indicating that, by and large, local IRB chairpersons, members, and staff are sincerely committed to their charge, the protection of the rights and welfare of human research subjects.

The Bell Report highlights a lack of communication and education within institutions about the requirements for such protections. These findings, as well as reports from the OIG and the GAO, lead to the conclusion that there is too little institutional support for the protection and welfare of human subjects.

It is important to note at this point that though the local IRB system grew out of earlier peer review programs, it is not a peer review system.

As a result, the federal regulations do not require a majority of scientific experts on the IRB.

Instead, the IRB is an open system that includes members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

The federal regulations require that an IRB include at least one member who is not affiliated with the institution and one non-scientific member.

For the purposes of my presentation, I will discuss the participation of the non-affiliated community member as a non-scientist, since institutions have interpreted the National Commission's Report to reflect such representation, that is, most non-affiliated IRB members are non-scientists.

The non-affiliated membership on the IRB provides a voice for the community of research subjects during the review of research. OPRR suggests that the non-affiliated member should come from the local community at large. The person selected should be knowledgeable about the local community and be willing to discuss issues and research from that perspective.

The OPRR guidance implies that the non-affiliated member's charge is to represent community concerns and, by extension, the concerns of specific subject populations.

Recognition of both the implicit scientific

bias in the traditional peer-review system and the need for community participation in the ethical evaluation of human research coincides with a societal shift in emphasis from the individual to the social environment in which individuals exist.

Through community representation, the IRB is able to acknowledge and address such important issues as the social context and impact of research; the heterogeneity of our society; the impact of scientific paternalism; notions of autonomy, beneficence and justice; the recognition that in addition to physical risk, scientific inquiry includes potential social, psychological, and economic risks for subjects; and the need to engage the potential subject populations in the decision-making process regarding research in their community.

The regulations require that the IRB be sufficiently qualified through the experience and expertise of its members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes to promote respect for its advice and counsel in safeguarding the rights of welfare of human subject.

The National Commission endorsed a balance of scientific, individual, and community concerns on IRBs

in order to guard against scientific self-interest and to demonstrate:

"Awareness and appreciation for the various qualities, values, and needs of the diverse elements of the community served by the institution or in which it is located. A diverse membership will enhance the local IRB's credibility, as well as the likelihood that its determinations will be sensitive to the concerns of those who conduct and participate in the research and other interested parties."

Community, however, consists of several distinct and sometimes intersecting groups, such as the community of potential research subjects; people located in a specific geographical area; people with similar interests, work, culture, or religious, racial or ethnic background.

The letter and spirit of the National Commission IRB Report and the federal regulations require sufficient scientific, cultural, and community expertise and therefore appear to support representative or democratic IRB membership, one that includes the participation of representatives of potential subject populations on the IRB.

The federal regulations recognize that research is a social act, involving particular social

relationships. Such awareness underscores an important aspect of the spirit of the regulations and the intent behind local review, that is, the democratic constitution of the local IRB in order to balance the interests of science, society, and the individual.

Representatives of subject populations should have a right to participate in the review process in order to protect and advance their own interests. The local IRB thus realizes and promotes a form of participatory democracy, where culture is recognized as the essence of human endeavor expressed in respect, recognition of differences, and inclusion.

The application of democratic principles to the composition of local IRBs and the review of human research engage the trust and require the responsible behavior of all parties involved in human subjects research.

Additionally, it acknowledges by Lawrence Gostin that genuine respect for human dignity requires deeper understanding of the patient's values, culture, family, and community.

The system of local IRB review represents a fundamental, societal, and regulatory shift from reliance on scientific expertise and self-interest as represented by peer review to acknowledgement of the

expertise in ethical matters that is held within the community of research subjects.

The local IRB provides the community of potential human subjects with a venue, where it can actively contribute to the research review process. The efficacy of the system of local IRB review is predicated on improved federal guidance on the role of the institution and the institutional official and on the inclusion of community.

Institutional responsibility requires more than compliance with the letter of the regulations. It also requires a willingness to apply the ethical principles that are the spirit of the regulations, to educate the research community, and to create an institutional ethos that governs the actions of all stakeholders in the protection of human subjects.

The research institution, with support from the federal government, has the authority and the responsibility to create a culture that is sensitive to the ethical imperative of protecting the rights and the welfare of people involved in experimentation.

As noted by the National Commission, the local IRB, with support from its institution, is perfectly situated to ensure collegial interactions, the effective review and oversight of research, the

participation of the scientific community, and the community of potential research subjects in the education of all stakeholders.

A system that encourages education, participation, and dialogue and calls on all parties to uphold the highest ethical standards will earn trust and support for its enterprise. Thank you.

DR. SHAPIRO: Thank you very much. First of all, let me apologize for failing to extent a welcome to Mr. Peckman and Drs. Holm and Schuster. I really apologize to you. It is really quite wonderful to have you here.

I think the way we will proceed is have each of our panelists make their remarks that they have for us, and then we will go to questions after that. So why don't we go next to Dr. Holm. Dr. Holm, welcome.

DR. HOLM: Thank you, and thank you for inviting me. I have some overhead slides, basically, just to reinforce what I am saying and giving it some structure. I should, from the beginning, state that I have a potential conflict of interest, since I am also, on Tuesdays when I am not in Washington, a medical researcher in an oncology department, and I should acknowledge a lot of people who I have been working together with over a number of

years in looking at research ethics. And they are acknowledged in my paper.

Now, what I am going to say, first, is something briefly about the history of the Danish research ethics committee system. Then the main part is going to be about its current structure and function, how it is composed, how members are appointed, what the tasks are.

And, thirdly, I am going to say something about, well, what would be the possible improvements within the Danish system? What are the things which could be done to make the research ethics committee system more effective in Denmark?

(Slide.)

And if I start with the brief history. The history of research ethics committees in Denmark is shorter than the history of IRBs in the U.S.

In Denmark, it all starts about 1975 with the Helsinki Declaration, which was accepted by the Danish Medical Association, of whom about 98 percent of Danish doctors are members.

Following from this, the Danish Medical Association and the Danish counties, who in the Danish health care system, are the hospital owners came,to agreement in 1977 that there should be research ethics

committees in Denmark, given that this is a requirement of the Helsinki II declaration.

A number of other organizations also joined in, but the research ethics committees which were established from 1980 to 1982 were extra-legal. They had no legal foundation. Even though both the Danish counties and the Danish Ministry of Health were parties to the agreement, there was no legal basis for the research ethics committees.

Whatever force they had was through the force of the Danish Medical Association and through the force of the Danish counties as the employers of medical doctors and the Danish universities, which are all state universities as employers of medical researchers.

Over the years, this became criticized, and in 1992, the Danish Parliament passed a law on research ethics committees which establishes the system that we have in Denmark today.

This also meant the Helsinki Declaration was superseded as the basis for the work of the research ethics committees, and they now work solely based on Danish legislation, primarily this law from 1992, but it was slightly amended in 1996.

Now, the next slide is about the current structure.

(Slide.)

And several features are distinctive of Danish research ethics committees. First of all, the fact that committees are regional; that is, they cover one or more of the Danish counties, which are the basic administrative units in Denmark.

Whether it covers one county or more than one depends on sort of the research activity in a given county. So the one for Copenhagen municipality with the largest Danish university only covers one, and in the rural parts of Denmark, a committee might cover up to three counties.

So counties are established purely on a regional basis, and there is no relations between the committees and individual institutions.

The other major feature which I think is distinctive of the Danish research ethics committee system is that all committees have a majority of lay members. The Danish legislation states that there always has to be a majority of lay members, and even before the legislation of 1992, there was parity between lay members and professional members. So it is the way it has functioned for a very long time.

Members can serve for a maximum of two four-year periods, and the appointment procedure is such

that lay members are appointed by the county council, or the county councils, if there are more than one county involved, and professional members are appointed by the Health Sciences Research Council after local consultation.

It is rare that lay members are active politicians, but there have been active politicians as lay members. There has also been a former prime minister of Denmark as a lay member at one time, but most lay members are appointed because they are members of one of the political parties and have an interest in this field.

Then apart from the regional research ethics committees, there is also a central national research ethics committee, which consists of two members from each of the regional committees plus a number of especially appointed members, some appointed by the Minister for Research, some appointed by the Minister for Health.

(Slide.)

Now, what are the tasks of these regional ethics committees according to the legislation? Well, the first task is assessment of all biomedical research projects involving human beings, gametes, embryos, dead human beings, cells, etc.

There are no research ethics committees for non-biomedical research, but the definition of biomedical is very, very wide. If you do sociological studies on patients, that would fall within the Danish legal definition of biomedical. But we don't have research oversight for sociology outside the medical field, for instance.

There is no distinction between privately funded and publicly funded projects or projects in private or public institutions, and no distinction according to the profession of the researchers. It is solely what type of research it is which decided whether it falls under the research ethics committees.

The committee assesses both the scientific validity and the compliance with the ethical requirements, as laid out in the law, and also the suitability of the lead researcher for doing this kind of research.

Multicenter projects are only submitted to one committee. This committee will then collect comments from all the other committees where there is a center and will make a decision which is valid for all of the committees involved.

The second task of research ethics committees in Denmark is monitoring of projects. According to

Danish legislation, the committees have a right to monitor projects, both while they are being conducted, and after they are finished, and there is also at least an implied obligation to monitor projects. I will come back to that later.

(Slide.)

The next slide briefly outlines the task of the central research ethics committee, which, first of all, issues binding guidance to regional research ethics committees, for instance, on payment to research subjects, on the use of radioactive isotopes, and the safety issues involved.

It also acts as an appeal body for committee decisions. If a researcher has been denied permission, he or she can appeal to the national committee, or if a committee is divided on whether a given project should have approval, they can refer it to the national committee.

Then a task which is not as specific is that having a central national committee ensures that there is communication between the regional committees and also a fairly high degree of uniformity of decisions between committees.

Now, what are the advantages of this system? Well, all of them are, of course, arguable, but I would

say that one advantage is that the commission is not institutional. Because the risk of institutional pressures either leading the committee to approve or disapprove of research are diminished.

Secondly, I would say that the high lay representation and the way lay members are appointed gives them a certain degree of democratic legitimation Then I think the national committee is a very important part of the system, because it gives a degree of national coordination.

Finally, I would say that the fact that all projects have to be submitted, that there is no private/public distinction, I take to be a positive feature of the Danish system.

Now, as I have outlined in the paper, there might be problems in scaling the Danish system, because Denmark is a fairly small country, and certain of the ways the Danish system works probably are not scalable.

Now, what would I take to be the improvements which could be made to the Danish system.

(Slide.)

Well, my first improvement would be to upgrade the administrative help that these committees have. I would say that they need biomedical ethics, they need legal, and they also, especially I think, need research

methodology expertise.

And I think that there is possibly an argument for not trying to represent this in the committee, because some of these areas are not, in a certain sense, interests which we need to represent in a committee, but expertises which should be available.

Then I think a requirement of protocols being based on structured reviews would be a possible improvement, and then also resources for monitoring of projects. Because although there is at least an implied legal obligation on Danish committees to monitor, they do not have the resources to do so.

So very little monitoring takes place. And I think it is an important part of any system of this kind that you actually monitor some proportion of research projects as they are in progress.

Finally, I think that Danish committees, as democratic institutions, could participate much stronger in public debates, both about research in general, but also about specific contentious research projects. Thank you.

DR. SHAPIRO: Thank you very much. Once again, we are going to hold our questions until we have heard from our third panelist, Dr. Schuster. Welcome.

DR. SCHUSTER: Mr. Chairman and members of the

Commission, thank you. Like all academics, I bring far too many slides. So I will be cognizant of the lateness of the hour and probably ask that some of them be skipped. Let's start with the first one.

(Slide.)

I was asked to speak about the advent of the new research alliance, which we have titled, MACRO, or the Multicenter Academic Clinical Research Organization. It is a little bit difficult for me to speak about something that does not yet exist.

It exists in principle. It is in the birth canal. Its birth will be this Friday at a launch event, if you will, and so I will be speaking in terms of how we conceptualize it, but not based on any actual experience. Next slide.

(Slide.)

I think it is worthwhile, of course, to ask why should academic institutions pursue a collaborative IRB process, which is, in fact, the underlying principle for MACRO?

Greg Koski, just last week, at a meeting of the AAMC, happened to speak to this very issue, and so without his permission, I took his remarks from his slide that he presented, and I think it nicely outlines the advantages and disadvantages

You can see them for yourself, and I am not going to belabor them. Next slide, please.

(Slide.)

More specifically, why MACRO in particular? Well, we just have to recognize and accept that the clinical research mission of academic health centers is under siege and that over the last decade or so, a considerable portion of our clinical research portfolio has moved away from the academic center and into the private sector.

That has to be acknowledged, and any system that is designed essentially to undercut our ability to meet one of our core missions, namely, clinical research, is a system that, in my view, has to be changed.

We need MACRO not to undercut human subject protection, but to help reinforce it. And I think I will try to explain how I believe this is the case, and at the same time, we need MACRO to reduce, eliminate where possible, unnecessary duplicative efforts, which only move us away from focusing on the real issues that are needed to address human subject protection. Next slide.

(Slide.)

So the underlying premise by which we

undertook the creation of MACRO is respect. It is respect for patients, because it does nothing to undermine their protection. In fact, as I again will submit, it is designed to enhance them.

It is respect for the sponsors, because they have a job to do, and it is widely perceived that the IRB process at academic centers, in particular, is so inherently flawed that they can do that job better outside of academic centers.

And it is response for each other, the MACRO member institutions, because it will be quite evident that there is no way that we could have this organization unless we had respect for each other's individuals and the institutions themselves. Next slide.

(Slide.)

The guiding principles that -- or the principles that guided us while we talked about and tried to develop MACRO are these: First of all, all IRBs must adhere to the same standards. Secondly, the mission and values of academic health centers are similar in most respects. Thirdly, the ethical issues in many clinical trials, not all, but in many trials are redundant and are not unique to one locale.

Accordingly, if one actually looks at the

nature and content of IRB reviews of many clinical trials, they are similar, and accordingly, it seemed an opportunity to move to a system where duplicative effort could be eliminated. Next slide.

(Slide.)

So the challenge that we had was: How can we improve the process; add value for sponsors; protect patients; preserve our academic values, including our local academic values; and our local academic culture. Next slide.

(Slide.)

The answer we came up with, if you will, is modified IRB reciprocity. That is, a system in which we accept, on balance, each other's review of a clinical trial, but with conditions. Next slide.

(Slide.)

I think this is one I will skip. I am not sure if the history of how we got here is all that important. You notice the lawyers were always involved. That delayed things considerably.

(Slide.)

So how will it work? Well, one of the important components is the so-called the PCCA, or the Protocol Coordinator to implement the Cooperative Amendment to the Multiple Project Assurances, otherwise

known as the PCCA.

The other principle is that one of the five institutions for any one protocol will serve as the primary reviewing institution. There is no new centralized IRB, and there is no one institution which takes over review for all of the other institutions on all trials.

Rather each trial is considered separately. So on any one trial, all five institutions may participate or only one, or some combination. One of them will be a primary reviewing institutions, and the others that choose to participate on that particular trial will be other participating institutions.

And the third component is a set of Standard Operating Procedures that we have all agreed to use and will guide our work in implementing this process. Next slide.

(Slide.)

These SOPs include a method to accommodate particular local research context characteristics. They prevent the duplication of effort with respect to IRB review, but at the same time, they provide uniformity of process within MACRO. Next slide.

(Slide.)

So here is an example of how it might work for

a particular trial. There are many variations on this theme, and I choose just one as the typical.

A sponsor decides to use the MACRO institutions, contacts a PCCA, that individual charged with implementation and oversight of the SOPs at that institution. Contacts a PCCA at one of the institutions, and then that becomes the primary reviewing institution.

The PCCA determines whether there is interest at the other institutions within MACRO and communicates with the sponsor regarding confidentiality agreements and receives the protocol.

The PCCA then develops an agreed-upon, already developed as part of the SOPs fact sheet, which highlights different issues of -- whether they be hot button issues and also issues that might be -- solicits information about local context which might be important based on a brief summary of the protocol that is provided in the fact sheet.

Sends the fact sheet, the protocol, and the investigator brochure to the other PCCAs. Now, the IRB at the primary reviewing institutions is now the IRB of record for this trail. Next.

(Slide.)

After review of those materials, the PCCA at

the primary reviewing institution collates the fact sheet comments, including comments about local issues, and then supervises, if not actually does, the IRB submission to the IRB at that primary reviewing institution.

The IRB then reviews the protocol according to its standard procedures and according to its standard timeline. Usually, there will be a request for revision. Those take place in standard fashion.

Once the trial is approved, if it is approved, those approved documents, including the informed consent, using a single informed consent which has the opportunity to have an extra page added for local context, the IRB minutes of discussion relative to the trial are forwarded to the other participating institution for that particular trial.

And then there is an administrative review performed at each of those other participating institutions to make sure that what was promised at the front end in the fact sheet and what was delivered at the back end in terms of the approved documents do, in fact, coincide with one another. Next slide.

(Slide.)

Maybe I didn't -- maybe it wasn't clear. So let me make it explicit. What we are doing now is

actually sharing information in a way that has never been done before. Although I know that IRB chairs and IRB members get together, I do not believe there has been another opportunity heretofore for any one IRB membership to review the actual review, if you will, of another IRB's discussion and attention to a particular clinical trial on a systematic basis.

It is that sharing of information among the different member institutions which we believe will actually help to not only strengthen the protection to human subjects, but will also help us improve the IRB process at the collective MACRO institutions.

Here is an example of what might happen after the trials starts. It is only meant to underscore the importance of the PCCA as the central person. The IND safety report from a sponsor would be sent to the PCCA. All communication then would be through the PCCA.

That person distributes that information to the principal investigator, as well as the IRB of record, as well as to the other PCCAs at the other participating institutions on that particular trial and then on to other principal investigators and their IRBs.

(Slide.)

We will skip this next slide. It is another

example.

(Slide.)

Some frequently asked questions. Can other institutions join? Not yet. Because our intent is to demonstrate to ourselves, as well as everyone else, that we can actually make this work. And rather than have it explode into a larger group of institutions, we want to get it right first.

But after a year, our intention is, in fact, if other institutions want to join, to consider asking them to join. Of course, there will be a need to agree to adhere to the standard operating principles, procedures, that we have at the time.

Is MACRO a Site Management Organization? No, it is not. It is an agreement -- it is not actually an entity -- it is simply an agreement among institutions to improve, to change the process for IRB review on a subset of clinical trials.

Does it pertain to NIH trials? Yes, it does. Does it cover contracts, legal contracts, on clinical trials with the different sponsors. No, it does not. Next, and I think this is the last slide. One more? Maybe not. All right.

Thank you very much. I would be happy to answer any of your questions.

DR. SHAPIRO: Well, thank you very much, and thank the three of you for the papers you have prepared and also for your presentations today. I have a series of questions to start off, and then I am sure there will be questions from other members.

Dealing with a MACRO first, because that is the freshest in my mind right now, could you -- PCCA. You used a lot of initials in there. PCCA seems to be a chief coordinator of some kind. I couldn't understand from what you said whether this was a scientist, an administrator. I mean, I just didn't know how to think of this person.

DR. SCHUSTER: It is the Protocol Coordinator for implementation of the Cooperative Amendment to our Multiple Project Assurances. So in order to bring MACRO into being, each of the institutions as an MPA institution had to modify its MPA with a Cooperative Amendment. That is, in fact, what was submitted to, at the time, OPRR for their approval.

Then once that was approved, we had to come up with a way to implement, and the way we chose to implement this procedure was to identify one individual, an administrator, at each institution who is a paper shuffler or, hopefully, eventually, an electronic bit shuffler, that will make sure that the

information that needs to be shared will, in fact, be shared by the different institutions.

DR. SHAPIRO: I see. So the example you used, where the sponsor began by contacting the PCCA -- I believe that was -- that is just one example. It could get initiated many other ways.

DR. SCHUSTER: That is correct. But once the decision to use MACRO, or the MACRO process, as a way to conduct a clinical trial at any or all of these five institutions, the PCCA becomes the person who is charged with making sure that the SOPs are followed.

DR. SHAPIRO: Thank you. Tom.

DR. MURRAY: Yes, thanks to all three of you for your patience and your concise presentations. My question is to Soren.

Soren, you described the experience in Denmark of groups with majority lay membership. I wonder if you could say a bit more about how satisfactory that experience has been for the lay members, as well as for the scientists or other expert members. Whether that has generally been well received and is seen by both groups to be functional.

DR. HOLM: Well, as I said in my presentation, it has a fairly long history now, and there was a great amount of skepticism in the beginning. And I also

think it is fair to say that for most lay members, it is a very steep learning curve.

Most lay members have an interest in the field, but has never seen a research protocol before, and it is only very recently that sort of induction courses have been put on by the central research ethics committees for new lay members and how you actually read the research protocol.

I think it is fair to say that after some time, lay members do contribute not only sort of for looking at the informed consent material, but also looking at issues of research design, inclusion of various groups, exclusion of other groups, and -- balancing of research risks.

So I think it does function, and the majority of lay members do not sort of hinder the function of the committees.

DR. MURRAY: One brief follow-up. Is there any provision made for continuing education of either the lay or the professional members? I mean, I know that New Zealand does that with a very similar structure of regional committees with a majority of lay members. They have regular continuing education courses.

DR. HOLM: No, not in the form of education.

There is an annual two-day meeting for all committees, which is, of course, only possible because it is still a small country, where common -- things which have been identified as common problems are discussed. But there is no formal education offered.

DR. SHAPIRO: Diane.

DR. SCOTT-JONES: My question is primarily for Steve Peckman, but any of you could respond if you have ideas about this. Your presentation was built around the notion of trust among the various participants in the research process, and I am interested in your sense of the extent to which trust exists between research participants and researchers or between researchers and others involved, such as research sponsors.

MR. PECKMAN: I think that is an important question. I think trust is built. And I think for some people, trust breaks down, and for others, trust is built up.

So, for example, between researchers and the IRB, UCLA's has had some history of discontent from the faculty towards the IRB.

But I have to say that when the new director was brought in in mid-1994, Judith Brookshire, she instituted the major philosophy of education, and so we educated IRB members, number one function. And they

have ongoing and continuing education, including attendance at national meetings.

We also decided that education of faculty was the cornerstone of any effective program, and we have built our program around that to the point now where we have didactic and on-line certification of investigators and staff.

Regarding subjects and investigators, I would say that as well. It is built rather than just occurring without any work.

I think, at UCLA, some of our problems have been very well known, and we have had to rebuild the trust of the community who participate in our research. We have rebuilt that also through a matter of education of our investigators in terms of the process of consent and writing consent forms.

And also the IRB has been very thoughtful and particular. Part of building the trust with the community is bringing community members onto the IRB.

We were a very typical IRB in 1994 with one lay community member amongst 18 scientists. We have changed that. We now have an institutional policy that says that for every four affiliated members, we have one non-affiliated lay member. So we have tried to address that as well.

Beyond that, we also have engaged in consent monitoring for problematic studies or studies that have had problems, where we ensure that the informed consent process is working by having someone there who is trained in the process and can facilitate that process.

DR. SHAPIRO: Thank you. Alex.

PROF. CAPRON: I want to thank all our panelists. The only thing more difficult than coming here to talk from Los Angeles is coming from Manchester or Copenhagen or wherever Soren has just come from. So I appreciate all of you, and likewise Dr. Schuster. And Let me begin with Dr. Schuster.

As I understand your presentation and the slides that you provided us in advance, MACRO is designed to make academic research centers more attractive to sponsors, overcome some of the barriers that were seen as making them as less competitive with the growing use of contract research organizations and individual offices.

In light of that, and yet in light of the comments that Dr. Koski made about the need for greater resources for the ethical review process, how have you responded on asking for an appropriate compensation as part of the sponsorship of research, not just for the costs of the materials and the time of the physicians

and so forth, but for your review process? Is there anything in MACRO about that?

My second question is: Is there anything in the institutional standards or rules of the individual institutions that would prevent MACRO institutions from being competitive on what they expect to be compensated on based upon a contingent agreement on the use of a payment that is contingent on the utility of the data that are produced for the sponsor? Do you have any specific provisions that would address that? So the two questions for Dr. Schuster.

DR. SCHUSTER: Let's start with the second question first, because I don't understand it.

PROF. CAPRON: If a sponsor is offering, say, a commercial pharmaceutical sponsor, is offering a certain level of payment, in many situations, that payment is key to the number of subjects that are enrolled and so forth. And there are two kinds of incentives that are built in by some sponsors, as I understand it and has been described in newspaper articles. One is a contingency based upon how quickly subjects are enrolled, bonuses and so forth for rapidly enrolling subjects.

And the second is some portion of the payment, or some bonus payment, that will be provided if the

data that are accumulated in the trial lead to successful approval of the product, as opposed to data which are not useful for that end.

DR. SCHUSTER: All right. I understand. Well, MACRO doesn't speak to that, because MACRO doesn't have anything to do with the conduct of the trial per se in terms of -- there is nothing about a contract with the sponsor. The budgets that are negotiated are negotiated independently by each institution and/or each principal investigator.

So whatever incentives, or lack of incentives, there might be for enrolling many subjects, or the other example you gave of contingent on the drug being approved, which as far as I am concerned is a clause that would never make it into one of our contracts, but be that as it may, MACRO doesn't speak to any of that.

MACRO is purely and simply about the IRB process.

PROF. CAPRON: But let me just ask you then, if you just pause, and in your role as the associate dean for clinical research at Washington University, do you know of anything which you cite to an investigator who brought you such a research protocol to say, we cannot -- our institutional policy addresses that issue. Or is this an issue that as far as you know is

not addressed in policies at places such as Washington University?

DR. SCHUSTER: Yeah. I can say that -- I mean, without having the book in front of me -- I will be 90-95-98 percent certain there is no explicit policy, but since -- at Washington University, the group, the contracting group, that is responsible for signing those contracts reports to me, we would never countenance that second clause. It just -- I guess we just stand on principle without having a principle to stand on.

The first question, if I understood it correctly, was about whether MACRO has any special compensation for ---

PROF. CAPRON: No, what my question really was: Since you are getting together -- on the one hand, you are getting together, as I understand it -- I mean this not pejoratively -- but, in effect, to market the capabilities of these high-class, prestigious institutions in a way that makes them more attractive than if they were just operating individually.

DR. SCHUSTER: Yeah, I would say that that is point A, but is not the be all and end all.

PROF. CAPRON: Yeah. But in that, at the same

time that you do that, we have heard that institutions really need, if they are going to do a good job, need greater resources.

And I suppose it would be a disincentive to a sponsor going to you, if you said, by the way, we have a 2 percent or a so many thousand dollar charge that our ethics process needs to do the job. And so when you figure out what we are going to charge you for this, you should add on X dollars, or X percentage.

DR. SCHUSTER: No, it is just the opposite. We are going to charge them less, because -- since we are only having one full IRB review and administrative reviews at the other institutions, we have agreed that the actual total charge will be less.

PROF. CAPRON: For Dr. Holm. We heard from various people, including Mr. Peckham [sic] the advantages of locating review processes within institutions, and clearly, your representation of the Danish model shows a different approach.

You didn't address a couple of arguments that are made as to why it is a disadvantage to be outside an institution.

It is sometimes said that the informal educational process that IRB members in an institution can bring to bear on their colleagues is lost. It is

also said the way that Mr. Peckham [sic] emphasized that the trust that can exist may not be there, because people aren't as familiar.

And, third, although I didn't hear him mention it, it is often said that IRB members know their colleagues, and that a protocol that comes in from Dr. Jones to do something and an identical protocol that comes in from Dr. Smith may be regarded as involving different risks, because not only of the technical capabilities of the physicians, but their known attitudes toward consent and the way they go about recruiting their subjects and so on, and that that institutional knowledge is valuable. And I wonder if you have any thought about whether that is seen in the Danish system as a lack that results from the disassociation of the review committees from the institutions.

DR. HOLM: I think for the first two issues you mentioned, I think that the advantages they might bring are probably not large. At least, in large institutions, it is hard to see how the few members of the IRB would have any significant impact. I think you would have to do something conscious about the IRB having an impact, and you could do that just as well for any kind of IRB.

The last issues, I think, is an issue in the Danish system. That for some of the IRBs which have many projects, it is a problem sometimes that they don't know the researchers. That might, of course, be both a positive and a negative side to that.

I think that one of the reasons that I emphasized that a substantial improvement of the Danish system would be a more active monitoring rule is that you would get a much more formalized way of collecting that knowledge, both about bad research practice, but also about good research practice.

And you would -- it would not just be hearsay or what you think about your colleague. But you would actually have some evidence to back you up.

PROF. CAPRON: One final question. I believe there are health ethics committees in Denmark as well. Are there not any that look at any issues in clinical ethics? Or are there none?

DR. HOLM: Not in Denmark. In Scandinavia, there is only some in Norway.

PROF. CAPRON: Okay. Thank you.

DR. SHAPIRO: Okay. Bernie.

DR. LO: I wanted to thank our panel and ask a question. You have helped us start to think through the issue of what are the advantages and disadvantages

of an institutional IRB as opposed to locating at least some of that review elsewhere.

And I was wondering if you could be a little more specific. I was going to ask Steve. Can you give us some concrete examples of the types of ethical issues that you think you resolve because you are a local IRB that a regional or cooperative arrangement, such as this MACRO project that is starting, is likely to miss?

I mean, what are the kinds of issues that you think you solve when you actually see a protocol, leaving aside the educational consultation things.

And then for Dr. Schuster, as you were thinking about planning -- because, obviously, you have put a lot of thought into this -- what are some of the potential risks you see in a -- I mean, to be sure, now, when a multisite collaborative clinical trials undergoes multiple reviews, you get a lot of redundancy.

But are there things that sometimes get picked up in that sort of redundancy that might be missed. Just as in the ICU, you have several people looking at the same data, are there sorts of things that you have heard about, and have you tried to take that into account the way you have designed MACRO?

DR. SHAPIRO: Dr. Schuster, you can go first. Okay.

MR. PECKMAN: What issues have we solved that are really locally ---

DR. LO: (Inaudible) -- the protocol problems that you picked up -- if we weren't local, we would have missed that one.

MR. PECKMAN: One real protocol problem happened in a project where an investigator wanted to initiate work using the waiver of informed consent for emergency research, where the radius of the research would be 10 miles from the institution. And if you know where UCLA is in the Westwood area of Los Angeles, it is in a fairly wealthy neighborhood.

However, that neighborhood changes as the hours click by during the day. So, for example, though the neighborhood to the north of the campus remains pretty consistent, because that is where people live, and they are pretty wealthy, as you go south, east, and west, it is mostly business, large business buildings.

And though a lot of the people in those buildings will constitute a pretty narrow subject population, that population that inhabits those buildings after five o'clock changes dramatically.

Because they have gone from the people who are employed by the businesses and offices in that building to people who clean up after them.

And so the subject population changes over time, and in order to address community consultation in this context, it was extremely difficult. And, in fact, the investigator had a very hard time engaging these populations.

We have a very large Latina/Latino population in the Los Angeles area, which changes its context and its history depending on what parts of town you are in. And so recruiting from different parts of town can be crucial to the concept of how informed consent and the process looks.

So, for example, in certain pockets, there are mostly immigrant Central American populations. But in other pockets, there are ongoing generational inhabitants from Mexico. And so there are different needs of those different populations, especially in terms of the process of informed consent.

The Asian-American immigrant population as well, which I touched upon briefly in my paper, and the use of homeopathic remedies and their interaction with certain kinds of drugs, needs to be addressed as well during the consent process and screening in drug

trials.

And then, finally, we had a incident with several potential subjects in cancer trials from the Persian community, where family members thought that they could consent for other family members, specifically, brothers for sisters. And this was an issue that had to be addressed as well in protocol development and review.

DR. LO: But could not those issues been addressed by a regional IRB that knew Los Angeles as being opposed to UCLA?

MR. PECKMAN: I think if they had representation from those communities, or awareness of those communities, it could be addressed. A lot of these concepts came about during the review as a result of members bringing them up.

I would like to add one more thing in terms of a comparison between a central IRB system in Denmark and a central IRB system in the United States. The Denmark population is almost half of LA County. That is a significant difference.

The population diversity in LA County alone -- as I noted in my paper, there are 80 different language groups in the LA Unified School District. Beyond that, the entire country of Denmark is a little bit larger

than the State of Maryland.

So when we talk about a centralized IRB review program in the United States, it is very difficult to make a comparison to European countries that work on different levels, different population disparities, and different language groups.

DR. SHAPIRO: Thank you. Dr. Schuster, do you remember the question?

DR. SCHUSTER: I do. And I think Dr. Lo has asked the key question, and I would frame my response by starting with a rhetorical question, which is: What is the definition of "local"?

Many of our institutions have multiple committees that meet on what might be, a weekly basis, more often, less often, and we all have had the experience that the same protocol submitted to one committee gets one kind of review, and the same protocol submitted to another committee of the same IRB at a subsequent time gets a completely different review.

Now, how does this work with local review? I mean, which committee is right? And which committee is wrong? Or are they both right? And it is clear that that kind of argument that can be extended anywhere upon the food chain from how many committees per IRB,

or how many IRBs per community or how many IRBs per region, or so on and so forth.

When we were putting MACRO together, or the concept of MACRO together, the first reaction everybody had was: How can you do this at a time when all of the concern is about not enough IRB review? Aren't you creating a system where you are essentially going to reduce the scrutiny?

But the fact is that we can have a reducto ad absurdum in either direction. We can have -- we can worry that we will, because of a lack of multiple reviews of the same thing, that some item, some issue, some detail, will slip through the cracks, important though it may be. And yet where do you stop? How many times does the same protocol need to be reviewed before we can pass on it as having been reviewed satisfactorily?

The other side can also be reduced to an absurdity in which we relegate the review so far away from those who are involved that it has little relevance to the people we are trying to protect who are involved.

So there has got to be something in between, and I think locality has nothing to do with it. I think it is all about the subject population from whom

the subject is being recruited.

If that happens to be for a particular context of a clinical trial, homogeneous -- in other words, it may not have relevance what race or gender or sexual orientation or language you speak -- obviously, except for respect to whether you can understand the informed consent -- then I don't know that locality has meaning.

Other kinds of clinical trials, obviously, will have relevance to specific sub-populations. It is that kind of clinical trail that needs to be represented in the review process, and as long as that is represented in the review process, my contention is that the subject has been protected.

The process that we ended up with in MACRO was a process which was meant to try and address these various concerns.

We are not relegating the review to, in whole cloth, to another institution, where there will be no opportunity to comment, to provide information about local review or local issues that might be relevant for a particular trial.

And also the opportunity to share the information about ongoing review, where we actually see how we individually end up reviewing a particular trial

for its ethical standards and ask ourselves the question in so doing, in effect: Would we have passed on this trial?

And if we didn't, why not? And if we wouldn't, shouldn't that information be forwarded back to the primary reviewing institution. Mechanisms are in place to do exactly that. So that is how I believe we have to try and address the issue.

DR. SHAPIRO: Okay. We are going to have two more short questions, given the time. Larry and then Alta.

DR. MIIKE: Mr. Peckman, I would guess that if I asked you the question that could you live with the system he is putting in, your answer would be, it depends on the devil of the details.

So what I want to know from Mr. [sic] Schuster is, when you talk about a lead IRB or institution, an administrative review by the others, what do you mean by administrative review?

It seems to me that when you start instituting your system, the advantage would be efficiency in sort of a coordinated review, and that you are going to be fighting over what is administrative and what is uniquely local.

DR. SCHUSTER: Well, a coordinated review, I

believe, would be a fantasy. It is nearly impossible to have five institutions to agree on doing anything together, academic institutions, and so asking them to coordinate their reviews in the name of efficiency on literally hundreds of potential clinical trials is just not going to happen. So I think that is a non-starter at the front end.

An administrative review means exactly what I said in my remarks. It means that an administrator, which is high up in -- either the director of the IRB, or his or her direct designate, will review the information provided in the approved documents to affirm that what was promised at the front end, in terms of what this trial was about, and what the issues were or weren't, and what the objective of the trial is, and so on and so forth and what the IRB at the primary reviewing institution, after its review, ended up approving -- that those are the same in substance and detail. That is the administrative review.

It is not another opportunity to challenge or change the review by the primary reviewing institution.

DR. MIIKE: Let me get it straight then. The other institutions and IRBs do not get to see the protocol ---

DR. SCHUSTER: No, that is not right.

DR. MIIKE: No, no, no. Wait. Let me finish.
Until the primary institution's IRB ---
DR. SCHUSTER: No, that is not right.
DR. MIIKE: That is what you just told me.
DR. SCHUSTER: No, no. I am sorry. -- I said things that caused you to misunderstand. The first set of documents that are sent to all of the institutions that agreed to participate are the protocol; the investigator's brochure; and this fact sheet, which is a summary. Most of our IRBs have something similar to that anyway, but we have an agreed-upon so-called fact sheet.
Now, obviously, these have to be made available to each institutions, because each investigator needs to review the protocol, and the investigator's brochure, to make sure he or she feels comfortable with the trial as designed and the intent to participate.
And that same information will be made available to all of the IRB directors. What is made available in the approved documents is the approved informed consent, the minutes of the primary reviewing institution's IRB discussion about that protocol, and any other relevant documents which might escape me

right now. So those are the approved documents at the back end.

DR. MIIKE: But I don't understand then in the initial dispersal of this information to the different institutions what their roles are at that point in time of the participating, not the primary ones.

DR. SCHUSTER: The role of the participating institutions' IRBs, or actually their administrative people, will be to look -- first of all, understand that the process only applies to a subset of all possible clinical trials, classes of clinical trials which are likely to generate controversy, or which are likely to involve ---

I am blocking on the term -- but, anyway, that will, for instance, involve other committees that are not part of the MACRO at this point anyway. And so we are not talking about all clinical trials.

-- No gene therapy as an example. No cancer trials as an example. Because they involve another committee that would have to be involved at each of the institutions, at least at this stage. Radiation safety is another example.

So the point is that the IRBs at the participating institutions review what has been submitted about that particular trial to say, is this a

trial which they believe, on the basis of the summary information, can be conducted under the MACRO process.

And from that summary information, are there any key issues related to local context that need to be known or addressed by the primary IRB doing its review? That is the opportunity they have for comment before the primary reviewing IRB actually has its meeting. And those are provided in written form through these PCCAs back to the IRB of record.

DR. SHAPIRO: Thank you. Alta.

PROF. CHARO: Thank you to all. I actually had questions for you, but I will focus on just one last clarification, if I may, Dr. Schuster.

And it has to do with this incorporation of comments from the other institutions that are not the primary reviewing institutions.

Besides comments that are based upon peculiarly local conditions like an ethnic population or a language group, to what extent do you anticipate that that will be the same mechanism by which there is a compromise or surrender on issues that reflect mere local variations, not because of any difference in local conditions.

But, as we all know, huge variations on things like how to incorporate women of child-bearing potential, with what degree of contraceptive protection? Or when and how minorities should be recruited? Or, what are the justifications needed for the enrollment of mature minors? Or additional protections for people who are decisionally impaired?

There are any number of areas where there is a great deal of discretion available, and IRBs develop traditions that aren't based on the fact that they are in Madison versus New Hampshire. But they are just traditions at that institution.

And I am wondering how you anticipate that is also going to be resolved as a matter of difference among the institutions?

DR. SCHUSTER: Well, of course, I can't know, since we have yet to do one. But my comments would be pretty much a reiteration of what I have said before.

I know that IRBs have traditions, and in fact, IRB committees within IRBs have traditions. The membership of a particular group is just like a study section at the NIH. Everybody gets to know each other, and after they get to know each other, they have a certain sort of internal standard about something that is true for all the protocols that they happen to

review.

I don't quite understand that as being the acceptable standard. Yes, it is local, but it doesn't make sense to me that it meets the protection of human subjects in general if the one committee can say, you must change your approach to a trial, because our committee says it. And another committee, within the same IRB, at the same institution, passes on that.

So I don't know how that will play out among multiple institutions. But I do put a great deal of trust and faith at the front end without having any data yet to show for this to support this trust and faith.

That this process, which involves the sharing of information about each other's review for really the first time, will be a healthy one and will expose exactly the kinds of variations in a real-time sense, as opposed to audit reviews of groups of subjects, where it is very difficult to then implement that.

And I believe that these five institutions are committed to a process whereupon, at the end of a year, and at regular intervals thereafter, we will see what we have wrought. And we will work to make it better.

DR. SHAPIRO: Well, thank you very much. Once again, let me express my thanks to the three of you for

your work on our behalf and for your presence here today.

Thank you very much. We look forward for this experiment with great anticipation and look forward to talking about it in the future.

Thank you all very much. We will adjourn today's meeting.

(Whereupon, at 5:45 p.m., the meeting was adjourned.)