45th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

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Eberlin Reporting Service
14208 Piccadilly Road
Silver Spring, Maryland 20906
(301) 460-8369

I N D E X

P R O C E E D I N G S

OPENING REMARKS

HAROLD T. SHAPIRO, Ph.D.

DR. SHAPIRO: Colleagues, I would like to get started if we could assemble. I would like to get our meeting underway this morning. Thank you all for being here.

Let me say just a brief word regarding the oversight report which we discussed yesterday.

We will be producing new drafts of the report together with the restructured recommendations along the lines that have been suggested yesterday and sending that to Commissioners by e-mail as soon as a new chapter is completed along with its recommendations.

Our hope is that we really will be able to, in the near term, have a complete redraft of the oversight report for your review, together with a new set of recommendations. Our objective would be at that time to feel good enough about the report to release it for public comment.

We, of course, are behind the International Report in the sense of our schedule. We still have the 60 day public comment period in front of us in which we can, ourselves,continue to work on this

report but I am anxious to get it out there for public comment even though there could be obviously in response to public comment or from our own views some changes before we get to finalize that report.

So I really would ask you to the extent that your time allows you that, as you receive the new chapters, to give it as expeditious feedback as you can, hopefully within a day or two of receiving the chapter, so that when we get all five chapters out, we really will be very close to deciding whether or not we are comfortable releasing it for public -- for the public -- 60 day public comment period.

So please be attentive to your e-mail. We will send probably all the stuff by e-mail. I think that will be the only way to operate. I am fully conscious of the fact that the holiday period is coming up and most of us have other kinds of commitments during that period. But nevertheless we will try to do as best we can.

I expect some of the redrafted recommendations and chapters to be available certainly early next week, perhaps this weekend, and so if we could get you to focus your attention on those as they come that would be very much appreciated because it would be nice to get this report out for the public comment to see what response we get and how that might shape our final recommendations.

So that is where we are on oversight. I spent some time yesterday after the meeting going over all the comments that have been made, all the suggestions that have been made, and there are some very substantial and very useful ones, and I think Marjorie has a pretty clear idea of how to proceed. We will have to see how it comes out when it actually gets down on paper. That is not accomplished yet so we did not finish anything. We just barely started.

But I think we have got the issues in front of us and it is just a question of trying to get them incorporated into some kind of effective way.

So, first of all, Marjorie, I want to thank you for your help on this. It has been really quite terrific.

And my plea again is to have quick feedback on the material that you get within the next week or ten days.

Are there any questions about that?

Okay.

ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH

DR. SHAPIRO: The rest of our agenda this morning is focusing on the international report. I will begin with an apology. In a few minutes I am going to have to absent myself for about a ten minute period to make a few important telephone calls but Eric will take over the meeting at that time, and I

apologize about that.

We have -- I think you have all received -- I think, Eric, this went by e-mail, am I correct? The kind of redrafted recommendations which include everything from a proposed new title to recommendations that have been altered as a result of our conversations we had in our teleconference call, I guess, a couple of weeks ago now. And I think you all have a copy of the proposed new recommendations with things underlined and crossed out. Underlined means added. Crossed out means deleted. And I think we are used to that way of going about things and we made an attempt to incorporate many good suggestions that came out of that discussion.

There still are, however, some issues which we need to discuss because I think there is not -- certainly not full agreement and in some cases not even close to full agreement on some of the issues.

And I propose that we start discussing these recommendations not one through -- recommendations from Chapter 1 through Chapter 5 but that we begin with those issues on which there is the least agreement or most uncertainty regarding where we want to come out since I think it is very important to resolve those issues one way or the other and then proceed through those which, I think, we have a rather broader agreement.

Now the issue which we -- you know, it is

hard to pick -- I do not claim to be able to rank these quite so perfectly as it sounded a few moments ago, but clearly one of the major issues that we had discussed, and not reached agreement on, had to do with this whole issue of equivalent protections and whether or not there has to be -- whether one IRB review is enough or you want to have two IRBs or more and so on and so forth. That whole set of issues which also came up in public comment yesterday. It is obviously a very important issue and I do not think we have fully resolved where we want to stand on that issue.

Second, at least on my list, is a question of a post-trial benefits, especially in the area where there have been unsuccessful -- what we think of as unsuccessful trials, that is Recommendation 4.1.

The recommendation I talked about before that really dealt -- and the most important one that deals with the equivalence issue is Recommendation 5.6. Whatever we decide on 5.6, though, however, has implications at the very least for other recommendations in Chapter 5 and perhaps elsewhere.

So there are, of course, other issues regarding what we are going to say about FDA and so on, which will come up as we go through our discussions. So our discussions clearly will not be limited to those recommendations but I propose we

start with those.

So why don't we just turn our attention to Recommendation 5.6.

PROFESSOR CAPRON: Did we do 5.3 before?

DR. SHAPIRO: 5.3 is directly -- obviously directly related to 5.6. I have no objection to that. I just want us to get focused down on this issue so we can certainly go to 5.3 first. That would seem fine with me.

Now let me turn to Eric to lead us through these recommendations, 5.3 and 5.6, and areas that surround those because I will have to leave in just a few moments to make my calls and I will be back shortly.

Eric?

DR. MESLIN: Sure. Just as a matter of overview, you have got in your hands both a public comment draft version of the recommendations, that is the September 29th draft. You have a draft, the redlined/strikeout draft that has December 6th on it. And you also have a memo from staff relating to assurances, IRB review and equivalent protections.

Alex's observation to start with 5.3 is very relevant because in some ways recommendations relating to how many IRBs are needed or how much ethics review is needed really relates to what criteria or what standards would be set with respect to the ability to declare another country's

guidelines to have equivalent protection status.

Alta, are you still on the phone or on the phone now?

PROFESSOR CHARO: I sure am.

DR. MESLIN: Okay. Good morning.

So, Commissioners, I have also circulated to you, and the public may also have this, Alta's e-mail, as well as the e-mail from Diane Scott Jones who could not be with us, so that at least you have the benefit of their thoughts.

Recommendation 5.3, and I am only going to refer to the December 6th materials since you are familiar with what was already being proposed, is meant to describe the responsibilities of OHRP. I will not read through these recommendations since everyone has them in hand. But depending on how the Commissioners feel about the equivalent protection issue, about which both Alice Page and I can say more, that will affect what you want to say about how many IRBs are required so we can probably begin with, I suppose, Alex if he wanted to start with that.

PROFESSOR CAPRON: With 5.3 then?

DR. MESLIN: Yes.

PROFESSOR CAPRON: I would just like some word of explanation about the change in the last sentence because, on the face of it, the previous wording took account of the fact that there are two points that are important. First, that the country

in question have a system which is found to be equivalent and the additional language about laws and regulations and spelling out that in the earlier sentences is fine.

And the second step is that the actual review body, the IRB equivalent, is established or accepted by the appropriate authorities in that nation as equivalent in stature to an IRB and the revised sentence just drops that out. I was not clear at all what you were trying to achieve with the revision.

DR. MESLIN: I think the intention in the big picture is to do what you had first described, which was to allow those countries who have competent ethics review bodies as determined by their national standards, regulations, laws or guidelines to have the same authority and competency as a U.S. IRB. It was not a dropping of one. It was the reference to Recommendation 5.6 that was thought to be the necessary link.

Now the drop -- the struck out version of the old 5.3, the line that I think you are referring to, Alex, that says "must treat review bodies established or accepted by the appropriate authorities as equivalent in stature" was, I think, thought to be redundant if the full discussion about what equivalent protection actually means, about which our memo says more. Is it just the procedures

or is it the substantive criteria?

The equivalent protection determination was thought to encompass all of that without having to specify that line.

PROFESSOR CAPRON: Well, it seemed to me that what we are urging here, what we are trying to do here is not write a regulation. What we are asking OHRP, or whatever the body is, to develop policy guidance that will set forth the criteria and process. There can be lots of commentary in our text about what that would look to. That is to say how equivalent protection would be established.

Since I do not -- perhaps all this is -- since I am not wild about the revised version of 5.6, clearly without the revision the revised language here is not going to work and, I mean, to me the order -- we had a very orderly process before and it was encompassed in that last sentence.

I mean, in the previous sentence, set up the policy guidance and once it is determined pursuant to that guidance that the nation has an equivalent system, say Canada for example, to take one example dear to your heart, then you decide, are these review bodies established pursuant to that and are they recognized within that system and, if so, they do not have to go through the single project assurance. That is all that it gets. They get treated like a certified U.S. IRB.

DR. MESLIN: I do not think -- and, Alice, you may have some comments on this as well -- but I do not think there would be anything to prevent putting that sentence back in because it is not -- it was not an intention to change that determination. It was actually an attempt to try and link 5.3 and 5.6.

Bernie?

DR. LO: Perhaps as much for efficiency as for clarity, I would agree with Alex that 5.3 should say what it said originally. You should have procedures and then once it is deemed that another country is "equivalent" then we should treat it just -- they should have an MPA just like any IRB here. We can refer "see also 5.6" but then let's not -- let's sort of save for 5.6 what happens in terms of who needs to review.

DR. MESLIN: So just so I am clear, you are suggesting that the sentence that was previously "once it has been determined" simply go back into --

DR. LO: Yes, I would vote to stay with what we had.

DR. MESLIN: Jim?

DR. CHILDRESS: I would vote for that as well.

DR. MESLIN: Alta, I know you did not say hand up but did you have a comment on this?

PROFESSOR CHARO: No, not yet. Thank you.

DR. MESLIN: Thank you.

Larry?

DR. MIIKE: Just a clarifying point. What we are doing here then is saying once you have a country with say equivalent IRBs then they are treated like any other multi-institution trials in the United States where you can have one institutional review or if institutions do not agree on that then you have multiple institutional review, right?

DR. MESLIN: That is what 5.6 would say. I think what Bernie and Alex and Jim by agreeing are saying is changing 5.3 or retaining the last sentence of 5.3 simply makes very clear that equivalent protection means your country should be treated, including its IRB, as equivalent to U.S. IRBs.

5.6 will say given that, how many IRBs do you need.

DR. MIIKE: Right. I read the last part of the change on 5.3 as encroaching on the recommendation in 5.6. I mean, that is basically right.

DR. MESLIN: Yes, but so the discussion here is --

DR. MIIKE: I only raise that issue in reference to Peter Lurie's public comment yesterday. This is not -- there is nothing prohibiting a U.S. institution from insisting that they also do review,

right, even if --

DR. MESLIN: Correct.

Alex, did that cover your points about 5.3? Okay.

MR. HOLTZMAN: Eric?

DR. MESLIN: Yes, Steve.

MR. HOLTZMAN: Not to get into rewriting but you may find it an easier way to make the point clearer here with the statement to the effect of charging OHRP, or whomever, to develop a list of countries which meet the equivalent standard and then set forth what is the basis for the equivalent standard. And then you can reference -- and call -- you know, you call those designated countries or whatever. You can get around some of all the repetition below and then go to the consequence of a country having been designated as having an equivalent standard.

If you want me to try, I can write it.

DR. MESLIN: You could.

Alice, did you at least want to mention some of the criteria issues at this point?

MS. PAGE: There are a number of things I wanted to bring to your attention that are in the memo that the staff prepared about this issue and I do not want to repeat them but I just want to highlight some of them.

First of all is the fact that the equivalent

protection section in the Common Rule has never been used by OHRP. There is no criteria that have ever been developed and in my mind, at least, there are some questions of what it means in terms of substance and procedure.

The other question I have is, it seems to me ,that there are two levels at which this needs to be examined.

First of all, it is with regard to whether the guidelines of a particular country provide equivalent protections the same as the Common Rule.

And then a second issue that has to be considered is the ability of the particular ethics review committee in the other country to review individual protocols. It seems to me that there may be situations in which not every ethics review committee in a country is capable of reviewing every particular type of protocol. So I think the matter has to be considered at those two levels.

Third is this need to carefully develop substantive criteria for determining what constitutes equivalent protections in the event that is where you want to go and the memo lays out four different items on page two, which, it seems to me, is a good starting point. It lays out three substantive requirements and then the fourth procedural requirement of the actual independent ethical review by a competent body.

If there are -- if there would be a determination of equivalent protections, it would mean that there would be no need for assurances and there would be no need for U.S. IRB review mandated at least by the regulations, although it has been mentioned that, as a condition of collaboration, a U.S. institution could still require U.S. IRB review.

The other thing, I think, the Commission should be aware of, is the direction in which OHRP is currently heading. It is also in page two of the memo. And it is our understanding from conversations with OHRP that very recently they have permitted foreign institutions in Canada and India, to follow their own internet national guidelines as part of negotiating assurances under the new federal-wide assurance. This permits investigators to follow their own codes with which they are more comfortable and familiar but it then allows OHRP to maintain its oversight authority.

DR. MESLIN: I would like to also put this into some important context lest the Commissioners or the public think that something is being proposed that ought not. One background point is that there have already been several public comments that haves come in from our public comment draft from countries such as Brazil and South Africa that have said that they very much want to continue to see U.S. IRB review.

And when we look at 5.3 and 5.6, I think, part of the opportunity that you should consider is whether the principle or the aspiration of countries moving towards a status of equivalent protection is a laudable goal in contrast with this should be a required strategy that must be implemented at this time.

I think having reviewed so many of the public comments and heard feedback, there is no single voice that says we all want equivalent protections now or none of us want equivalent protections. This is an ongoing evolving situation where many countries are just developing their own ethics review capacity. Others, yes, principally from the more developed nations with very well established ethics review systems, find the imposition of U.S. rules, principally procedural rules for completing administrative forms and registering their IRBs, to be burdensome.

So we certainly would not want you to conflate those various views around one perspective that equivalent protection must be granted now and, therefore, all IRBs in the U.S. are somehow prevented from or encouraged to step aside from their current responsibilities.

So I think, to put it simply, you have a choice before you and that is irrespective of 5.3, which I think can stay as it is. Then you get to

speaking about 5.6, and we have laid out a number of options. You could certainly take a more aspirational approach and recommend that this is the kind of thing that you would like to see occur that countries work towards developing a standard so that they have the capacity to conduct ethics review.

PROFESSOR CHARO: Hand up.

DR. MESLIN: Yes, Alta. Go ahead.

PROFESSOR CHARO: I get nervous at the tone we might be perceived as having in the report if our report, talks about trying to encourage other countries to adopt protections that are equivalent to ours. I mean, we get back into the issue of the exportation of our particular priorities in the United States. And I think there might be a way to accomplish much of what we want to accomplish without taking that risk.

It seems that we could take advantage of our old friend "the presumption" to adopt the following kind of scheme: That first as it says in 5.3 we ask our own governmental office to look around the world and identify countries that have policies that are equivalent to ours that essentially we can opt into and we also specify that we would like them to look, not only at the substance and procedure at the national level in those countries, but also to look at whether or not they have got internal procedures that allow them to evaluate their own review bodies

and in a sense accredit their bodies.

The second thing we do is the following: As it now says, if they do not have what we call substantially equivalent procedures, then certainly U.S. IRB review is required for those who are subject to U.S. regulations or those who want to have their data accepted by the FDA.

For those countries that do have, you know, the substantively equivalent protections, I think we might use a presumption in which we say the presumption is that people subject to U.S. regs, people that want to eventually get their data accepted by FDA, have to go through a U.S. IRB unless they can show that there is a body in the other country that is capable of doing the job in a way that we would recognize is equivalent to how we do it and that might mean that they are able to just show that there is a finding by the federal office that this country has equivalent protections and has a method for accrediting its IRBs. It might be an individualized showing based on the details of that IRB, although it is much more burdensome.

And for people who are already subject to IRB review through their institutions, this is not a big deal. It would mean passing some paper up to show their IRB why it is that they do not need to go through a full review there.

For those who are not subject to U.S. IRB

review to begin with, for example, a private sector researcher who is thinking maybe down the line I am going to submit my data to the FDA, there is a bit of a gamble here. That researcher can go out and do this work with nothing but the review committees in the foreign country and is gambling that when you come back, if you ever come back, and submit that data to the FDA, that at that time, this investigator, or the sponsor, can show that the foreign review committee's work was handled in a way we would recognize as equivalent.

Or if you are not much of a gambler you go to a private IRB or to an institutional IRB here and you get the same kind of sign off that an institutionally based investigator would use.

And in this way maybe we can keep the U.S. IRB in the picture unless there is good reason to feel that the U.S. IRB can excuse itself and excusing itself is, of course, voluntary.

It also means we do not export our standard so much as we insist on applying our standards to our people.

DR. MESLIN: Bernie?

DR. LO: I would like to follow up, Eric, on your suggestion that we consider this more of an aspiration for the future and also to follow-up on Alice's perceptive comments that this is very complicated, and you have both the equivalence of --

the determination of equivalence and also a question about the functioning of actual individual IRBs in the country which may be quite variable.

And, I guess, I am a little concerned of trying to look too far ahead to a process that is going to evolve over time. I mean, right now, as I understand, we do not have procedures. There is just the beginnings of declaring that other countries are equivalent and we -- I think one needs to see how that plays out before one sees what the end results would be.

I think we should be very clear why we are trying to do this and, as Alta points out, we are not trying to export our values. We are trying to be respectful of values and approaches that other countries may have very legitimately and very reasonably developed, and we are also trying to cut down on red tape.

And those two sort of drives should be very clear and we should be very clear that we do not fall into the trap or the perception that Peter Lurie pointed out yesterday that this is seen as somehow weakening protection by taking away review by bodies which right now are best constituted to give review.

I think we should sort of hold this out as down the road if things work out. We would like to treat IRBs in other countries with a lot of respect, both in terms to their substance, their procedure and

their determination, and maybe at some point, we may say that one IRB in another country alone can provide adequate review just as we are trying to work out ways now of saying if several U.S. institutions, all of which are gold star, collaborate, maybe not every institution has to review every protocol as deeply but even that is controversial.

So I would like to sort of not try and project too far ahead but to sort of be very clear as to the reasons behind this aspiration.

DR. MESLIN: Jim?

DR. CHILDRESS: I would like to echo Bernie's comments. I think they point in the right direction for our trying to get around the kinds of problems that have emerged as this 5.6 has evolved.

And I think both the considerations about red tape in terms of efficiency and also the concern to respect the values of others point -- both of those point in directions that we should over the long run be heading but for now I am quite comfortable in basically opposing the current direction of 5.6 and going back to building in the U.S. IRB review.

DR. MESLIN: Larry?

DR. MIIKE: Well, I am not too sure that I agree with what Alta was saying about the perception of superiority by exporting standards. I think any kind of equivalency determination does the same thing

because it is our country saying what is equivalent to our standards.

I am not too sure that I want to back off so much. For one thing, as long as U.S. IRBs from the researcher's institutions insist on and have the option of and insist on also doing review, and you are giving the host country IRBs a chance to get better and better, in the interplay between those two IRBs there should eventually come a time if there is progress going on where the U.S. IRB begins to feel comfortable and can accept the review of the foreign country IRBs.

It seems to me that the only way it can do that is to have some aspirational goal for those foreign IRBs, whether it is by standards or by equivalency determinations. So I would push ahead with this, although I agree that I would soften the tone and the direction of this particular recommendation.

But I would leave open the option or not insist on U.S. IRB review since any U.S. institution that feels uncomfortable about solely host country IRB review will insist on doing the IRB review and just the interplay between those two host and sponsoring country IRB should lead to improvement.

DR. SHAPIRO: Okay. Alex, and then I have a comment because I think where we need to come out on this at least for the moment.

Alex?

PROFESSOR CAPRON: I would prefer to see us stick with the recommendation as it was in our September 29th circulation. And it seems to me that Larry's comment -- the reasons he cites cut in the exact opposite direction of his conclusion.

If an IRB in the United States does develop a good working relationship with an IRB abroad so that it is not just that that IRB has gone through whatever formal process, either getting an assurance or being recognized under 5.3 as an IRB within a system that has been found to be equivalent, and that good working relationship develops, in effect -- although the U.S. IRB is still having to make the approval as you suggest, Larry, they will have confidence in the local IRB, which is on the ground where the research is being done and they will begin to defer to it. And it becomes a matter that it is not imposing a whole lot of extra hoops for them to jump through that the U.S. IRB still has to approve.

DR. MIIKE: I do not see where we disagree. Why --

PROFESSOR CAPRON: Well, then you are agreeing. I thought you were saying the opposite, which is if the U.S. IRB wants to -- if the U.S. institution wants to have its own IRB review it, it can do so but it does not need to.

Recommendation 5.6, as it was drafted, said

you must have the IRB at the U.S. institution approve the project.

And my point is simply that if the real work is being done by a competent IRB abroad and the U.S. institution is comfortable with that, although it will formally still have to make the IRB approval, it will, in effect, be --

DR. MIIKE: I am talking about a situation where there has been a determination of equivalency and so it is the option of the U.S. IRB.

PROFESSOR CAPRON: See, it is not the option under 5.6 in the draft of September 29th, and I favor the draft of September 29th.

DR. MIIKE: Whichever draft we are talking about, I think it is clear about where I stand on the aspiration of moving towards equivalency.

DR. SHAPIRO: I would like to make a suggestion about where we ought to come out on this because it really -- the discussion is leading in the exact same direction our discussion of the conference call that we had where we had an informal discussion on this.

And it seemed to me as a result of that discussion that the clear majority of the people participating in the discussion wanted at this time to have -- retain the requirement of U.S. IRB approval. And I think the -- and I think I sense the same thing here today with different kind of

variations and nuances.

So my suggestion is that we think of having a section in this Chapter 5 regarding long-term objectives, prospects, aspirations and so on, which might speak to the issues that have been raised here regarding hopes to encourage efficiency, decrease red tape and so on. That is a long-term aspiration.

I think I agree with Bernie and others who have said similar things that we are too far away from that determination of equivalence now because, as Alice points out, although these recommendations talk only about the national guidelines, the real critical thing is an effectively functioning IRB system where it is equivalent underneath that.

And we are just too far away from that and too far away from any experience with that that would be reassuring and so that -- and, indeed, as others have pointed out, we have some evidence to the contrary.

And so I think we ought to leave whether -- I do not want to speak to 5.6 as really drafted word for word but the sentiment of that, I think, is the right one to keep in our recommendations. That for the moment that we insist on both IRB -- I will say both IRB reviews -- I know there may be not IRBs somewhere else, the ethics committees. I do not want to trip over that for this moment.

But that we draft the actual recommendation

now to take effect now if people were to adopt our recommendations as still requiring both and then we can draft a section regarding where we would like and hope that people might proceed to at some future moment when we have somewhat more confidence that that is a reality that we would know how to implement it but the evidence is that we are just so far from that now that I do not think we can write a coherent recommendation in that respect.

Steve?

MR. HOLTZMAN: This is not a disagreement with you at all, but as I read these recommendations, it is very clear that the paradigm we have in mind is NIH, for example, or CDC or whatever research but we are capturing privately sponsored research, which is subject to FDA regulation, right, where notions --. When we talk about there should be U.S. IRB review, there is no U.S. IRB in play when I sponsor a trial over in England, my issue is how do I ensure that the data from that study in England or wherever can be used in support of my FDA registration here in the United States. And that is where I take advantage of things like ICH and whatnot.

So my question is, I do not know that we have been clear enough here that we are capturing a whole other set of activities where the paradigm is ill-fitting at best, what is the current situation, and are we recommending a change in the current

situation. I think we have to be very clear about that.

DR. SHAPIRO: I completely agree with that. The issue of data that is acceptable or appropriate for submission to the FDA and what regulations cover or what restrictions cover that is extremely important to clarify in a number of points here.

Yes, Larry?

DR. MIIKE: Let me get it clear then. What you are concluding is that we move toward equivalency and yet we still require U.S. IRB review?

DR. SHAPIRO: I want to just distinguish in my own mind where the committee has aspirations to go long-term and what its current recommendations are now.

DR. MIIKE: But I am interested in what we are actually going to be recommending. Are we going to be recommending equivalency as some future goal or something to be tried?

DR. SHAPIRO: Yes, some future goal is what I had in mind and meant to articulate. Maybe others would disagree. That is what I had in mind.

DR. MIIKE: So there is no change.

DR. SHAPIRO: In that respect that is right.

DR. MIIKE: We are not suggesting any change in the relationship.

DR. SHAPIRO: In that respect, that is right.

DR. MIIKE: I do not know if I can agree with that.

DR. SHAPIRO: All right.

DR. MESLIN: Can I just -- Steve asked a question and it is important that -- this is when we had said earlier there are a number of domino effects of which way you go. So one of those domino effects is what to do about the FDA which currently requires only one IRB and also would require only compliance with Helsinki, and if you read the regs carefully, current Helsinki might actually be in contradistinction to what HHS regs are.

So you have a couple of options. One of which we suggested to you in the December 6th proposed -- staff proposed revised recommendations. And very simply you could either exempt the FDA from any of this equivalent protection or you could recommend that the FDA regs be modified to include equivalent protection or you somehow draw a circle around FDA and say it does not -- everything we are saying about multiple IRBs and the like does not apply to the FDA.

You have to be explicit about that. We have given you only one suggested way of doing that but it -- that is by no means the winning proposal that Steve has just identified what -- if the current system were retained, meaning if you retained 5.6 as it was in the September 29th draft, you could not

simply say research subject to U.S. regulations conducted in other countries would require IRB approval in the host country and by a U.S. IRB. You could not do that unless you also recommended that the FDA regs be changed in order to be consistent with that because research data that is going to be submitted to the FDA does not require two IRBs.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Because effectively what the FDA has, if you will, is an equivalent system even though it is not called that. They make a determination of whether the trial was undertaken in conformance with the substantive ethical principles. If not, it will be not allowed to submit the data.

DR. SHAPIRO: Will someone please remind me? I think they insist on the Declaration of Helsinki as the guidelines that they use? The FDA?

MR. HOLTZMAN: I think specifically international standards is how they --

DR. MESLIN: It says international standards but Helsinki is specifically mentioned as the example of international standards.

DR. SHAPIRO: Bernie?

DR. LO: Steve raises a very, very important point of if we say you get two reviews in the example he delineated, the second one being the FDA review, we have really taken the host country out of the process of reviewing the protocol through an IRB on

site. And to the extent that we are trying to have -- if not uniform, at least similar rules and procedures for all research being carried out that is ethically similar. It is troubling to me that we would allow -- that not to have the host country have an IRB, flawed as that IRB may be, have an independent review of what is going on in some country.

DR. SHAPIRO: I did not understand Steve to be saying that but, Steve, maybe you should respond. I heard you say something different than that.

MR. HOLTZMAN: Right. No, what I said -- how it is done now if I want to conduct a trial or a trial we are conducting, for example, right now in Edinburgh, it is submitted to the local ethics review board there, and we conduct the trial. The U.S. only comes into play if we decide we want to submit that data in support of a U.S. drug registration.

DR. LO: Oh, you said you do not have the U.S.?

DR. SHAPIRO: That is right.

MR. HOLTZMAN: That is right. We make that -- so when that moment arises effectively the FDA then asks a question, was this done in conformance with ethical standards. If not --

DR. LO: It raises the --

PROFESSOR CAPRON: Question or clarification?

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: The same would be true if you were doing the research in Atlanta. That is to say you do not have an IRB. You -- if you go to --

MR. HOLTZMAN: Except that if I am doing it in Atlanta, right, I will be at an institution that will be submitted to a U.S. IRB.

PROFESSOR CAPRON: Right, but the point is that if Harvard down the street from you decides -- or across the river from you, the medical school -- decides to do research with someone at Emory, the Harvard IRB will review it because the Harvard researcher is the co-PI, and the Emory IRB. When you do that research you rely -- and you go to Emory and it is done in Atlanta -- you use only the Emory IRB because you do not have a U.S. IRB for your own people because the research is being -- as far as you are concerned -- is being done by whoever you have contracted with to do it. Is that correct?

MR. HOLTZMAN: Right. We are the sponsor. We are not the investigator.

PROFESSOR CAPRON: You are the sponsor. You are not the investigator.

MR. HOLTZMAN: Right.

PROFESSOR CAPRON: Whereas, Harvard's faculty member is a co-PI or whatever on the -- and so Harvard reviews it.

What we need to recognize -- my sense about

all of this was if through the 5.3 type process we either have those organizations that assurances because they are dealing with a U.S. sponsor of a federal sort or those that are determined to be equivalent because the FDA is using the same kinds of standards and criteria under its requirements that that organization should through that process be recognized as like a U.S. IRB but that the process would be the same as if whichever type of either co-investigator, Harvard, or sponsor, Millennium, would be involved if it were a domestic project.

And so if it requires two U.S. IRBs to approve it when it is a domestic project, there is no reason to reduce that when we are dealing with a foreign IRB which, as the chair has already suggested, we are not yet totally comfortable that that system, however nominally equivalent, has evolved to that level.

And so it seems to me that we just have to make clear that our expectations vis-a-vis the process do not contradict what is already provided in regulations.

Right now you can, from what you say, not just as to Edinburgh, but as Bangkok, if you had a drug you were developing over there, if you are confident that the IRB there will in retrospect be found by the FDA to have given approval that would meet the FDA's requirements, you are not going to use

an American IRB first. You are going to just use the Bangkok IRB. Is that correct? That is as of today. Okay.

DR. SHAPIRO: Bernie, did you want to make a comment?

DR. LO: Well, I would suggest we actually look at the FDA regs of was there data from foreign country submitted to -- I am sorry. I was just suggesting that we actually look at the actual current FDA regs to see what it says about the type of study Steve mentioned of a study conducted in another country about to be submitted to IRB review.

And this gentleman has a copy of the FDA regs and at 312.120 is the section on foreign clinical studies not conducted under an IND. Now is that what you are -- okay.

In general, FDA accepts such studies provided they are well-designed, well-conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be utilized to support clinical investigations in the U.S. and/or marketing approval.

And then when you go further, though, it does not actually say -- it has to be conducted in accordance with principles. It does not say that the process has to include IRB review in another country. They do refer to the Declaration of Helsinki as an

example of principles and that does recommend IRB review so it is not clear that is actually required.

MR. HOLTZMAN: I was speaking --

DR. LO: Right. But I guess my concern, Steve, is whether you do it as a matter of good practice because of the -- you know, the nature of your company and whether other companies say, well, we are doing it in accord with the principles but we do not have to have an IRB in the host country look at it, and that is what I would be concerned about. That sort of option.

DR. SHAPIRO: Steve? I am sorry, did you have your hand up?

MR. HOLTZMAN: Well, I am answering your question. If you are a company -- this is not about ethics right now. We are just talking pure business, right. You are trying to get a drug approved, right, and you want to have it marketed in major world markets, all right.

Even if you were totally unethical you would want to make sure that your data was acceptable in front of the major registering authorities, all of whom have signed up to similar things through ICH, and so the answer and the major market countries all have, okay, a system of review that is essentially in spirit the same and includes independent review by something usually called an ethics committee.

DR. SHAPIRO: In the host country, right.

DR. LO: But then to turn it around, then there would not be any opposition from companies to saying that should be an explicit recommendation, an explicit requirement rather than something that is kind of implicit in the regs, right, and people are willing to do it now to get FDA approval so that a more explicit requirement would not be seen as a deterrent to conducting the studies.

DR. SHAPIRO: Eric?

DR. MESLIN: I hate to do lots of reading of the text but we may be doing the same thing. Alice, do you want to, maybe just give the -- for the benefit of the Commissioners, just that other clause of the same reg that everyone is reading from?

I am sorry the public does not have a copy of the FDA regs committed to memory or in their hands but we have --

PROFESSOR CAPRON: Before you do that, would these always -- this was something that was without an IND. Suppose you have a drug that is in the IND process in the U.S. and then you decide it would be relevant to also do a trial elsewhere with the expectation that since you are putting money into it, you want to use the data that comes out. Is there any difference when it is with an IND and not with an IND?

Because what I understood it to be read is a drug not with an IND, not having the IND is relevant

only that you are not shipping it interstate in the U.S. so maybe the usual concerns about having the investigational new drug application is not -- I mean, approval is not at issue of that.

MR. HOLTZMAN: Without getting into that, what you are asking is if there is a protocol that is being conducted under an IND.

PROFESSOR CAPRON: Yes.

MR. HOLTZMAN: All right. And that protocol was being performed outside of the United States.

PROFESSOR CAPRON: Yes.

MR. HOLTZMAN: All right.

PROFESSOR CAPRON: Is the rule that was just read to us any different for that section?

MR. HOLTZMAN: I am not an FDA specialist at Millennium.

PROFESSOR CAPRON: Is anyone able to answer that because it --

DR. _____: (Not at microphone.) (Inaudible).

PROFESSOR CAPRON: Please use a microphone and identify yourself. Here, come to the table.

DR. JANNI: My name is Otto Janni (phonetic). About a little over a month ago I was a physician at the FDA. Any study that is going to be reported for registration to the FDA requires an IND. So really for a study that does not have an IND to be submitted to the FDA, the intent is not necessarily

for registration. That is issue number one.

The second point is that, and it deals with the requirements for registration, as was mentioned in the book that they have -- of course, the study has to be well randomized and well controlled. And it has to meet the Helsinki requirements as generally accepted and that, of course, includes the IRB and informed consent issues.

But an important part of it that is omitted or not being discussed so far, and which relates to the discussion that has gone on before, deals with the requirements of the local country. It is a two-part issue. The Helsinki requirements have to be complied with and the local regulations are to be complied with also. So the company has a responsibility to show that those two factors apply.

I wish to say, just to highlight what Mr. Holtzman has said with regards to these discussions and the need for inclusion of industry, industrial research, internationally in these considerations because industry research is exploding and I think more research -- not that I think -- I know more research is being done internationally and more will be -- even more will be done in the future, and we need to give that consideration as well.

Thank you.

DR. SHAPIRO: Thank you. I want to see where the Commission stands on a number of issues

here. First of all, we will come to the FDA issue in a moment. It is an extremely important issue. There are recommendations in here regarding that and we certainly have to deal with it.

But let's deal with the -- what I consider the first part of this at least in terms of our consideration, not necessarily the most important but the first part of this, that is in dealing with whether we are going to have something called equivalence, Larry asked very appropriately whether the Commission wants to leave the option open for the moment that equivalence could be achieved. It may be difficult but it could be achieved.

Whereas, I had suggested that we put equivalence and everything that might flow from that as an aspiration which will be achieved some time in the future. In the meantime in the context of 5.6 we would require both IRB reviews. Both meaning the one in the host country and one here.

I still feel the same way about that. I think we have to deal with the FDA. I am going to come to that in a moment.

But how do people feel about that? Yes?

MS. KRAMER: Could either you or Larry explain how he envisions equivalence? I am assuming he means that there would be opportunity to establish equivalence now.

DR. SHAPIRO: Well -- or sometime.

MS. KRAMER: Well, soon.

DR. SHAPIRO: Yes.

MS. KRAMER: As opposed to aspirational.

DR. SHAPIRO: Well, I do not want to answer for Larry.

MS. KRAMER: No, but I would like to know how he -- what kind of a process he sees moving --

DR. MIIKE: I have no process in mind but I do not want to put it off in the vague just in future. I think we should set some goals.

DR. SHAPIRO: Yes?

PROFESSOR CAPRON: I think we are using the word "equivalence" in two different and confusing senses. Equivalence can now be achieved, as it were, by an individual IRB getting a single project assurance that is only given when it is -- when OHRP decides that, in fact, they are using processes and applying standards that will give protection and an assurance should not be negotiated.

Under 5.3 we are saying if a whole system meets the equivalence standard, which is already in the regulations, the system should be able to be recognized and its components. That is to say an IRB recognized by that system should be treated as though it were a U.S. IRB with that ability.

Then we come to the question, well, once you have that, what flows from it? Under the present

U.S. system what flows is that both U.S. IRBs will look at it. These are totally separate issues. And the fact that the Emory IRB, to go back to my example, is equivalent to the Harvard IRB does not eliminate the need for both of the IRBs to be involved because they both have a stake in what happens.

The researcher from --

DR. MIIKE: But it is not required that both of them -- the one can defer to the other.

PROFESSOR CAPRON: They can defer in effect but there is still the -- Harvard, as an institution is saying, our researchers are involved, we need to pass on that.

There is nothing in 5.6 as originally drafted, as I said a moment ago, that would stop an American IRB that had developed a relationship with an IRB in a developing country to the point that it is confident that that IRB, which has either an SPA or the whole system has qualified it under 5.3, to in effect defer to it but it still requires that the American IRB sign off.

DR. MIIKE: You are saying we do have an equivalency system already. Then what are we aspiring to?

PROFESSOR CAPRON: Well, what we, I think, would recognize in any American IRB is that most of the approval processes they deal with in other

countries are not now equivalent and they need to act as though they are functioning as the only IRB because a lot of the time the approval will come from someone saying, "I am giving ethical approval," and it is the Ministry of Health and the letter will go on, as we know, to say, "And we are so eager to have your support because..."

DR. MIIKE: I suggest that you guys revise -- write your recommendations out and I will respond in writing.

PROFESSOR CAPRON: Excuse me --

DR. MIIKE: We are not going to get anywhere here. I do not think we even agree on what we are talking about.

PROFESSOR CAPRON: We have --

DR. SHAPIRO: Larry?

PROFESSOR CAPRON: Larry, we have 5.6 as drafted as circulated in September. My suggestion was that we stick with that. There is language right here before us. The only question that has arisen this morning is, is the recommendation or the commentary going to be clear that the FDA situation where you have a sponsor that does not usually have a U.S. IRB any different?

DR. MIIKE: (Not at microphone.) Put it in writing and I will respond.

DR. SHAPIRO: Other comments about this issue?

One way of posing this -- we all understand we have to deal with the FDA issue but one way of posing this, as Alex has suggested, do you prefer the original 5.6, which is before us, or the current 5.6 as one way to pose the question. How do people feel about that?

Anybody have any comments about that? Eric?

DR. MESLIN: I just wanted again to remind Commissioners not to beat too much on the proposed 5.6 but among the reasons that staff wanted Commissioners to be aware of some potential domino effects were those situations in which, as is said in subpart A.1 of the proposed 5.6, if the reason for conducting -- of having IRB review or ethics review committee review is to afford research participants the benefit of a review that will concern themselves with protection of those human subjects, those human participants, then in those cases in which research is being conducted wholly in the country and the research participants are being recruited only from that country, then among the reasons that we endorse IRB review in this country is being the protection of human participants, that argument for local review in the U.S. becomes weakened because there are no human participants in the United States for whom the U.S. IRB would be exercising its concern and consideration.

Now there are many other reasons why a U.S.

IRB would and should and should be entitled to review a study when all of the human participants are located in another country. Those reasons may be related to their special expertise that they would provide to the host country's IRB, special ethical considerations that do not have local consideration, but those are -- that is a very different scenario than the Harvard-Emory example where presumably research participants are in both locations and the IRBs in both locations would be entitled to.

PROFESSOR CAPRON: That was not my example. My example was research is being done in Atlanta and a Harvard researcher is going there because that Harvard researcher is an expert on the drug or the organ system or whatever, and the same is true if the research is being done in Nairobi. The Harvard IRB, as we all know, in assessing risk and benefit may have expertise which the Nairobi IRB does not have. It is very routine, as any of us who have sat on IRBs know, to have someone on the IRB say, "You know, there are some problems with the drug interactions here. I do not think this is a -- send it back. I want an explanation of why they are not doing this liver function test that I would expect to see done here because..." blah, blah, blah.

Now one of the things about IRBs is they bring a lot of expertise not just on consent forms and so having the Harvard researcher go down to Emory

and the Harvard IRB says, "Before he goes or she goes, we want to bring our expertise to bear." Now it may be that they will look at it quickly and say, "The Emory IRB has approved this. It looks straight forward. We have no problem. Approved."

DR. SHAPIRO: Steve?

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Alta, you will be next. Steve now.

MR. HOLTZMAN: Just for clarity, there is the situation where the NIH gives money to both Harvard and Emory and the work is conducted at Emory. There is the situation where it is given to Emory and this individual investigator from Harvard comes and participates in the study. I am trying to figure out what is the triggering event --

PROFESSOR CAPRON: What you need is a subcontract there and you have to file as part of your NIH application a subapplication that looks just the same in effect, and it has the same check off box, are human subjects involved, has the IRB approved it.

MR. HOLTZMAN: So if the NIH makes a direct grant to Professor X at the Karolinska, right, is there any U.S. IRB involved at all?

PROFESSOR CAPRON: I do not think so.

MR. HOLTZMAN: Okay.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I think that part of what is making this even more complex is that the rules that currently govern, that are in our minds, do not consistently bind researchers to go to their own institution's IRB at all. Some institutions currently have MPAs that say their investigators have to go through the local institution regardless of funding source and others do not. And so the Harvard and Emory examples become complicated because they could -- the answer could vary depending on the MPAs.

We are now writing on a fresh slate in the context of the oversight report coupled with this one and I find myself wondering if there is something that is kind of in between Harold's suggestion and Larry's suggestion. And that is that we start by going back to something close to the original suggestion that U.S. IRBs have to review the data if it is somebody who is already subject to U.S. regulations and the analogy for FDA stuff would be that a U.S. IRB has to have looked at it to have a kind of guaranteed safe harbor for receipt of the data at FDA and use of the data by FDA.

Next we ask that OHRP actually issue a set of criteria by which the national systems and also the individual IRBs or research committees within a system can be evaluated as substantially equivalent or not. And we recognize that because that has not happened, it is aspirational.

We also ask that FDA collaborate with OHRP to have an identical set of criteria so that we do not have different criteria within the Federal Government but one set of criteria on this point.

And then finally we say, "At the time that such criteria have been created and adopted throughout the Federal Government then U.S. IRBs will be permitted to defer to an IRB -- to a research committee in another country that meets all of the relevant criteria." And in other settings where we are talking about the FDA receipt of data, data that is generated in studies that were reviewed only by the foreign review committees can be accepted if those committees met all of the criteria that have been outlined. And in that sense we kind of cover ourselves for the near future and set out a plan for how to handle it in the longer term future.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I would agree with Alex to go back to the original 5.6 that is on this thing as striked out. I just think it is getting so complicated that we are losing sight of what it is we are originally trying to do and I think if what we want to do is say a host country ought to have -- an IRB in the host country ought to be able to -- ought to review this type of research in addition to a U.S. IRB that is now currently in place, then we should say that.

What we are now seeming to talk about, what situations can we take away the U.S. IRB review either because it is not now required in the situations that Steve was alluding to or way off in the future we are going to have this equivalence and certification of host country IRBs.

I just think, you know, as Peter Lurie's suggestion yesterday, that sort of sends the wrong message. That if right now what is protecting subjects in many international studies is the U.S. IRB to talk about taking that away at the current time I think is heading in the wrong direction.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Alta? Excuse me. Bette is first. Alta, just --

PROFESSOR CHARO: Uh-huh.

DR. SHAPIRO: Okay. Bette has ceded three minutes of her time to you, Alta.

PROFESSOR CHARO: Thank you, Bette.

Bernie, I do not disagree with what you have said because I completely agree with you that a strong statement needs to be made that however we do -- however anybody does the substantial equivalency criteria that the first and most important thing is do they protect human beings.

But the second thing that I do not want to lose sight of is that we have heard immense amounts of testimony about the bureaucratic complications of

doing work across national borders and in many areas about how this actually has served to delay or plague very important research that we would like to promote.

I want to see if it is possible to have the facilitation of research, the simplification of the bureaucracy kept as a strong second priority after the human subject protection and not have it lost completely from our discussion and our focus.

DR. SHAPIRO: Bette, do you want to say anything right now?

Bernie?

DR. LO: No. I agree with that, Alta. I would just sort of want that to be laid out that we can do that without removing the requirement for U.S. IRB approval. We are saying that the U.S. IRBs (a) have to be more mindful of what is actually happening in international research and conditions in the host country and (b) get a lot more efficient. And, also, we are saying we have got to cut back on the xeroxing back and forth but that can all be done still having U.S. IRB at the current time look at what is going on.

We want them to do that for research conducted in the U.S. as well, you know, become more efficient and less paperwork.

DR. SHAPIRO: Okay. We have a lot to accomplish this morning and although we could talk

about this for a long time, we have to really decide, not on the exact wording because we can come back and review that, but whether or not we are going to -- again putting -- we have to come back and address what we want to ask the FDA. Let's put that temporarily aside for the moment. Whether we really want to insist for now that we really want what I would call -- just to say the original 5.6 versus the current 5.6 and decide which way the Commission wants to go for the moment.

Either way, we are going to have to have a section of the report that deals with various long-term aspirations and what we hope we might achieve going down in the future dealing with issues of efficiency, red tape and so on as Jim said a little while ago.

And so let me just pose it starkly that way without worrying exactly words. It is not a vote. I just need a sense of where we are so we can go on and discuss other aspects of this.

How many Commissioners would prefer we stick close to the original 5.6 which is before you now? Raise your hands.

(A show of hands.)

DR. SHAPIRO: Seven. How many would prefer something quite different?

(A show of hands.)

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I am still flipping pages over here trying to make sure I have got the right one in front of me.

DR. SHAPIRO: Well, it is not a decisive -- you are not the last vote here --

PROFESSOR CHARO: Put me down as abstaining so that you can move on.

DR. SHAPIRO: Yes, Arturo?

DR. BRITO: I am in favor of keeping the original 5.6 but the only thing that I heard that makes me a little uncomfortable with that, and I would like some clarification, and I know we are going to get to this but it will help me make a firm decision, is if we keep the original 5.6 is there still room for the new 5.7 or something similar to it? There is.

DR. SHAPIRO: Yes.

DR. BRITO: So there is not going to be any difficulty with modification?

DR. SHAPIRO: Right.

DR. BRITO: Okay.

DR. SHAPIRO: We have got to face the FDA issue. Okay.

Yes, Larry?

DR. MIIKE: Just for clarification.

DR. SHAPIRO: Yes.

DR. MIIKE: Then we are keeping 5.3 as the old and not the new?

DR. SHAPIRO: I have to go back and read 5.3 before I answer that directly. There are dominos that affect this.

DR. MIIKE: Because if we keep the old 5.3 and the old 5.6 they do not -- they contradict each other.

DR. SHAPIRO: Yes. We do -- as I said before, there are domino effects here with how this goes. I have to go back and read it more carefully because I can answer your question.

Eric, do you want to now deal with --

Bette, I am sorry.

MS. KRAMER: I did not vote because I do -- I favor keeping the old 5.6 except that I would like to see the encouragement -- I would like to see encouragement to the development of IRBs in the local countries encouraged other than waiting for it to be captured in a lot of language that is going to come later that is going to be aspirational about a myriad of things.

DR. SHAPIRO: Well, there is a whole host of recommendations in this report regarding improving the capacity of local IRBs and so on.

MS. KRAMER: Right.

DR. SHAPIRO: That is in a lot of different places.

MS. KRAMER: Okay. But we heard so much testimony about the difficulties involved in not

working with a local IRB that I think it would be a shame if we did not capture some of that in this place.

DR. SHAPIRO: We will do our best. We will do our best to do that.

Steve?

MR. HOLTZMAN: I think we all agree that the gist of where we were coming from on this was we are not trying to erode protections. We are trying to address the fact that there are bureaucratic nightmares and that there are, however achieved, equivalent protections. We should try to get rid of more bureaucracy. I think that was the motivation behind all of this.

When I look at 5.6 as currently written or the -- not currently, the September 29th, 2000, as currently written, okay, it will need to be reworked because I am not sure what is said by subject to U.S. research regulations. Aside from the FDA case, all right, there is also my Karolinska case.

I think that is subject -- I think it has got to now make reference to -- unless we are now saying there should be an additional IRB review where one does not currently exist, then we need to make clear, which would be a result from trying to get away from bureaucracy -- we need to make clear that which specifically. I think it is those sponsored by U.S. Government institutions that we are making a

reference to here, which -- and involving U.S. investigators.

DR. SHAPIRO: Okay.

Eric, would you prefer we -- we have a number of issues to straighten out here and we cannot straighten them all out here this morning but would you prefer that we take a rest from this particular issue because we are going to have to gather together some thoughts about just how to change 5.3 and 5.7 and so on that is consistent with this, and we go to consider -- just jump back. This is incomplete. We have not completed our discussions here, understand that, but jump back to 4.1 and let's have some equivalent kind of discussion on 4.1 and see where we come out on that issue, and then we will take a break and see how we can best reorganize all this.

PROFESSOR CAPRON: Our discussion of 4.1 will not, I hope, be equivalent to our discussion of this issue.

(Laughter.)

DR. SHAPIRO: 4.1 deals with the issue of post trial benefits, both in the successful and unsuccessful trial. I think everyone has read Larry's e-mail on this and, indeed, a lot of people have supported the sentiment Larry had. At least some of the e-mail I saw was very supportive of Larry's view. So why don't we just turn to Larry first and see what his view is on this matter.

DR. MIIKE: Okay. First of all, I support the old 4.1 and not the revised, and here is my reasoning: If you remember when we started this project we felt compelled to say that it was not an undue inducement to provide effective therapy as part of a trial because we were worried about the inducement effort in these countries.

Then on another issue we got into what kind of trials do we think were ethical to conduct in these countries, and we came to the conclusion that trials on therapies that were relevant to that country's needs.

From that we move on to say if it is relevant to the country's needs, what reasonable efforts need to be made to make sure it was actually provided once the trials were successful.

And from that we came to the conclusion that, well, at least for the trial participants if a therapy was effective, for some reasonable time post-trial it should be provided to them.

And then all of a sudden we come to this position in the revised recommendations, which I supported by the way all of those, then we come to the revised recommendations and I was not in on the telephone discussion that led to this, is that somehow the new recommendation says that even if the trial is unsuccessful that the control therapy -- the control group therapy should be provided not only to

the controls but to those who had been on the experimental drug. So all of a sudden, it has become a guarantee that if you get into these trials you are going to get treatment, whether or not there is a successful outcome or not.

And I objected to that on the basis primarily of who would resist wanting not -- who would resist being enrolled in these trials? That is the classical case of undue inducement.

I sympathize with trying to continue on in some way treatment for which patients who truly volunteered to participate in these trials get that but I think it sort of is stretching the point to get to saying -- from going from saying if we have a successful therapy because of the derivative issue about it is needed in a country and reasonably should be made available or at least should be made available to trial participants. It is a stretch to then say even if it was unsuccessful they should have a treatment that is really not a new drug but a therapy that is not available in the country.

DR. SHAPIRO: Yes, thank you. And Larry has made that point and made it very effectively right now, and there -- also, I do want to point out that Alta has provided some material which does not speak directly to this point but I just want people to be conscious of it because it contains some language whether or not we drop that part of the

recommendation, which I think actually is useful and clarifies things, but it is not directly related to the issue we are discussing now, namely are there any additional benefits that we want to insist on following -- in the case of an unsuccessful trial, which is what Larry has pointed to now.

So I would just like to get Commissioners' opinions.

Jim?

DR. CHILDRESS: I share a lot of Larry's concern here, and if we ask what our fundamental sort of moral concern here is, it seems to me that we not make the participants in the trial -- and this may create a problem also for the control group -- worse off after the trial. That is we have an obligation to them during and after the trial, in effect, not to make them worse off.

If -- and as Bernie has pointed out in one of his e-mails, there are so many situations, though, that we would have to think through if we were trying to be -- develop a position here that would really take account of everything, we would have to spell out a variety of situations where -- obviously in some cases the -- what is provided in the trial itself is one time only and nothing is needed afterwards. Then there will be situations where you have to continue treatment over time and so forth.

So it is difficult probably to capture

everything we want in a single recommendation but if this is our major concern that the participants, in effect, not end up worse off as a result of participating in the trial, that they have access to what is needed after the trial to continue any benefits that they were gaining during the trial, that I think points us in a direction that may be -- we may be able to gain consensus on.

But it may also have more implications for the control group than Larry has admitted because they may well be in the same kind of position. They are receiving something as -- in the control group they would not otherwise have received and it has benefited them, and that may need to be continued as well.

DR. SHAPIRO: Other comments or questions on this particular issue, or other aspects of 4.1?

Steve?

MR. HOLTZMAN: Eric and Alice can help out here. It seems to me there were a lot of public comments about that the paradigm in mind here is the pivotal trial but what are we really referring to because trials go on for years with all different studies. Which group are we referring to? And I do not know -- I was not a participant in the last meeting -- whether this was discussed and how are we -- what do we intend when we say this?

DR. MESLIN: I think you summarized what the

public comments had said and there are really two points that I think came out quite loud and clear. One was whether the Commission either should define what it means by successful or leave this as aspirational because this is not, you know, a biostatistics or a clinical epidemiology Commission. It is a bioethics Commission. So it is a statement of what it would hope would be the case and leaving the definition of what counts as success to others was a very prominent theme in the comments.

The other type of comment that led to staff wanting you to at least consider this, whether you adopt it or not, of course, is up to you. It did not flow from any conversation at the meeting. It really came from the public comments. Was that it was -- there was an asymmetry in the recommendation. If we are not going to -- if we are defining successful, however poorly, and what happens to folks afterwards then we better say something about what happens to folks in unsuccessful or in trials that do not provide that kind of information.

So those are the two reasons for you seeing it like it is. I do think that Alta had made some suggestions for what 4.1 would look like, which are less say dramatic but that was in her e-mail that was circulated.

PROFESSOR CHARO: I just have a logistical point, please.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I apologize but I actually have those things that I sent out only on my home computer and I am sitting in my office. If there is anybody there that happens to have e-mail capacity that can re-e-mail them to me, it would be great because I cannot follow the discussion concerning the things I said a week ago.

(Laughter.)

DR. MESLIN: We cannot e-mail but we can probably fax it to you.

PROFESSOR CHARO: That would be terrific. Thank you.

DR. MESLIN: In the time that it takes I could read you what you said.

PROFESSOR CHARO: No, no, no, do not take the time for everybody. It is okay.

DR. SHAPIRO: Alex?

MR. HOLTZMAN: I thought the --

PROFESSOR CAPRON: Go ahead, Steve.

MR. HOLTZMAN: If I can finish this.

DR. SHAPIRO: Yes.

MR. HOLTZMAN: But the comment was not just about what is successful versus nonsuccessful. It was also making the point that someone participates in a Phase 2A dose ranging study. It is now four years later, all right, and the trial proved successful or unsuccessful. What are your

obligations to that person who participated in the dose ranging 2A four years ago, during that four year pendency of the continuation of the trial and after the trial? There were a series of comments about that.

I am not saying -- well, I am just asking a question. What do we intend and that is what they were asking.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: You know, my -- we do not have the text in front of us. We have just the recommendations. And so I may totally misremember not only our discussions about it but also the text. But my recollection, Mr. Chairman, that this was a point of particular interest to you and that the argument that we are getting into now does not quite capture what was involved. It was not a sense of obligation because you had made a contribution.

It was a sense of obligation because you were now receiving a benefit, which if ended the day the research ended would -- although it put you back in the position you were in before the research -- would appear to have put you in a worse position and would appear to have walked away from an obligation that the researcher qua physician has taken on for your care.

And so the notion of successful here is not in the drug has been proven to be so successful that

with this trial the dramatic evidence is available to immediately get licensing or get approval or to establish to the world through New England Journal article that we have found the cure for whatever or the treatment for whatever.

It was simply people are now -- perceive themselves to be receiving some benefit, i.e. it is working. And when it is not successful they will not be perceiving that they are getting that benefit.

If, to flip it around, we got to the question, well, what about the placebo group, there it got to be a sense, well, if their neighbors are all getting better taking that and it is -- the code is broken and you now see they were not getting better because they were taking the placebo, within that group, which we imagine being people who are having contact with each other and know each other, you know, may know that they are all in the trials, it would be seen as an unfairness not to bring them to an equivalent position for a period of time.

This, as I recall, was -- so it -- all of the issues that come up about, well, what happens when it is -- what do we mean by successful or if you are at Phase 2 and it is only years later, really were not germane to what we were struggling with here and maybe the difficulty that we are having is an indication that what we were struggling with, there is no solution to on a regulatory basis and we have

to simply rely -- one would have to rely on the good sense and good will and decency of the people involved to say that if people are doing dramatically better with a drug you do not cut them off the day you end the trial. You figure out how to take care of them and you figure out how to be fair to the people who are getting the placebo and you do not do this through some elaborate regulation.

I mean, maybe that is the answer that this is just that we are dealing with something for which uniform rules and language cannot fully capture but I think that was what we were dealing with.

DR. SHAPIRO: That was certainly my own motivation here and I still feel pretty strongly about it, although I recognize these difficulties that you raise. And what particularly convinced me of this was I could not imagine an informed consent process that would deal with these issues because it is in my mind not possible for someone to imagine what it is like to be better and then worse again, and that is -- have an existential almost issue which is very hard to capture or, if not, impossible to capture in an informed consent process and I wanted to do something -- I mean, Alex explained -- I do not want to -- that was my motivation for this.

There are a lot of practical difficulties here. I mean, I understand. And when I was thinking about it just to answer your question about the four

years ago person, I really was not thinking of them at all. That was not the population I had in mind. I understand that it takes not only Phase 1, Phase 2 and Phase 3 but many Phase 3 trials and how do you know when the tipping point comes and you say, yes, we are there. It is -- all those difficulties I do not know how to resolve.

Steve?

MR. HOLTZMAN: So, Alex --

DR. SHAPIRO: Steve, then Bette and then Bernie.

MR. HOLTZMAN: I do not disagree with anything you said, Alex, and I think the conclusion you came to probably is where I end up, which is you cannot -- the problem with the way we wrote it, it gets you into all of these difficulties where someone says I want to comply with -- I want to comply with the spirit of this or I am going to get hammered because the letter is very unclear. And I think we just need to try to deal with it. That is -- and that is what I took to be the spirit of the public comments is I hear you NBAC, I agree with the spirit of it, what do I do with that person in that Phase 2 dose ranging who is not on the treatment anymore, all right, where you know they are feeling better, Alex, but do I give it to them for the next three years. It is not a matter of cost. I could. I am not sure medically it is ethical to do that until I have more

results.

DR. SHAPIRO: We try to deal with that issue by language in this recommendation which really leaves all these details for a matter of discussion. That is how we try -- I am not saying that is the best way to do it or the most effective but that was the way this was tried, you know, attempted to handle it here.

Bette?

MS. KRAMER: If I am understanding the argument properly then there never is a stopping point because at whatever point you stop you would again be making them less well off than they were. So it is really a question of continuing them on indefinitely.

DR. SHAPIRO: Well, I think one can make that argument. My own view is I recognize that that, you know, is just not the -- that cannot happen, was why I left it for some time, and maybe during that period of time, you know, people can -- you can deal with the issues but I understand that. You could easily argue it. You can go on forever. I understand that argument. I just did not myself think that we could require that or should absolutely require it but I certainly understand the argument.

Bernie, and then Larry, and then Alex and Trish.

DR. LO: Yes, I want to try and pick up on

the line of thought that Steve and Alex and you have. It seems to me there is a clear case that we start with and we end up with a recommendation that covers a whole lot else and I agree that the clear case is the pivotal Phase 3 clinical trial that shows a dramatic clinical result that is clinically statistically significant and there we say it would be unconscionable to sort of say to someone we prove this drug works, you did better on it, and now we are going to stop you because the trial is over.

As we get away from that situation things get murky for all the reasons you have said and then I think we are using doing better in a very ambiguous sense. You can be doing better in the sense that it is proven in a clinical trial that a population of patients like you with that intervention does better than the population with some other intervention.

That is very different than my saying I feel better or I personally did better with your intervention that it may well be the case that it is an unsuccessful trial and yet I had a clinical response as an individual. And I am not sure how to play out Jim's moral principle that you should not leave people worse off than what they were during the trial. I mean, Jim sort of -- I mean, up to -- before we got together on this the argument was you could not make people worse off during or after the trial than anywhere before the trial. Now we are

saying you cannot make people worse off after the trial than they were during the trial if I sort of can extend the line of thought that Jim was very helpfully proposing.

But then I think we need to be very clear what doing better or doing worse means and I think that if it is a subjective clinical response or if it is an objective individual clinical response that is different than a statistical response. And if it is a subjective response I am feeling better even though there is no objective way of measuring that, it leads us yet to another scope of things so this is really complicated.

DR. SHAPIRO: Larry?

DR. MIIKE: Just a clarifying point. When Alex was talking about this, he mentioned the word "regulations." I never have assumed that our recommendations in this area would be in the form of regulations. These are exhortations to people involved, the sponsors and others, to provides these kinds of benefits, whatever we recommend, but I have never heard us say that it would be mandatory.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: Well, I am wondering whether part of the hang up here, and it exists also in Alta's language, is that word "successful" and another part of the hang up is just to make clear, and I accept Larry's comment that this is an

exhortation, but the extent to which the exhortation is towards a decent and good faith process rather than any one universally specified result.

I wonder if what we could talk about is "arrangements should be negotiated to continue to provide those interventions that provided subjects with apparent benefits" and the language that we have that the question would be, Bette, the duration, extent and financing of this obligation. And certainly one aspect that would be an endpoint towards it would be when the research intervention has been approved and becomes accessible. We deal elsewhere with accessibility in the host country more generally and whatever obligations might arise there.

But the idea was certainly this cannot be from most sponsors, including the U.S. Government, a life time commitment to provide any particular set of interventions. But rather than getting into the details of, well, if it works, you give the placebo group what the active group were receiving and if it does not work you give the active group -- just speak in more general terms of those interventions that provide an apparent benefit because that is really what we are talking about. Not walking away when someone is apparently doing well with your intervention and just saying January 1st the trial ends and you are back to wherever you were. We just wash our hands of you.

I mean, that is, Larry, to use your word, that is what the exhortation is. Do not do that. Figure out, work with them, and I do not know what this does for your -- the issue of undue inducement. I mean, we have already heard that for some people just participating in the trial, and this is not true just internationally, it is true for uninsured people in the United States, it may be their only hope of getting any medical attention. And, you know, yes, at some level that is an inducement that is very hard to walk away from when you are sick and you have no other prospect.

Whether the notion that if it worked we are going to continue to do it beyond the end of the trial is over reaching. I do not know that that makes that much difference to me frankly in evaluating that argument.

DR. SHAPIRO: Carol? Trish, excuse me. Trish is first and then Carol.

Trish?

PROFESSOR BACKLAR: I can wait.

DR. SHAPIRO: Thank you.

Carol?

DR. GREIDER: I recall there was a lot of discussion about these different issues when we had the phone conversation just before Thanksgiving and it seems like there is sort of a continuum of language with the language that we had in the

original 4.1 and even the modified 4.1 being more directive and then there is a continuum of language that goes down to more aspirational kind of language.

And I think that we all have an idea about the spirit of what we would like to say but how do we capture that spirit in the language? And I apologize that I do not have it before me but I know we had a long discussion on that teleconference about some more aspirational language, which I think sort of grew out of some comments that came from the NIH on this specific recommendation. And so perhaps if we could get back to a little bit more aspirational language that would put us, you know, in more of a compromised sort of position.

DR. SHAPIRO: Arturo?

DR. BRITO: There are two main issues here. One is the pragmatic part and the other one is Larry's points about undue inducement or therapeutic misconception, however you want to word it.

For the first one I was convinced by arguments by the NIH's responses and others that we are very concerned about promising too much for an indefinite amount of time may actually -- well, it would be very impractical and would also create a situation where you may have less research that is needed in developing countries going on. I really favor -- and I encourage others to look, and I have it in front of me because I brought it knowing we

were going to be talking about this recommendation, some of the NIH's suggestions so I favor language in that order where you are talking about negotiations that precede negotiations between the two countries, the host country and the sponsoring country.

And if we are really talking about collaborations and what we are trying to aspire to here between the countries is, I think, the negotiation part is important to have an understanding and make a decision between the countries what is and what is not expected. And I am not sure promising too much to all the participants is what we want to achieve here but I favor more the language on the order of what they recommended.

On the second issue about undue inducement I -- you know, one of the ways that -- I am not sure it is going to create more -- make it more complex or not is what we are really talking about here is sponsor -- the U.S. sponsored trials in developing countries of subpopulations within that country that are vulnerable basically.

Why is it that we concentrate only on the participants in the trial? Why is it that the subpopulations is not what we are concerned about? And this may help take away from undue inducement.

For instance, if you sponsor in a developing country the certain subpopulation of that country, maybe the negotiations should talk about the

provision of what becomes effective or what is proven to be a treatment that works basically, medication or something that works to a certain segment of that subpopulation, whether or not they participated because then this takes away from the idea that if you participate, well, you are going to get life long treatment or treatment for the next five years and this makes it a little bit more equitable but it has to be very clear.

And so those are two suggestions I would have and I just really encourage others to go back and look at NIH's suggestions and their explanations leading to that.

DR. SHAPIRO: Trish, and then Carol, and then we are going to break.

PROFESSOR BACKLAR: This is not just a problem in international research. This is a problem also in this country and I am not at all certain that we have addressed this adequately in our oversight report.

I think that it is exceedingly important. I am not going to be able to give you an idea of how precisely we should do it but there is some issue here in which we are using people to benefit others but if they benefit themselves and we abruptly stop whatever treatment has been working for them, in a sense one has abandoned them, and in truth they have been guinea pigs.

So, I mean, I go back to what Jim said about not making people worse off and there is this element of abandonment and we certainly have many cases in this country where we know where people did benefit during a research protocol and were abruptly terminated and became exceedingly ill afterwards.

So it is very important and one should not be put off by the obligations implicit in this. That is all.

DR. SHAPIRO: Carol?

DR. GREIDER: I was just going to request either Arturo or Eric read the actual language for the recommendation that both you and I thought was a reasonable kind of a language from that NIH -- either you or I think Eric might have it, whichever.

DR. BRITO: Okay. The recommendation for 4.1 is that research proposals submitted for research to ethics committee approval should include, and they have three points here, a description of the process by which investigators, study sponsors, host country authorities, international assistance organizations, representatives of prospective research participants' communities, and other relevant parties have negotiated the conditions under which the research will proceed.

The second point: Plans for ongoing negotiations and arrangements for provision of any research intervention that was proven effective to

all participants at the conclusion of the trial, where applicable.

And, third, other important interventions that will be provided to the participants during the research if these participants would not otherwise have access to equivalent interventions.

DR. SHAPIRO: Bernie, and then we are going to break.

DR. LO: I agree. I like that language better but it seems to me what it leaves out is the aspirational component that Jim and Alex and others have pointed to. It does not say you ought to do your best to provide a benefit that is proven decisively in a pivotal clinical trial after the trial so you do not cut people off after you prove that what you give them works not just for them but for, you know, a whole generalizable population of patients.

I mean that notion -- I think Alex said -- of somehow doing your best, doing the honest, decent thing under reasonable constraints is missing in the NIH procedural description and that is, I think, the insight that Jim was sort of, you know, pushing us towards.

DR. SHAPIRO: Let me just ask one subquestion before we break, and that is to go back to Larry's initial point here and the point he made also in the e-mail communication, that is the

distinction between successful and unsuccessful trials.

Alex had suggested -- I do not think suggested but at least was speculating about language that went to apparent benefit, which would not distinguish between the control group and other groups. It is just anyone who received an apparent benefit would create some apparent obligation.

Larry was suggesting on the other hand that we do sustain a distinction and he seemed to think it is fair to say happy to go along with this, however phrased, for the successful trial but did not think it was appropriate -- if I am getting you correctly, Larry -- in the unsuccessful trial.

And I just wondered if there is any comments on that particular issue, that is creating or maintaining this asymmetry between the successful and unsuccessful trial. If anyone wants to have any comment on that, that would be helpful as we redraft this.

Carol?

DR. GREIDER: I agree strongly with what Larry said. The encroachment of the language to include providing something for people in an unsuccessful trial I did not agree with when we had the conversation.

DR. SHAPIRO: Other comments on that? Alex?

PROFESSOR CAPRON: Well, I just wanted to

make clear what I was trying to do was two part. It was moving away from this notion of successful, which I think gets us into the morass that Eric described as we are not a biostatistics Commission and we are not setting up a definition of what p value proves that something has been successful. And went back to the underlying interaction with the subjects, whether they could be control or active. And that is you are doing something, you have made them better off, when the trial ends do you continue to do something or do you stop.

And that gets away from a statistical proof of success to the perceived benefit to the subject and on that basis it would be hard to distinguish the placebo from the others because you maybe have made the placebo off because your interventions actually help them as well. That is what I was saying.

DR. SHAPIRO: Steve and Larry?

MR. HOLTZMAN: I think we need to remember what Bernie said and try to think through the implications is that I can have a drug which fails and is not successful in the population but worked in you in the trial. All right. What is the obligation that is being assumed?

I think it strikes at the heart of Jim's observation. If we -- on the question that arose that if we move the obligation to making you no worse off than you were in the trial, taken literally there

would be an obligation to provide the drug which was not approved if it worked in that individual.

DR. SHAPIRO: Larry and then Bette?

DR. MIIKE: A couple of things. One is that on the issue of successful versus unsuccessful. I think that is a clearer distinction to be made than getting into the morass of who benefits from any of this research. That is my opinion.

The other point is that what Arturo had mentioned about reminding us that, you know, really this started off as we want experimental trials of drugs relevant to the country's population, and we talked about providing it to subpopulations, et cetera.

I think we only reached a compromised position with the actual trial participants because it seemed like it was within the realm of practical financial possibility and it seemed like since they were the ones most at risk that that is the one we focused on.

But I think that what Arturo said makes more sense to me in the sense that the negotiations can go and say that if this is a trial for a particular disease within the subpopulation. What kinds of reasonable negotiations can go on for providing that to all of them? That would take away the undue inducement part, I think, for the most part.

PROFESSOR CAPRON: Are we eliminating 4.2?

DR. SHAPIRO: No.

PROFESSOR CAPRON: 4.2, that is exactly what 4.2 is about.

DR. BRITO: I know that. I was just saying that that is things that we are already -- we are covering and that it makes sense and then let's not forget that that is also part of our recommendations.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: You know, listening to Arturo and Larry gave me an idea that may be worth thinking about during the break to figure out if it has any merit. We are all caught up here about the fact that we are talking about continuation of access immediately after the trial's conclusion and that is a point in time that we all understand. It does not necessarily mark a time in which we understand what the situation is with the intervention.

Is it possible that as an alternative we might be -- we might want to recommend the following: The trial ends and there has to be some responsible way for people to be weaned off of whatever they have been on, on trial, which would be the case here in the United States as well. No difference.

But that if the intervention is subsequently at any time in the future introduced into the country, in other words after everything has gone on in, you know, multiple trials, multiple countries, et cetera, if the intervention ever is now going to be

made available in that country that people that participated in a trial in that country ought to be given some special consideration in order to ensure access when and if the intervention is, in fact, introduced country-wide because the people who participated in the trial may very well be distant from centers of distribution. They may be too poor to purchase it at the price at which it is going to be sold in that country.

And it may be that a way we can think about our obligations to trial participants is not immediate access at the conclusion of their participation but when something really has been "successful" enough that you are going to start marketing it or doing it in a country, that they not be shut out after they have been used to, in fact, develop the very thing that is now being introduced.

DR. SHAPIRO: Okay. We are going to take a break. I just want to say, Alta, I have had that exact discussion on this issue precisely as you raised it with a number of people running trials, and when I suggested precisely your suggestion their main response was it would be a logistical nightmare, that they do not know how to keep track, they do not know how to find and it sets up something which at least -- I have no independent view of this but I was told it would be logistically -- however attractive in principle, it would logistically be almost

impossible. That is what I was told but again I am just repeating secondhand information.

Let's -- we have to think over a number of these things so let's take a break for about 15 minutes.

(Whereupon, a break was taken.)

DR. SHAPIRO: I would like now to -- let me just inform you. We are going to try to distribute on the basis -- I have asked Eric and Alex and Bernie to work as a small group to redraft some of the material circulating around 4.1, 5.6, 5.3 and so on, reflecting some of the comments that have been made here this morning. So I do not want to turn to that now.

We have a rather brief time left this morning and I want to just begin with going through the various recommendations we have here, beginning at Chapter 1 to see -- we need not discuss any particular one in detail but I want to just go through them to see if you are satisfied or have additional comments and questions about any of them.

Presumably Eric will be back here in a moment.

I am just going to go from Chapter 1 through and we will see how far we get because we might as well put some of this -- perhaps some of this behind us.

So let's look at Recommendation 1.1. I am

not going to try in any way to describe it. I think it is fair to say that the changes that are indicated here, that is both the materials crossed out and the part that is underlined, is directly responsive to the issues that were brought up during our teleconference or our conference call, I guess, is a better way to describe it but let me see if there is any further reactions at this time.

Yes, Arturo, and then Alex.

DR. BRITO: I have one suggestion for a change and it was changed from "industrialized country" to "developed." I am not sure why we are not including sponsoring country there as a descriptive.

DR. SHAPIRO: Direct me to the line. I am not focusing on it directly. Where is it?

DR. BRITO: You know what? We are -- never mind. We are on 1.1.

DR. SHAPIRO: Yes. Okay. All right. I thought -- I do not have to go to the eye doctor again anyway.

Alex?

PROFESSOR CAPRON: Since I think we are at the point of, as you have said, sort of putting it to bed, I wanted to get all the language right, and I believe under "C" we should add the word "that" after "harm."

DR. SHAPIRO: Right.

PROFESSOR CAPRON: "Risks of harm that are reasonable in relationship" to make it parallel to the other points.

DR. SHAPIRO: Correct. Thank you.

Any other comments on 1.1?

Eric, we are just going to go through these one by one. We are on 1.1.

DR. MESLIN: We have not done the title yet.

DR. SHAPIRO: No, we will go back.

Anything else on 1.1.

You have also some recommendations which I had ignored a moment ago on the title. You have two proposals up there. I guess the question is what the Commissioners prefer.

PROFESSOR CAPRON: We also have one from Trish which Diane had come out in favor of. Ethical and policy issues in international research: Clinical trials in developing countries.

And in addition to Diane, I would say that I think that is a good title.

DR. SHAPIRO: Do you want to read that again since I do not have that in front of me?

PROFESSOR CAPRON: Ethical and policy issues in international research: Clinical trials in developing countries.

DR. SHAPIRO: Is that satisfactory? Carol, do you like it? Does anyone have any objections to that title?

Bette, remember you have to shout if you want to speak.

MS. KRAMER: I am saving up my voice.

DR. SHAPIRO: All right. Okay. Let's just go -- Arturo, I am sorry.

DR. BRITO: Well, just to -- I had a previous objection to this but it does not sound like it is in a majority view so I will refrain but I just want to say I worry about the word "developing" in a title just because I think it is going to put some people off and it is almost a little bit -- even though I understand what we mean and we all understand what this means, it is just -- it comes off a little condescending honestly but that is my interpretation and that is the last I will say of that.

DR. SHAPIRO: Thank you. Let's then go on to Recommendation 1.2.

Eric, do you want to just outline the various options that are suggested here?

DR. MESLIN: I think what we presented in the first red line, three different versions, we just wanted to be as clear as possible that when you were considering to whom this applies. I mean, we think that the first one is the one that is most clear, "that are subject to U.S. regulations."

The second recommendation flowed from a discussion that Commissioners have had. Many

Commissioners have not supported the adding of context and expected level of health care in the recommendation.

I should direct you to Alta's e-mail which makes several -- Alta, are you still there?

PROFESSOR CHARO: I am, indeed.

DR. MESLIN: Yes, okay. Which makes a suggestion for reformatting -- reorganizing the recommendation because she had mentioned the issue of FDA data acceptance.

And, Alta, did we give it back to you? Do you have yours?

PROFESSOR CHARO: I do. Thank you very much.

DR. MESLIN: Okay. So I think there are just two issues to address. One is whether Commissioners still do not want to include any responsiveness to health needs should be considered in the context of the expected level of health care in the host country, that sentence, and the following sentence, whether you want that or not.

And as a matter of interest, Diane, who had initially suggested it in her recent e-mail, has said she does not want to include it if that helps you.

And the second issue is whether something like the revision by saying "that are subject to U.S. regulations" should be included.

And the third issue is whether you like

Alta's additional reformulation, including her suggestion about the FDA.

DR. SHAPIRO: Carol?

DR. GREIDER: I would just like to endorse Alta's reformulation of 1.2. I think that reads very clearly.

DR. SHAPIRO: Other comments?

Thank you.

Trish?

PROFESSOR BACKLAR: I also did not like the adding "responsiveness."

PROFESSOR CHARO: I am sorry, Trish. I am having trouble hearing you.

PROFESSOR BACKLAR: I did not want to add "responsiveness" to health needs should be considered in the context, et cetera.

DR. SHAPIRO: It is the last four lines of the option under 1.2. Is that clear, Alta?

PROFESSOR CHARO: Thank you. Hand up.

DR. SHAPIRO: Yes.

PROFESSOR CHARO: I was wondering if there is a way to amend -- I am going to look at my own version but it would be equally applicable to whichever one we ultimately choose -- to amend the phrase "responsive to the health needs of a country" in a way that might answer Diane's concerns, and that would be to say "responsive to the health service delivery needs of a country" because then we are not

talking the intrinsic disease burden. When you talk about health service delivery you are necessarily talking about the interplay between disease burden and all the logistical aspects of providing care.

DR. SHAPIRO: Does everyone understand Alta's suggestion in this respect? Does anyone not understand it? Well, you understand it.

Let me say a word about this since I do not want to reinsert Diane's suggestion. She now has withdrawn it. Although I thought it was a good idea at the time. I will let that go for now.

My main concern was that responsiveness to the health needs be interpreted as something that was within the reality of achievement over the next reasonable horizon so that if you attack a problem that is responsive to the health needs but there is no probability that that will ever actually have any impact in the next two decades, it strikes me not within the spirit of what we are thinking about.

And I do not know if Alta's suggestion right now really satisfies that. I would be satisfied with it because at least it reminds me that that is an issue and it is two words instead of the three lines. And but that was the motivation why I supported that originally but maybe there is other views of this.

Larry, and then Bette.

DR. MIIKE: I just wanted to get back to Alta's suggestion on the FDA. It seems to have been

accepted.

DR. SHAPIRO: Yes.

DR. MIIKE: I think we need to discuss that one a little bit more. It asks the FDA to take on a totally different role in the approval process.

DR. SHAPIRO: Okay. Let's come back to the FDA issue. I agree it is very important.

Steve, I apologize. I had your name on here before and I just missed it.

Who else? Bernie?

MR. HOLTZMAN: Yes. Before going -- I would like to get clearer where we are. There is two different -- very different issues at stake, right.

DR. SHAPIRO: Right.

MR. HOLTZMAN: The first is to whom and so to speak how does this apply and then what -- how do we understand responsiveness.

DR. SHAPIRO: Right.

MR. HOLTZMAN: So "are subject to U.S. regulations" is narrower than U.S. researchers and sponsors, correct? Unless we achieve what we want in our other report. So it would seem to me that I would -- now Alta says to the broadest formulation, which is the one I would support, which is that if you are a U.S. researcher or a U.S. sponsor you should not do research elsewhere unless it is responsive to the health needs. Full stop. And Alta says that sounds like research censorship.

I think what we are saying is it is unethical to perform human experimentation with potentially harmful experimental drugs in people unless there is a reason to believe it is responsive to their health needs. Otherwise they are guinea pigs. So why are we getting into a formulation about the FDA and IRBs and everything else? If that is what we mean, I advocate we say it.

DR. SHAPIRO: It sounds sensible to me.

Bernie, and Bette?

DR. LO: I agree with Steve's last suggestion but I also wanted to get back to the responsive. I actually like -- I agree with Harold's line of thinking. I think we need to say something about responsiveness and to make sure we try and say something that takes it out of just a problem exists in the host country. I am not sure what the right language is. I am also not sure that Alta's formulation of health services needs quite captures that. I think, Harold, your comments could probably be in a supporting text but I would like to get something like that into the actual recommendation but I am afraid I do not right now have the language to do that.

DR. SHAPIRO: How do people feel about that issue quite aside from -- maybe, as Steve said, there are a couple of issues working around in here and not just one issue. One is the responsiveness issue. A

second one is who is it that is covered by this aspiration here.

Now you want to -- could you repeat your phrase a few moments ago, Steve? It sounded --

MR. HOLTZMAN: It is the language that is here.

DR. SHAPIRO: Yes.

MR. HOLTZMAN: Just the language. It would read "clinical trials conducted in developing countries by U.S. researchers and sponsors and/or sponsors..." right "...should be limited to those studies that are responsive to the health needs of the host country." Full stop.

PROFESSOR CAPRON: It is the language that is right here.

DR. SHAPIRO: Yes.

DR. MESLIN: But it is the first "or" that you are looking at, right, Steve?

MR. HOLTZMAN: Yes. Delete "that are subject to U.S. regulations" and then delete the second "or U.S. researchers and sponsors and others subject to U.S. regulations."

PROFESSOR CAPRON: Is there any others? I mean, what does the third alternative there refer to? I mean, is there -- other than a sponsor or a researcher, who else is there? There may be. I just --

MR. HOLTZMAN: A regulator.

PROFESSOR CAPRON: Conducted by a regulator?

DR. SHAPIRO: No.

MR. HOLTZMAN: A regulated sponsor and conducted by -- any. Philanthropies.

DR. SHAPIRO: Sponsor.

PROFESSOR CAPRON: We are not writing a regulation.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: If the Sloan Foundation sponsors something they are a sponsor for the meaning of this --

MR. HOLTZMAN: It can also be other companies, pharmaceutical companies.

DR. SHAPIRO: Okay. We are not writing regulations here. I actually believe this, no matter who it comes from, but even the last one -- I mean, they do not have to be covered by our expectation if they do not feel like they are covered. Right?

PROFESSOR CAPRON: Well, the argument there would be if they were going then to come to the U.S. with the data they should have been held to the same standard as a U.S. researcher or U.S. sponsor in the first place.

So, Steve accedes that the third alternative is equally to the point. His point, I think, was the thrust of the sentence should simply say clinical trials should be responsive. I mean, when they are -- period.

And leave to the elaborating text some explanation that when we say "responsive" we mean it offers something which actually will respond to it and not just abstractly is relevant to a disease.

DR. SHAPIRO: Other comments?

Steve?

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Just a moment, Alta.

Steve is next, then you, and I have Bernie.

Bernie, I will get you next time.

And Bette, also.

Alta?

PROFESSOR CHARO: First I want to say that it is possible that the phone connection is different than before because now it is barely possible to hear you all so I apologize if I missed something but I am very sympathetic to the idea that as a form of decent behavior nobody should be doing research with populations in developing countries, which we are treating functionally as if they are in some sense vulnerable, unless the research is expected to be responsive to the health needs of that country.

And I can live with a recommendation that is written like that provided that in the text we recognize that although that might be a decent standard of behavior, there very well may be some legal obstacles to trying to enforce that standard of decency on all American citizens. What we can easily

do through law in order to further this goal is to place constraints on those people that approve research like the IRBs, constraints on federal agencies like the FDA that have to accept data for registration purposes, indeed the EPA for registration purposes.

But if you try to actually limit the action of an individual citizen operating privately you do run into some potential legal problems with the appropriate scope of governmental authority by the U.S. Government over U.S. citizens in their private actions.

So I think it is worth recognizing that and saying if you want to say it in the text that accompanies recommendations that we anticipate that the easiest avenues for beginning to implement this recommendation may well focus on the IRBs and the FDA acceptance of data.

But I do not think we can make a recommendation that we expect it is going to be legally enforceable against all U.S. private citizens operating privately abroad.

DR. SHAPIRO: Bette?

MS. KRAMER: I am in favor of limiting the recommendations in the language that Steve has suggested. What I had wanted to say before the break, and it keeps coming up really in terms of every recommendation, so although I did not get to

say it then let me say it now, and that is I have a concern -- you know, it is very hard -- it is very, very hard sitting at this table to do anything that is not going to advance the difficulties or to minimize the difficulties in the lives of these people, to advance their societies beyond where they stand now.

And it was very apparent when we were talking about what are the obligations of sponsoring -- the sponsoring research or agencies following a trial, et cetera. And, you know, I think it is just beyond the scope of this body or this report to try to correct all of the ills of their society and I am concerned that to the extent that we try to go too far that the -- our report will lose any impact because it is just going to become impossible to comply with it.

I mean, I was going to say this goes back to what we were discussing before the break but it comes up again when you look at the language. It comes up for me that is when I look at the language of Alta's suggestion where she talks about taking into consideration responsiveness to the health care delivery. I do not see the exact language right now but the health care delivery.

DR. SHAPIRO: It was the health service delivery.

MS. KRAMER: Right, the health services, et

cetera.

DR. SHAPIRO: It just came in over the --

MS. KRAMER: Right, exactly. I mean, I just think we need to bear in mind as much as we would like to -- as much as we would like to accomplish a whole lot out there to bear in mind what we are about and not come up with recommendations that are going to make research so impossible and so costly that we are going to end up having an adverse effect, and that is minimizing the amount of research that is done.

DR. SHAPIRO: Let me suggest something on this one, too. I think there is a sense around this -- agreement we ought to simplify 1.2 and the text that surrounds it will bring up a number of these associated issues that have been dealt with. Of course, we cannot legislate against the private action of U.S. citizens operating on their own somewhere. I mean, those kinds of issues we can deal with in the text and this is not a regulatory -- we are not writing regulatory language here or enacting legislation.

So let's proceed on here. I am thinking we will take the simple -- really Steve's suggestion on 1.2 and cover all the other issues that seem important here in the text and just go ahead with that.

DR. MESLIN: Can I just get a clarification

from Steve? You wanted an "or" between researchers and sponsors when you reread it. Do you want to -- is that what you really meant?

MR. HOLTZMAN: I actually think that since we are -- in the direction we are going with the simplest clearest rec and then addressing things such as how do you enforce like in the text such as Alta's suggestion, maybe it just is clinical trials conducted in developing countries should be responsive, full stop. Do not get into U.S. researchers, sponsors, et cetera. With "and/or," I will leave that to you grammarians.

DR. SHAPIRO: Okay. Did you want to make a comment?

PROFESSOR CAPRON: I liked the suggestion before Steve started modifying it.

DR. GREIDER: Yes, I did, too.

PROFESSOR CAPRON: I would just say the third alternative there, clinical trials conducted in developing countries by U.S. researchers and sponsors and others subject to U.S. regulations should be limited to those studies that are responsive to the health needs of the host country. And I would move that -- and everything else goes into the commentary. The very important points Alta made.

DR. SHAPIRO: Are people satisfied with that? Okay. That is what it is. Let's go on.

There are a series of recommendations that

come out of Chapter 2. Actually three of them. Recommendation 2.1. I am not going to read it but does anybody have any comments, concerns or objections regarding 2.1?

What about 2.2?

Bette, I am watching your red light. Do you have --

MS. KRAMER: Excuse me.

DR. SHAPIRO: No, I want to be sensitive since I apparently ignored you before.

MS. KRAMER: No.

DR. SHAPIRO: Trish?

PROFESSOR BACKLAR: In my e-mail to everybody I was concerned always about the use of the word "appropriate." I am not certain that -- well, in here it would be all right I suppose. Okay.

DR. SHAPIRO: Okay. Any other comments on 2.2?

Okay. 2.3? Any comments?

All right. Let's go on to the recommendations. A longer series of recommendations that are in 3.

Eric, let me turn this over to you since you have a number of different alternatives and recommendations here and you may want to provide some explanation.

DR. MESLIN: In 3.1, the September 29th version contains a sentence, "moreover the consent

process always should include all the basic elements of disclosure found at 45 CFR 46..." et cetera. That was felt both by the public commenters and upon reflection of the staff to not be consistent with the basic premise of the recommendation, which is the first sentence. So we gave you two options.

One is that we just deleted that phrase and then made it more general to refer to ethics reviews committees. The other option is to make this a U.S. based recommendation and that is what recommendation 3.1 alternative is.

The other part of that alternative recommendation 3.1 is something that Jim was speaking about before and that was we were using the phrase "as exemplified by the basic elements of disclosure" found at 45 CFR 46. The alternative is what staff is proposing because it is a bit more specific to U.S. IRBs and then it is much more -- it is much easier for us to refer to the U.S. disclosure requirements.

DR. SHAPIRO: Thank you.

Alex?

PROFESSOR CAPRON: This is going to be embarrassing. I cannot remember whether it is 45 CFR or Helsinki that has some language about the situation of the subjects being such that they can make voluntary choices. It is in Helsinki? Yes. So there is nothing else in 45 CFR that goes to voluntariness?

DR. SHAPIRO: I do not think so.

PROFESSOR CAPRON: Okay. So that because certainly the substantive ethical standard of informed consent -- maybe we could simply underline what I am concerned about by saying the substantive ethical standard of voluntary, informed consent. The two concepts are both essential for what we regard as the informed consent process.

DR. MESLIN: Alex, Alice has just pointed out that in the regs the term "voluntary" is found if that helps you.

PROFESSOR CAPRON: In that case I would --

DR. SHAPIRO: Just add it to the first line.

PROFESSOR CAPRON: I would just add it to the first line and actually I like the notion of the exemplified reference, the second alternative, because it makes it a little more definite what we are talking about without saying you have to click off those elements if you are using some other guidance document like Helsinki.

DR. SHAPIRO: Carol and then Larry?

DR. GREIDER: I was just wondering if we are going to put in the exemplified if we need to point to a specific regulation. The beginning of that recommendation talks about the ethical standards and can we point to something like the Belmont Report or something that is not necessarily a very specific regulation if we want this to be a general principle

rather than playing to a very specific U.S. regulation that may change or may not be found.

DR. SHAPIRO: Well, my own sense of that is (1) this second part of it dealt with disclosure as opposed to just consent. It deals only with the elements that surround disclosure. It is in an exhibit somewhere in Chapter 3. I have forgotten what the exhibit was, 3.5 or something.

And I think that is -- my own feeling is that is covered by "as exemplified." This may change over time, I understand, but it really is in my view such a good listing of what is required for disclosure as opposed to consent, which is a much broader topic that we should include something like this, whether that is it or not.

Eric?

DR. MESLIN: Well, no, I mean, I think Carol makes a good point for the reasons that Jim, if he were here, I think would also make. The substantive ethical standard of informed consent involves both disclosure, understanding, voluntariness and decision making capacity. Some of those points are described in the principle of respect for persons in Belmont and the application of the principle of respect for persons talks about all of those things.

We may be mistakenly equating the basic elements of disclosure or it may appear to be that we are doing that, equating the basic elements of

disclosure which is just what you have to tell people with the substantive standard of informed consent, a point we make earlier in the chapter that says it involves voluntariness, adequate information and the like.

So whether you want to refer to Belmont or whether you want to refer to other principles in addition to this, you certainly may want to do that but I think the text would definitely have to do that.

We tried to get around equating that directly by saying "as exemplified by" rather than saying this is identical with or if you just satisfy the disclosure requirements at 116A you have done informed consent. So I think you make a good point.

DR. SHAPIRO: Is the error here that you are thinking about and trying to deal with disclosure and voluntary informed consent in the same sentence? Maybe that is where it sort of brings people some confusion on this as opposed to saying something -- have a full stop somewhere and saying with respect to disclosure you have to do this and that. Maybe that would help clarify the issue that Carol raises, which is an interesting issue. I think that would help clarify. I do not have the language, unfortunately, right at the moment.

Larry?

DR. MIIKE: Just an editorial comment. In

the alternative recommendation 3 even though you explain a footnote on the first page, a difference between ethics reviews and IRBs, I think a lot of people just think it is an editorial mistake when they look at ethics reviews in the beginning and then all of the sudden see IRB over there. They are not going to get -- you have got to be more explicit when you are talking specifically about the U.S. situation.

DR. MESLIN: Are you talking with the 3.1 or its alternative?

DR. MIIKE: The alternative.

DR. SHAPIRO: The alternative which introduces IRBs.

DR. MIIKE: There is a footnote that explains it is different but a lot of people are going to miss that footnote.

DR. SHAPIRO: And so your suggestion is, Larry, that we do what?

DR. MIIKE: Well, either just repeat the footnote there just -- you need to key someone that we are talking about something different and it is the U.S. and not just general term.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I would point out to Larry that I think we cannot worry about those people who do not read the footnotes in detail.

(Laughter.)

DR. SHAPIRO: This guy keeps his stuff on tape. What can I tell you, Larry?

DR. MESLIN: So what I am hearing is that you like -- you think you like recommendation 3.1 and its alternative but you want to be sure that Carol's point about the consistency between the disclosure requirements and -- or the apparent inconsistency between the disclosure requirements and the standard of informed consent are satisfied. I think we can deal with that issue.

DR. SHAPIRO: Okay.

Carol?

DR. GREIDER: That was part of my point but the other more general part of that point is if we are making a very high level global recommendation, it just seems inconsistent to point to a very minute specific regulation rather than an overall principle. And if there is a principle we can point to, to make a general overall principle, it would be preferable to pointing to something very specific in U.S. regulation.

DR. SHAPIRO: Alex, and then Eric?

PROFESSOR CAPRON: I favor in this case the Miike approach. The general Miike approach, which is I think what the chairman started to say was to put a full stop after the word "process" and then discuss in the text that one element of informed consent is disclosure of information, see our side bar where we

quote 116A, another element or aspects of voluntariness may be some language from Helsinki that talks about it.

I think in other words that the Belmont Report provides -- you know, et cetera, et cetera. That there are a number of -- this is not a regulation. This is an expectation for meeting a broadly accepted view of what is voluntary informed consent.

Now when we get to the second question then is I do not understand in the revision of 3.1 that you have here you added the word "ethics review committees," which would say this is an expectation of the foreign as well as the U.S. And that was based upon comments that we got that we should say there that this is -- whichever committee is looking at it should do this.

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: Then I guess what I am favoring is recommendation 3.1 as revised, not alternative one, and I would so suggest that we have a straw vote pretty soon about that.

DR. SHAPIRO: Why don't people read 3.1 in view of the discussion we just had and see how they feel about 3.1 as revised, which is the first one up. I do not know if I am using the right language here.

Larry?

DR. MIIKE: Can I ask Eric again to briefly

explain why there is an alternative that limits it to U.S. IRBs and leaves out foreign ones?

DR. MESLIN: It was just a progression having realized that the second sentence of the original 3.1 that began "moreover the consent process always should..." it, to many of the public commenters, seemed that we were imposing U.S. procedures in our -- from our regulations upon what was supposed to be an aspirational goal.

So we did the easy thing first and that was simply to delete that offensive phrase. By doing so, we were not speaking only about U.S. IRBs anymore, we were speaking about these committees in general.

We gave you an alternative in case you thought it was presumptuous to tell every other IRB or ethics review committee in the world how they ought to operate so we said if you want to limit it only to U.S. IRBs we can give you the "as exemplified" language.

DR. MIIKE: I would say then that I agree with Alex and we should go with the first but then you can deal with the -- telling people we would just change the "maybe" to "should."

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I have two points. I agree with Larry. I think it should be to ethics review committees.

And then there is a grammatical issue, which

is, well, in either event it is not clear to me that it is the researchers must not deviate from the standard. Right? I mean, if you think about it, that is -- I find myself wanting to write some things very simply like "no research should be undertaken that deviates from the ethical standard of voluntary informed consent. Researchers should only propose and ethic review committees should only approve research that meets this standard."

DR. SHAPIRO: It is just when you put it that way -- because I was speaking to Eric this morning -- I really do not know what is wrong with just the first sentence actually. I think the second sentence --

PROFESSOR CAPRON: Can become commentary.

DR. SHAPIRO: -- becomes commentary. If you make a general statement then, of course, it covers everybody and the rest is just commentary. And -- which means that, you know -- I mean, your language is actually the language I would prefer here. It is just very general and covers everyone and makes the point, and then we can make whatever, you know, comments we want in the text.

DR. MESLIN: I want to make sure -- Steve was saying two things, though. One was the general -- this is what research should not deviate from. Your second sentence was researchers should not propose and a committee should not approve. What you

said when you agreed with his general view --

MR. HOLTZMAN: That second sentence could be commentary as you would draw the conclusion or you can actually -- if you want to include it in the recommendation it would still be a very general but high level --

PROFESSOR CAPRON: Built in suspenders.

MR. HOLTZMAN: -- statement. Right. It draws the first immediate conclusion from it and it also puts an onus on research. I think again one of the things I want to see is in all of these that the onus lies with sponsors, lies with researchers, lies with IRBs, lies with ERCs. Just making it clear it is everyone's responsibility.

PROFESSOR CAPRON: So it is researchers should not propose or conduct; sponsors should not support; and IRBs should not approve research that deviates from that standard.

DR. MESLIN: But that would be a commentary.

PROFESSOR CAPRON: Excuse me.

DR. MESLIN: Now we are saying recommendation commentary --

PROFESSOR CAPRON: No, that --

DR. SHAPIRO: That is an open issue.

PROFESSOR CAPRON: He thought it was good to have built in suspenders here that you could draw the conclusion and make it clear. I think that is what you were saying, right?

DR. SHAPIRO: I like the language that Alex has suggested regarding researchers propose, IRBs approve, sponsors undertake and so on and support.

MR. HOLTZMAN: More language in the recommendation is okay as long as it is literate and in that fashion it works.

DR. SHAPIRO: Okay. So I think we have what we need on 3.1.

Eric, do you want to talk about what is now 3.2, which is a result of having put a number of suggestions together?

DR. MESLIN: So this was a lumping proposal. Many commentators or public comments explained to us that we were repetitive and redundant in the September -- not we, the recommendations were. And so what you see before you is 3.2 combines several issues relating to ways of disclosing information that are culturally sensitive, maximize participant understanding, and that this should occur through a process of consultation before the research begins.

And the last sentence was a specific suggestion by one of the public comments that pointed out that you cannot always do this. You cannot always involve community. You cannot always ensure that this process occurs. Sometimes it is not necessary or not needed but that the onus should be on investigators to explain why you should not be trying to do these things.

DR. SHAPIRO: Comments on 3.2 as it is currently structured?

Alex?

PROFESSOR CAPRON: I favor the old version. When you look at what is there in those four recommendations and compare it to this combined one, I do not think you come away -- I do not come away with the same sense of particularly the community consultation.

And the only thing from the revised one that I would use would be that last sentence where it might be worthwhile adding that to 3.5. I do not think in this case the absolute economy of expression by lumping everything into one 10 or 12 line recommendation is that much better than having the four recommendations with their accompanying text that explains something about what we are after.

DR. SHAPIRO: Other views on whether we should put these together as suggested here or leave them separate even though some observers have thought it was just too much -- too repetitive in one sense or another? Any views about this?

There does not seem to be strong feeling one way or another about whether we do it. Anybody have any strong feeling about this?

Yes, Arturo?

DR. BRITO: I am not sure how strong the feeling is on a scale of ten but I, frankly, like

this even though I know it is long. I think it reads very well and it is very clear. So I do not have any problems with this, the way it is written -- the revised version of 3.2 combining all the elements.

DR. SHAPIRO: Larry?

DR. MIIKE: Rather than combining all four together I can see combining 3.2 with --

PROFESSOR CAPRON: 3.6.

DR. MIIKE: -- 3.6 and 3.5 with 3.7. They are separate issues. Just a question on the current one. Why is it IRB and not ethical review in your proposed revision? I seem to be stuck on that.

DR. SHAPIRO: Eric?

DR. MESLIN: That is a good question. We may have just missed that one.

PROFESSOR CAPRON: I would second Larry's suggestion.

DR. SHAPIRO: I think that is clear in this one.

Any other questions?

DR. MESLIN: And the suggestion was combining 3.2 with 3.5 and then 3.6 plus 3.7 and --

DR. SHAPIRO: No, no. 3.5 and 3.7. 3.2 and 3.6.

DR. MESLIN: Sorry.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I want to apologize. I am

going to need to excuse myself to go and teach the last class of the semester and we have not gotten up to 3.9 so when you do, if I may ask, I have provided some alternative language on that that I would just ask that you take a look at. Only because I thought that it was slightly clearer and added some emphasis that I feel strongly about. Other than that, I wanted to thank you for putting up with the telephone and just sign off.

DR. SHAPIRO: We will certainly look at your language specifically when we get to 3.9.

PROFESSOR CHARO: Thanks very much. Happy holidays, everybody.

DR. SHAPIRO: Thank you.

Eric, do you have any view regarding -- obviously I do not have a strong view on this matter.

DR. MESLIN: 3.2.

DR. SHAPIRO: On what we put together here. I do think Larry's suggestion is a helpful one, that it is -- I think it has gotten the right things that are most important to go together but how do you feel about that, Alex?

PROFESSOR CAPRON: Well, you know, I did favor -- let me just say that the advantage of keeping them separate, all separate is that they all come at slightly different aspects. 3.5 and 3.7 both do deal with the community but they are actually talking about slightly different things. I mean, one

is talking about community education and consultation where the design of the research project itself may be affected by that consultative process.

Whereas, 3.7 really talks about something which is the community process and where there may be culturally appropriate ways of reaching people and getting them to understand what you are saying, which are not immediately obvious to people from another culture. And that in a certain way really relates more to 3.6, which is why 3.6 and 3.7 come in sequence. Going to the community is one way of devising appropriate means to ensure participants do, in fact, understand the information.

Now we could -- obviously we could lump the whole report into one giant recommendation because everything is --

DR. SHAPIRO: Now there is a thought.

PROFESSOR CAPRON: The knee bone is connected to the thigh bone. But having them as separate allows us to make a point and discuss it and then have some orderliness. So I could live -- this is not something where I am ready to fall on my sword. I think I probably most favor keeping them separate. Second would be Larry's approach.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Also not falling on the sword, I like them separate because these are the issues that come up and the questions, and if one is

reading this you expect to see each of these addressed, and it is not -- there is a reason why they came out separate initially, which is this logic of the discussion.

DR. SHAPIRO: With everybody failing to fall on their sword, I will make a decision on this and we will just go on. We will just keep it separate and I think we do -- do not want to lose -- as Alex already pointed out, we do not want to lose that sentence which is at the end of the currently --

PROFESSOR CAPRON: When it is not possible or relevant, that sentence.

DR. SHAPIRO: That is right. That has to go with 3.5, I think it is, and we will just deal with it that way. Okay.

Quite aside from the -- any other comments on these sequence of recommendations, whether you consider them in your mind as lumped or separate? We are actually going to deal with them separately. Are there any other comments about them other than taking that last sentence and attaching it to 3.5 in an appropriate way?

PROFESSOR CAPRON: We are also following Larry's observation that these are standards for the ethics review committees of all sorts, right?

DR. SHAPIRO: That is right.

Okay. Let's take a look at 3.8. Any comments or questions regarding 3.8?

DR. MESLIN: I just want to make sure we are on the -- are you using the December 6th, which has -- you are just going straight on to 3.8 after we have done this lumping and splitting?

DR. SHAPIRO: Yes.

DR. MESLIN: Okay.

PROFESSOR CAPRON: We are talking about old 3.8? The original 3.8.

DR. SHAPIRO: I am looking at -- oh, it is the old 3.8, currently 3.7 in this particular -- it is the old 3.8 and it is currently the 3.7 in this particular document. So it is one that begins with "culture or custom requires permission of the community leader." That is the one I am looking at now. I guess I will use the new number 3.7.

PROFESSOR CAPRON: We know where you are.

DR. SHAPIRO: You know where I am and then we will figure out the right number in due course. Any comments or questions?

Yes, Bette?

MS. KRAMER: I am sorry I missed the discussion on November 22nd. Why has the initiative switched from the community leader to the individual?

DR. SHAPIRO: I do not think that is the intention of this recommendation.

MS. KRAMER: I am sorry. Are you on 3.7?

DR. SHAPIRO: 3.7.

MS. KRAMER: Oh, I am sorry. Excuse me. I

did not get the -- I am sorry.

DR. SHAPIRO: No, I was -- I am responsible. I have been calling it the wrong number here. It is the one where "culture or custom requires permission of a community leader," et cetera.

MS. KRAMER: Excuse me.

DR. SHAPIRO: That is the one.

MS. KRAMER: Sorry.

DR. SHAPIRO: Okay. Let's go on to the next recommendation which begins "when the potential research participant wishes to involve family members." That one.

PROFESSOR CAPRON: What about old 3.9?

MS. KRAMER: We have not gotten there yet. We are on 3.8.

MR. HOLTZMAN: We are at the new 3.8, which is the old 3.10.

PROFESSOR CAPRON: Well, the old 3.9 is 3.6.

DR. SHAPIRO: We do have to come back to that one. You are right. I have not took that off yet so -- but let's do --

PROFESSOR CAPRON: Who is on first?

DR. SHAPIRO: "When a potential research participant..." that recommendation. Any comments or questions regarding that one?

Okay. Let's go up to the one that is 3.6, which I can read out, it is a very short one. "Researchers should strive to ensure that individuals

agree to participate in research without coercion or undue inducements."

PROFESSOR CAPRON: The point of revision here was to broaden outside of community leaders because we have got comments saying that there are a lot of other concerns?

DR. SHAPIRO: That is my thought.

PROFESSOR CAPRON: Eric, are you with us?

DR. MESLIN: I am sorry. What was the question?

PROFESSOR CAPRON: Where did -- what came -- what sources of comments led us to drop from community leaders? I mean, is the sense that there were other sources of inducement?

DR. MESLIN: Yes.

DR. SHAPIRO: Yes, Larry?

DR. MIIKE: Except that when we drop it off it sounds like our mom and apple pie kind of a recommendation. Who can be against something like that? Whereas, when it was referring to community leaders that was a really potential situation or a real situation.

DR. SHAPIRO: Another way of resolving that is to say from community -- well, I do not know. You may think it is back to apple pie if you say from community leaders just to make -- or others.

DR. MIIKE: Well, I thought the initial impetus was that in these collected --

DR. SHAPIRO: That is correct.

DR. MIIKE: Yes.

DR. SHAPIRO: That was the initial impetus.

DR. MIIKE: So I would prefer the original. I would prefer the original.

DR. SHAPIRO: All right.

PROFESSOR CAPRON: In which case the order should stay the way it was because this is really a minor point -- not a minor but a subsequent point.

DR. SHAPIRO: Yes. How do people feel about that?

Who prefers the original?

Bill?

MR. OLDAKER: I agree with Larry.

DR. SHAPIRO: Okay. Steve?

MR. HOLTZMAN: I agree but I would suggest we go back and look at all of these or staff does and ask the question where we can say research and sponsors. Certain of these responsibilities clearly can lie only with the researcher, e.g. the production of the protocol. Certainly these other ones I think you can lodge with the sponsors and give the joint responsibility to the sponsor as well.

DR. SHAPIRO: A good point. Thank you very much. We will do so. Any other comment on what is currently 3.6?

All right. Let's go on to what is currently 3.9. This is the recommendation Alta wanted -- has

asked us to look at her language so everybody just take a minute. I think you all have copies of Alta's language as it appears in her e-mail. And you -- let's just take a minute so you all can read it and/or re-read it if you have already gone through it and then, Eric, maybe you could suggest what you think about this.

DR. MESLIN: The reason that was it proposed to be changed in the first place was the public comment draft. The public comment draft recommendation stopped after the word "men" and yet in the text itself there was care taken to specifically identify the narrow exception to that otherwise absolute rule. It was so important an exception that we spent a paragraph and a half describing it, and a number of public commenters and staff concurred, and felt that the exception should be placed right in the recommendation so that it was clear from the moment that you read it.

Alta has just simply made some suggestions that would, I think, clarify what we have said and in particular her suggestion of keeping a comment about competent adults I think you should consider because we were worried about the issue of someone speaking for someone else and that applying simply to women -- simply to male heads of house and/or other adults. So I think in my own view and other staff may want to comment Alta's suggestion, I think, is a useful

revision but it is entirely up to you.

DR. SHAPIRO: Steve, and then Larry?

MR. HOLTZMAN: So, first off, I would endorse putting the exception in to the recommendation for those people who only read the recommendations in footnotes. The second point is I think Alta's rewrite of the preamble, I think, is clearer and better. On the third point I endorse her suggestion to reinforce the point that a man cannot consent for a woman, which was her point C.

And then the only question I would have is there was in an e-mail from Eric Cassell, if I understood the gist of the e-mail, is he seemed to be able to imagine a clinical trial which -- where the benefit would be for children wherein that benefit only could be accomplished through the inclusion of women. And so he was raising the question whether our -- in our language B, in Alta's language, B-2, and I could not imagine the trial he was thinking of. Okay. But just -- so -- but I thought it was important to raise.

DR. MESLIN: The only thing I would add is that when -- maybe Alice wants to speak to this because she helped write it with Ruth, the original reason for writing this recommendation, of course, was to highlight consent involving women. And that is all I need to say. That was its purpose and that is why the rationale was given in the text and why

the narrow exception was carved out. So that is just background.

DR. SHAPIRO: Larry?

DR. MIIKE: I find Alta's C a little redundant because it -- I guess it is just being done to emphasize the point but it is redundant because the rest of it does not say that. It talks about someone supplementing a woman's consent. It never says that it can substitute for it. But I am just pointing it out. I do not have any strong feelings about leaving it out.

DR. SHAPIRO: Well, I think Alta, as you point out she obviously says here, also recognizes it is redundant. She is just anxious to make the point again. But let's see how others feel regarding this recommendation.

Carol?

DR. GREIDER: I would just like to endorse Alta's rewrite of the recommendation despite the redundancy.

DR. SHAPIRO: Including the redundancy, right.

Bette?

MS. KRAMER: Likewise.

DR. SHAPIRO: Okay. Does anyone feel differently?

Do people feel satisfied with that?

Yes, Alex?

PROFESSOR CAPRON: Yes. We are actually not going to have this as per recommendation 3.7/3.8, that language that she has we are not going to use. Just say in no case may a competent adult --

DR. SHAPIRO: That is right. Okay.

Then we will go ahead with that addition -- with that substitution and put that in.

What about what is currently 3.10?

Eric?

DR. MESLIN: Right. So there were in the -- again in the public comment draft there were three recommendations together which some -- a number of our public commenters reminded us that the recommendations are already things that can be done and we do not need to spend too much time telling people to do what they are already doing or could do. That is a good rule.

And, secondly, on the issue of waivers and audit by a competent body, the text was admittedly quite sparse on providing the justification for audits and waivers and what would constitute appropriate body and the like.

And staff tried to lump only the relevant parts of those three recommendations into what is now proposed as 3.10 because that is the part that says what is new and what is different. So the provisions of 116(c) should be modified to allow researchers working in developing countries and subject to

regulations to obtain waivers of one or both of the requirements. That is the requirements for written and signed consent.

Alta has made a proposed revision to that revision. The only significant change she has made is the last sentence of her e-mail which my understanding from what she was proposing was that this was a way to get at the sort of assessment of the use of this waiver system without having to go through an audit by a competent body and she is proposing the sentence "waivers should be granted only if an alternative mechanism is proposed to allow post-trial verification that all research participants gave consent."

Obviously there is no text to support it so it is -- on its face you would have to decide whether you would like to see something like that. In which case we would have to construct with Alta's help the text for it.

I mean, we should say that it is -- we are not quite sure how it would work and what kind -- what would count as a mechanism that allowed post-trial verification to occur.

DR. SHAPIRO: Comments regarding 3.10 and/or Alta's version of 3.10?

Alex?

PROFESSOR CAPRON: I just need a clarification. What amendment are we looking for?

If 117(c) -- could we have the language of 117(c) just read to us?

DR. SHAPIRO: Eric, do you have the language?

DR. MESLIN: Yes. Except as provided in paragraph (c) of this section, I will read that in a second, "Informed consent shall be documented by the use of written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative."

Subparagraph (c) says, "An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) that the only record linking the subject and the research would be the consent document and the principle risk would be potential harm resulting from a breach of confidentiality; each subject will be asked whether the subject wants documentation linking the subject with the research and the subject's wishes will govern.

Or (2) that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

PROFESSOR CAPRON: Okay. So what I gather we want to have is not so much the word "modified" but amended. We want an additional exception that in

a developing country context where written consent is not -- and signing documents is not culturally acceptable or customary that the requirement either for writing written documents or for signing thereof can be waived. Is that right?

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: So I would just -- to clarify that -- add an "S" at the end of the word "requirement." Allowing IRBs to waive the requirement. It is the requirements for written and signed documents. And then down -- and to say amended to obtain waivers of one or both of these requirements to reflect culturally appropriate norms or something. We have to say what the drift of the amendment is. Is that acceptable?

So I am looking at Alta's language and at the end there to explain amend to reflect culturally appropriate norms. We are not writing the regulatory language but that is the point of it that there would be a number three under (c) here. Is that -- am I getting the sense?

DR. MESLIN: Absolutely. And just to remind Commissioners that in the oversight report we do address the same issue and what the proposal that you had before you was that this national office should issue guidance that allows for flexibility in the method and use -- I am sorry. In the method used to document informed consent and that takes into account

local variation in what is considered adequate or appropriate documentation. So whether you are cultural or local variation.

The other thing, of course, is that in the oversight report you will be considering whether you will be changing or modifying or amending or otherwise dealing with all the waiver criteria but for the time being this report is coming out first and you may want to deal with the existing waiver criteria.

So the suggestion is you could take Alex's version or use the phrase "local variation" or something like it to be consistent but you had the right sense.

PROFESSOR CAPRON: Well, you know, yesterday when we talked about local variation in and of itself that suggested something that might be simply bad practice.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: Whereas culturally appropriate norms, I think, conveys what we want.

DR. SHAPIRO: Right. Let me go back now to 3.10 where we are now. Does that -- with that suggested modification, which I believe is entirely appropriate, are people satisfied with 3.10?

What about Alta's -- I want to come to that now. What about Alta's last sentence? I guess it is also the second sentence. That is that these waivers

can be granted only if an alternative mechanism is proposed to allow post-trial verification, et cetera. How do people feel about that additional requirement? That is that waivers can be issued but only if there is some mechanism for post-trial verification.

Steve?

MR. HOLTZMAN: I agree with the spirit of it. It is not clear to me that it has to be post-trial. It could be ongoing. The gist of what we are saying is signed consent forms -- written and signed is not always the best way to get informed consent in a given culture, IRBs can be sensitive and approve something if it has got an alternative mechanism, whatever the form of the mechanism as long as it is solid.

DR. SHAPIRO: I also have a lot of trouble with the post-trial part of this because (1) it does not accomplish what we want and (2) it is a much harder thing to accomplish. I cannot even quite envision what the mechanism would be in most cases.

So let's assume that we think of this sentence without the post-trial.

Yes, Steve?

MR. HOLTZMAN: Do we really have to reference CFR in this? I mean, I think what I just said -- albeit it can be said more eloquently, the gist of what we are trying to say, even if CFR did not talk about waivers right now, so in principle I

do not see -- recommendations in my book should not go to citations of CFR for making amendments.

DR. SHAPIRO: I think we do not need to have it in the recommendation itself. I quite agree. You can point out in the text that this is what is required to do this and I think that is actually more consistent with the way we have been writing the recommendations under 3 here. So why don't we do that because we have really been making those kinds of changes all the way through here?

Okay. Eric, anything else that you would like us to deal with on 3?

DR. MESLIN: No.

DR. SHAPIRO: All right. We still have some time left. What would be most helpful to you? We may not get all the way to 5. Do you want us to go to 5 or deal with other recommendations under 4 now?

DR. MESLIN: I think we probably heard what we can hear about 4 assuming that --

DR. SHAPIRO: 4.1 I do not want to deal with right now.

DR. MESLIN: Right.

DR. SHAPIRO: That is being redrafted.

DR. MESLIN: Right. Well, you can certainly go to 4.2 if that will --

DR. SHAPIRO: Okay. Let's go off that way. Let's see what comments or recommendations are with respect to 4.2. 4.1 we are going to be, of course,

redrafting.

Arturo?

DR. BRITO: I mean, 4.2 is going to depend a lot on redrafting 4.1.

DR. SHAPIRO: Right.

DR. BRITO: I am not even sure it is worthwhile.

DR. SHAPIRO: That is true.

DR. BRITO: Because a lot of it is --

DR. SHAPIRO: That is a good point.

DR. MESLIN: Let's go to 5.

DR. SHAPIRO: In that case we are on 5.1. This is where your industrialized comment may come up, Arturo. You may or may not want to mention it again.

DR. BRITO: I prefer -- now I cannot find it, of course. I found it before. But anyhow I prefer here in 5.1 that instead of using the word "developed or industrialized" that the word "sponsoring country." I am not sure what the rationale for using that. It just sounds --

DR. SHAPIRO: Sponsoring country or with the researchers from sponsoring country.

DR. MESLIN: Well, I am -- if we are all reading from December 6th what we are suggesting here is -- well, I am not sure, Arturo, what your concern is. Maybe that is my problem. The proposed change is first changing it from "industrialized" to

"developed" and then adding a sentence. And what was the -- I was not sure what --

DR. BRITO: Just replace -- instead of using "developed" or "industrialized," you made the change from "industrialized" to "developed." I suggest going further and say the sponsoring country. Why is it -- I am not sure why -- we are really talking about U.S. sponsored research internationally. I mean, I am not even sure why you say -- why you don't just say the U.S.

DR. SHAPIRO: What would happen or what would be wrong with putting a full stop after "partners?"

Eric, does that offend something we are trying to accomplish here?

DR. MESLIN: No, but the administrative hat that I wear consistent with my obligations as the designated federal official require that I let everybody know that we are no longer in quorum. When Alta left we lost our quorum.

DR. SHAPIRO: Okay. So we will just --

DR. MESLIN: I just want to be clear that now that people have left the room, any of the discussion we are having at this point is discussion or you can stop the meeting if you wish or I just wanted to let you and the public know that once Alta left the phone I started to count heads.

DR. SHAPIRO: Okay. We will come back to

this but let's carry the discussion on in any case so the draft will be before us when we review it next and we will have the benefit of our current discussion. We will not decide on anything.

Well, one suggestion I have is just to put a period after "partners."

Carol?

DR. GREIDER: I agree with that but just to finish the sentence, "more equal partners in research" or just to finish the sentence out.

DR. SHAPIRO: Right.

DR. GREIDER: Just grammatical.

DR. SHAPIRO: Right. Any other comment on 5.1?

Any comments that you think might be useful on 5.2?

Now 5.3 is directly interconnected with the redrafting we are doing so I do not propose we stop on 5.3 right now. That may be altered substantially depending on how we redraft.

And I think that is -- that is true also of 5.4. So let's just skip over that now.

5.5 and 5.6 is obviously -- and then that -- as is 5.7.

I think this is a good point to move to some other topic if you have any other.

Okay. Let me just review where we are here just for the purposes of information.

NEXT STEPS

DR. SHAPIRO: We will, as with the oversight report, be starting to distribute alternatives to those recommendations that we have not approved, which includes everything in five and I think maybe everything in four -- and everything in four, indeed, which will have to come back. But you will be getting new drafts of that plus new drafts of the chapter and supporting text.

I think from here on out I really think we have to see text and recommendations together. Otherwise it is just not really quite as helpful. So we will do the same thing as we have done in the oversight report, although we are in a different stage. Mainly distribute drafts and proposals as they become available to give you the best chance to review them.

We are very dependent on your expeditious feedback on this because we will see where we are at the January 18th meeting. We could at least aspire to that being our last look at this report if that works out okay. If it does not work out, it does not. And we just -- we certainly have to be satisfied before we move ahead. But we are trying to be as expeditious as possible so even though the holiday season is coming up, let's try to be responsive as we get e-mails from the office.

So thank you all very much. I wish everyone

a good holiday season and look forward to seeing you in January.

(Whereupon, at 11:54 a.m., the proceedings were adjourned.)

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