46th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

Sheraton Premiere at Tysons Corner
8861 Leesburg Pike
Tysons Corner/Vienna, Virginia

January 19, 2001

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# I N D E X

P R O C E E D I N G S

DISCUSSION OF DRAFT REPORT: CHAPTER 5 (cont.)

DR. SHAPIRO: Before we begin, let me tell you where we are. I do not know how many of you had a chance to go through the new draft of Chapter 5 that was produced yesterday.

I went through it last night, had a number of conversations here this morning, as a result of which we have changed some of the recommendations because I did not think, or we did not think, they really captured fully the kind of issues we had laid out very briefly yesterday on that page and a half of logical flow of our thinking, if I could call it that. And so, they are being redrafted onto one page, all the recommendations from 5.

They should be here in just a few seconds, and I think we can start with that. As a matter of fact, here is the material. I do not know if this is it or not.

We will also, since we did not distribute last night the right version of 4 as we told everyone, once we go through this, we will then move on to -- Maybe we will take a break and read what we can of a revised Chapter 4, and see what we can add to that, and the rest we will have to do by e-mail and so on.

So this, I guess, is being handed out now. Has everyone got, I guess this is on two sheets of paper -- It begins with recommendation 1.3, which will be a new set of recommendations, or a recommendation that comes in Chapter 1, and we will explain that in a minute. And then, the recommendations on 5, some of which have just had very small edits, some of which are new, and reflect the discussion we had around the material presented yesterday.

So, let me turn to Eric to describe how we attempted to restructure things in order to achieve what we wanted to yesterday, what we laid out after lunch, just how we want to deal with these issues. Eric?

DR. MESLIN: Okay. The first point was in the logical -- Well, I do not know how many pieces of paper people have in front of them, but if you have the Alta/Steve/Alice/Eric logical flow document that began with the very generic principle that people should be protected, and then went to what was item 2, and had a 2(a), (b), and (c) in it.

It was felt that those were important enough statements that they could actually go into Chapter 1, that they were not related exclusively to ethics

review, or assurances, or equivalent protection. Moreover, they could be -- they could foreshadow what was coming in 5, and once you got to Chapter 5, you could refer back to the very strong statement about research meeting the substantive principles and protections outlined in the report. And in terms of item (b) of that document yesterday regarding data, that, too, could be referred back.

So, I put on this two-pager that was just handed out, recommendation 1.3[PROPOSED]. It is just called 1.3 because there are two recommendations in Chapter 1 at this moment. It does not mean that it should not go into 5, but that is where it is if you were glancing through Chapter 5.

DR. SHAPIRO: Can I say a word about that before we go on, Eric?

If you look at recommendation 1.3, or proposed recommendation 1.3, and compare it to the material we were looking at yesterday, if you recall, we had (a), (b), (c), with the three characteristics. It does not deal with (c). And we will have to make a decision whether (c), which I think is important in my own view, should be dealt with in the text as a sort of level of aspiration, hope, and so on, or whether we should actually formally have it in a recommendation in

some form. That is still an open issue. I do not have a strong feeling about that myself.

My only strong feeling is to include the sentiment and the aspiration, but whether it should be a recommendation or not, we have not been able to write it yet, so it is just an open issue. It is not that we have forgotten, and it is not that we should -- I do not want you to interpret 1.3, this initial draft here, as having rejected (c); (c) as we discussed yesterday has to be dealt with, either in the text or a recommendation.

But let's deal first of all, not with the details of 1.3, but whether it does make sense to other members of the Commission to put this recommendation in its final form up in front. I think it does strengthen Chapter 1 a good deal, actually, and really says something in Chapter 1. And then it will have to be repeated in 5 as we will see in a moment, because it is dealing with specific issues.

But does that seem reasonable to Commissioners? Alta.

PROFESSOR CHARO: Yes, I concur with the sentiment and with the placement. Would you be open at a subsequent time to testing out some alternative formulations to see if any of them turn out to be a

little easier to read?

DR. SHAPIRO: Absolutely. No, absolutely. This one was actually done quickly this morning. And so, I do not want to worry in detail -- Yes. As a matter of fact, I would welcome and encourage some help in actually articulating these, because I think they are somewhat awkward, some of these. At least, they have an awkward feeling to me in some cases.

Okay, Eric.

DR. MESLIN: Right. Well, the other thought was that the chapter could be slightly reorganized to reflect the points about ethics review and equivalent protection in their opposite order following from that logical flow.

Let me just walk you through what should not be remarkable, recommendation 5.1, 5.2, and 5.3 on the handout. 5.1, I believe it was Jim or someone who had made a slight grammatical suggestion for changing the recommendation. That is why I put in square brackets [SMALL EDIT], but it would appear in the same place. It is the same statement, just slightly modified for clarity. 5.2 would appear in the same place, and is unchanged. 5.3 is the recommendation that follows from assurances, and the suggestion there is to move it up earlier with a very small edit, and

the small edit is putting the words "after a suitable period" at the beginning of the recommendation, rather than at the end. Those are essentially unremarkable.

What then follows is three -- I am sorry -- four recommendations that try to capture what was in the logical flow, but in no way, shape, or form should be considered final, or you know, well worked out. 5.4 borrows from what was previously -- I hate to go back and forth with numbers, but borrows previously what was in the recommendation 5.6. But leaving aside all of those numberings, 5.4 is the two IRB review recommendation.

It also has a longer statement that Harold had wanted to put in about what do we do with the FDA. That statement, which is a separate paragraph under 5.4, could be, if you want, it could be part of the recommendation, or it could be a separate recommendation. It is the principle you have to decide on, and that is why putting recommendation 1.3 on the table in front of you allows you to make the decision about the FDA.

And very briefly, if you are talking about two IRBs, do we want to make sure that the FDA is covered? If the FDA is covered by 1.3, then you can simply restate the principle of what was item (b) in

the statement from yesterday in this paragraph. Not accepting the data from clinical trials conducted in countries that do not have two IRBs is the ethics review version of what the broader statement of not accepting data from countries that do not satisfy the -- from trials that do not satisfy the substantive principles in the report.

Do you want to go through them, or stop at --

DR. SHAPIRO: Why do not we stop and see -- I notice in 5.4, we have determination by an appropriate U.S. federal agency, and in the FDA one, we have by OHRP. I take it we are just not sure which phrase you want to use, and you have tried one in one case, and one in the other case. I guess my understanding is, but please correct me, that more than one agency can issue sort of equivalence status, I think. Is that right?

DR. MESLIN: Yes, that is true, although it has never occurred, and OHRP is the office, or OPRR was the office.

DR. SHAPIRO: I am quite happy with OHRP, but others might feel differently. Alta?

PROFESSOR CHARO: Well, on that point, and then one other, if I may.

On that point, personally, what I would like to see, consistent with the way we are going in the Oversight Report, is that there be an office, a single office, that does this for the federal government, and without necessarily knowing where that office will be, whether it is in an independent agency, or OHRP, or in the State Department, but a single office that has the authority to do it federal-wide might be consistent with other directions we are taking, and help to cut through some of the problems here.

Second, on 5.4, there is a slight inconsistency between 5.4 and some of the text, some inconsistencies within the text, that are developing, of course, from the many, many iterations here. And it has to do with exactly what it is that people, that other systems, have to show in order to be considered what we are calling substantially equivalent. In some places in the text we suggest that the minimum is identical to the three pillars identified by USAID. It is simply review, risk-benefit analysis, and consent. In other places we have suggested in the text, and now explicitly in 5.4, that it is everything that is in the recommendations of this report, which goes beyond those three things, and includes such things as equity issues

among subjects, and gender concerns, et cetera. And I think we need to make a very clear decision about which one it is going to be, and make sure it stays the same throughout.

I am very comfortable with making it the more rigorous standard because I think that the things we did outline here are not all that detailed and complex with regard to what we think the on the ground ethical issues are, as opposed to the complicated things we are imposing on our own sponsors. But it is certainly something I am open to debating.

DR. SHAPIRO: Okay, well -- Larry.

DR. MIIKE: If we get specific on 5.4, and say it should be OHRP, then the text explanation and description has to be changed, because it just sort of states objectively that USAID can do this, DHHS, et cetera can do that.

On the FDA thing, it does not matter to me whether it is a separate recommendation or -- It seems to me that it could stay as included in there. But what happens in the interim in those cases where there are no U.S. -- You know, the issue we were talking about yesterday.

DR. SHAPIRO: My understanding -- I will have others who are more knowledgeable than myself

speak, but my understanding is the FDA would have to change its regulations in order to achieve this. And there would have to be some interim period of time.

DR. MIIKE: And by the way, I like the flow of it all, because if we had done it this way, I would not have objected in the earlier meetings about insisting on a U.S. IRB review. The way it is set up now is that here is the aspiration. And I mean, it just puts it in a different emphasis on it all, and I am comfortable with it.

DR. SHAPIRO: Okay. Other comments?

I want to go back to the issue -- not the issue but a general issue raised by Alta. This chapter has more than one inconsistency in it, and you have pointed to one which is an important one for us to get. The text really does need quite a bit of work here, and any other suggestions people have, things we might miss as we go over this, I really would appreciate it. I really had not caught this, and I am very glad you pointed it out. And so, if there are other things like that, please let us know, because that is really quite important.

DR. MIIKE: There is another fairly simple one. Early in the chapter it says the Common Rule requires review by a researcher's institution, and

later on it says it does not, so -- And I think Alex read the pertinent language that said that. It says yes, but --

DR. SHAPIRO: Okay. We have a few of those ourselves, "yes, buts."

Okay. Eric, anything else you want to point out regarding these revised recommendations?

DR. MESLIN: Alta has something.

DR. SHAPIRO: Alta, I am sorry.

PROFESSOR CHARO: At the risk of driving you all completely around the bend --

DR. MESLIN: Cannot go any further than we are now.

PROFESSOR CHARO: Cannot go any further than you are now already, is that it? Okay, for the record then, I just want to note the subtlety about the description of the FDA and its use of data here so that people can either decide that they do not want to have to decide, or they can decide what they are going to decide.

We have at the top in the current formulation of 1.3, the suggestion that the FDA not accept data from certain kinds of trials for use in approving various things, which I am hoping implicitly everybody understands means relabeling, et cetera. We

then have in 5.4 a broader statement which has to do with that they simply should not accept data, period.

Now, there are reasons why the FDA will accept data that go beyond approving a particular drug, device, biologic, or even relabeling it. Sometimes data is being accepted because it is being used in order to bolster the case for an entirely different product, and what you are trying to do is show why there is a need for a new product, and how the risk-benefit analysis might work out. There are other times when foreign data is being used just to illuminate, although it is not specifically the data that the manufacturer is relying upon in the approval process. And then, there will be the possible rewrites over the course of time in which we might even see even more general language which simply says that, you know, federal agencies should not use data, and that broadens it even further in terms of their noticing this data for completely non-regulatory purposes. And you may decide that this is getting way too picky, which is a fair decision at this point, or we could decide what level of restriction we want to place upon them, which in turn depends upon exactly how outrageous we think it is to do research that fails to meet all of these protections. And sad to say, of course, there are

going to be degrees of outrageousness in what goes on, and it is hard to capture that in language like these recommendations. But I did want to alert us to this kind of subtle, not inconsistency, but subtle differences that are percolating in what we are saying.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: The phrase that was in the paper you brought back yesterday was "use", and I thought that was a fine word, a more comprehensive one.

PROFESSOR CHARO: It was what, Alex?

PROFESSOR CAPRON: It was "use".

(Simultaneous discussion.)

PROFESSOR CAPRON: -- to be should not be used. Now, there it said "should not be used to approve", and your point is that there are decisions other than the approval where it might be used. But if the idea here is a dual one, both that it is wrong to do such work, and we ought to make it clear to people, and that the best way to do that is a prophylactic rule which says if you do it, you will get no value from it. No value. It will not be useful to you. We ought to say that.

I mean, just make it clear that this is something that should be excluded from the process, because including it not only encourages people to do

it, but implicitly says, well, it was okay to do it. So, I would favor -- I appreciate your underlining the need to make a decision on it, and I would favor the broadest language.

DR. MESLIN: For 1.3 as well?

DR. SHAPIRO: I think we should make a decision --

PROFESSOR CAPRON: Yes --

(Simultaneous discussion.)

DR. SHAPIRO: -- 1.3. That is my main concern, that it would be the same thing in 1.3 and what is now 5.4. Having been one of the authors of this, I never even thought about the issue. I mean, it just happened from the language that came out as I was writing at breakfast this morning, but --

PROFESSOR CHARO: So, if as the table continues to think about this, if it turns out that the consensus is to go for the broader language, would that mean also to stop talking about the FDA particularly, and say federal agencies should not conduct certain kinds of trials, federal agencies should not accept certain kinds of data, and leave it as general as all federal agencies? In practice, I think the FDA is virtually the only agency that would have any use for it, but I can imagine that there are some, like USAID,

that might on some occasions be accepting this kind of data. And should we just broaden this, and say, you know, federal agencies?

PROFESSOR CAPRON: How about USDA? Isn't it possible that on foodstuffs they might rely on foreign trials?

PROFESSOR CHARO: Yes, I suppose. In clinical trials, the nature of the data is kind of limited, but it could be, you know, vitamin trials, for example. So, should we just say federal agencies, and stop referencing the FDA particularly?

PROFESSOR CAPRON: Why not?

DR. SHAPIRO: If it relates to clinical trials, I am comfortable with it. I mean, there is a lot of other data coming from these countries which we use for various purposes, like agriculture or other reasons, which are not generated by clinical trials. I am not trying to reach -- I do not think we should try to reach that data.

PROFESSOR CHARO: No, no. Clinical trial data only, but now not -- Should we stop referencing the FDA, and just say federal agencies should not accept clinical trial data that does not meet the standards set out here?

DR. SHAPIRO: I understand. Larry?

DR. MIIKE: Well, let me try this then. Suppose CDC or NIH wants to see a trial that was conducted for a particular drug and they want to replicate it. But the trial they want to replicate does not meet these requirements. Are we banning that? Do you see what I mean? I am getting to if you use the word "use" really broadly -- You see what I am getting at? Can they design a trial that is to test the efficacy of a drug that was done in a trial that would not meet our standard?

PROFESSOR CAPRON: In other words, they are using the other data to --

DR. MIIKE: (Not at microphone.)

PROFESSOR CAPRON: But that is to say, everything except the parts of it that were unacceptable.

DR. MIIKE: Well, if the data comes from a trial that did not meet our standards, then I am simply asking the question that, if they see it might be a worthwhile drug, and they want to see whether it is true or not, and you know, we do many replication studies. Are we prohibited then from doing that? I am just thinking whether the word "use" is going to be too broad.

PROFESSOR CAPRON: Let me just understand

if I can, Larry. In other words, the use would be the realization that looking at that trial, it was not conducted in a way which -- And therefore, they are using it to prompt themselves to say we need to do another trial. They are not relying on the data; they are rejecting the data.

DR. CHILDRESS: But it is because of the data they want to conduct the trial.

DR. MIIKE: Right.

PROFESSOR CHARO: Larry, you know, recognizing that we are not writing statutes or regulations here, so the words are important only to the extent that they have a kind of tone that sends a sense of what the meaning is, would the phrase "accepting data" help? Because that carries within it a slight implicit tone of accepting and giving a kind of regulatory use to it, whereas -- You know, I understand your point about the word "use", but -- Because we cannot go completely nutzoid here.

DR. MIIKE: Oh, no. I understand. I mean, the simplest way to deal with this is explain in text what we mean by that, and what we do not mean, you know. Right?

DR. SHAPIRO: I mean, in general, I favor -- I mean, I would have to think about this more, to

be honest, but in general, I am sort of inclined towards the broader definition. I am not quite sure, Larry. I still do not understand -- I apologize -- the problem you pose. I know there are some inadequate trials conducted at some point, and now somebody wants to replicate that trial, or just --

DR. MIIKE: No, I am saying it does not matter if it was inadequate or not. Suppose there was -- When you do a study of efficacy of a drug, one trial is never enough.

DR. SHAPIRO: Correct.

DR. MIIKE: So suppose something very significant was done in an African country, or some other country, which could be a very significant finding. And NIH wants to see on a larger scale whether that is true or not. By the way, I am for a broader use. I just get worried that if we use it so broadly, then -- On the other hand, we are just advisory, so people --

(Simultaneous discussion.)

DR. CHILDRESS: In response, Harold, I think what it means is using the data to formulate a trial to see if you can replicate those results, but you are using the -- Without those data, you would not be going to develop a clinical trial here along those

lines. Is that right, Larry?

DR. SHAPIRO: My own view, without trying to write -- I am going to have to think about this, but my own view is that we want to signal that, you know, you cannot profit, as I guess Alex used the word, you cannot profit by doing bad, unethical things. But we will have to worry about this. I am not -- We will have to get the words. Arturo?

DR. BRITO: If we go with the broader category, federal agencies, then I am not sure how the second part, if we agreed that the second part of recommendation 5.4 is going to be included in the recommendations, how that differs from what we are saying in the proposed recommendation 1.3. That said, because at the onset we do include the broader category, maybe it would be prudent here to specify the FDA, because what we are really concerned about here, I think, is with clinical trials, is the approval of medication, or some device, based on data from unscrupulous research of some sort.

So, I think if we include the broader category at the onset, I think it might be wise to go ahead and point out the FDA, because what I am hearing, and from what I know, I do not think there are too many other agencies that we are really concerned about with the

use of data in this kind of scope, or the concerns that Larry brings up.

DR. SHAPIRO: Of course, the general proposition is made in 1.3, and what 5.4 does is talk about a specific thing, the number of IRB reviews, and that is just to make sure that when we write this -- I am not trying to defend the exact way it is written -- that we include the FDA at least in requiring the two IRB reviews unless equivalence determinations are made. But okay, we will have to think that through a little more.

Alex?

PROFESSOR CAPRON: I want to make sure I understand the structure. The reason for having 5.6 and 5.7 come after 5.4 is that the way that you are going to lay it out in the text is that 5.4 speaks of a determination which can come about either specifically as to a foreign IRB, where they do whatever they need to do on an assurance basis, and they say this IRB is operating in a way which we okay, or the route that 5.6 and 5.7 allow, of this system-wide. Is that correct? And it does not make sense to get to the system until you have done the other. Okay. Because otherwise, the logic --

(Simultaneous discussion.)

PROFESSOR CAPRON: If we were only saying, well, there should be a system for endorsing IRBs. If the IRB has been endorsed, then it should be acceptable to only have one foreign country IRB review. Otherwise, it would just seem logically to flow the other way. But if you are coming to this point and saying now there are two ways of meeting that criterion, one is they say you met the assurance, the other is this route, then I can see how it would be laid out, and I just want to make sure that that is what you are planning to do. Is that right?

DR. MESLIN: Yes, using, again, the logic statement from yesterday, where we had item 3, "substantive protection can be assured by an ethics review committee. Host country review is necessary, and a U.S. IRB is necessary to supplement it, unless the host system has been determined to achieve all of these things --" Alta had some text that essentially described that this means for the near future that dual review will always be required.

And then, one would then have to move towards how would it be that it would not be required. It would not be required when -- so, the chapter which is really a bit -- has been moved in some ways to show it to you, is to put the equivalent protection argument

after the ethics review argument.

PROFESSOR CAPRON: I would like to take up another point that Alta brought up yesterday about the system of accreditation, or whatever. Short of a system of accreditation, what does it mean for an IRB in another country to get an assurance? That is to say, what is the process by which somebody sitting in Bethesda, or Rockville, or wherever they are, figures out that it is appropriate to say an IRB at some institution far away meets the criteria for an assurance?

How do they negotiate it? Do they send people out? Do they -- I mean, and you see the problem here is if we are taking the step of saying that it is possible to do this, to have equivalent protections by either of these routes, we know that the second route requires both that good criteria be set up by OHRP, and that they be applied, and as far as we know, outside Canada, and England, and a couple countries which are not in play in this report, that is not happening any time soon.

But on the first route, what we will say -- I think we have a responsibility to the public to describe in a little detail what is going to happen there, and how reliable we think it is in determining

that, indeed, the substantive ethical protections outlined in this report could be met. We could know, for all the reasons that Alta was talking about yesterday.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: In the text of Chapter 5 that we received last night, there is discussion about deeming a system substantially equivalent, and not individual research institutions. I think this is a crucial point because we have heard testimony from former OPRR staff that they did not go out to do site visits before issuing Single Project or even Multiple Project Assurances for foreign institutions. It was a paperwork battle. Putting words in their mouths, I would suggest that any institution that had the fortitude to survive the paperwork blizzard had demonstrated they probably had other resources that meant they probably could fulfill their responsibilities. It was a kind of rough proxy based on torment.

DR. SHAPIRO: The ultimate bureaucratic solution to a problem.

PROFESSOR CHARO: That is right. I do not know that it is possible, really, to do an individual review of foreign institutions. And so, the

determination that a system is substantially equivalent is going to have to be done with enormous care, with regard not only to their stated principles, which is all that is used in some cases now under the current system, but with a lot of attention to their practical abilities as a system, and their experience as a system, and their track record as a system, in regulating their own institutions.

And by this measure, I might point out that other countries could easily have decided that our system is not all that reliable, since it does not require prospective accreditation, and licensing, and forced education, and relies on post hoc, sporadic site visits. I mean, we are talking about setting up a standard that is so rigorous we might have difficulty fulfilling it. So, we have to somehow make it rigorous, but also, not make it more rigorous than the one we impose on ourselves. But I do not know that we can get much further than that.

But I do think it means that we have to make a clear finding. A finding of substantial equivalence is not a trivial thing, and should not be done lightly, because we are putting a lot of trust in it. Again, it is a little equivalent to the whole criminal justice system, where you essentially find

that another country's justice system is equivalent enough, that we do not consider there to be a fundamental problem when U.S. citizens are tried under their laws, jailed in their prisons, and treated to their conditions.

DR. SHAPIRO: But I mean, I think the issue of determining substantial equivalence in a system is as you have described, and I do not want to add anything further to that. That is why I think we all think it is far in the future.

But I took it, Alex, that your point was, should we be saying something more than we are saying about the quality of the assurance process as it exists today. We do have lots of Single Project Assurances that have been issued as this research goes on, and the question is, should we have any observation, provide any observation, regarding the quality of that program, or concerns about it, or -- I took it that was the question.

PROFESSOR CAPRON: Yes, that is exactly it. And I would wonder if it would be possible, if we have not done this already, to talk to the people at OHRP about this, to talk to people at the State Department, and ask whether a liaison arrangement between the scientific officers of embassies abroad in

which they would be trained in a way about, in effect, doing a little on the ground site visit with a report back to whichever office like OHRP is going to issue the assurance. I mean, have we explored any of those things where we might be able --

In other words, if we are going to suggest something, we ought to find out whether there is any basis, or if people think, yes, we could do that. We could have a little coordination here. And then, make that a recommendation. Just try to be helpful rather than just critical.

But I think we need to wave a little bit of a flag saying from what we know now, it is unlikely that the assurance process is anything other than -- I like Alta's language -- a rough proxy for your ability to do ethics review, simply because you have enough internal institutional bureaucracy to handle all the paper we are throwing at you.

DR. SHAPIRO: I think what we can do in the time we have here is we have a section on assurances in here, and I think we need to, at the very least, raise these issues, and at least plant a flag there even if we are unable to really, you know, do a careful and thoughtful analysis of where we are. So, I think that is a very useful suggestion.

MS. KRAMER: Could we acknowledge that although this is aspirational and may be difficult to even fulfill altogether, that there is the interim arrangement of accepting the local review for purposes of community consultation and advice on parts of what would be an IRB review, though not in its entirety?

DR. SHAPIRO: I am not quite sure -- Bette, I do not think I quite understood what you were asking. Maybe I just did not hear it correctly.

MS. KRAMER: Well, I think I am not saying it well.

DR. MIIKE: May I respond?

DR. SHAPIRO: You can.

DR. MIIKE: Well, I think 5.4 does that. It does not say that the local IRB -- It says that there has to be local IRB review. It does not say what the quality of the local IRB review has to be in the specifics, and that is why there is a back-up by the U.S. IRB.

And by the way, I do not think -- My understanding of 5.4 is that -- and I think I know what we are talking about, an assurance versus a substantial equivalent system -- in 5.4 we are saying until such time as a country has a substantially equivalent system, this double review goes on.

DR. SHAPIRO: Correct. That is correct.

DR. MIIKE: But anyway, to answer you, Bette. We are saying in 5.4 that there is to be local IRB review, and we are not waiting for that local IRB review to take place until they are substantially equivalent, and that is why there is the back-up of the U.S. IRB.

DR. SHAPIRO: Well, I am presuming that either the local IRB could be encouraged, just as we encourage our IRBs, to do community consultation. That is what you are concerned about, I think, is whether, as I understood your question, the local IRB should, in your judgment, be involved with community consultation.

MS. KRAMER: Right. I just meant not certainly as part of a recommendation, but just in the language, to empower them, even though they may not be able to take it over in its entirety.

DR. SHAPIRO: Okay. David?

DR. COX: I am becoming more and more troubled by Alex's comment, because I completely agree with it. You know, this business of we know in our hearts that there is some places that are equivalent, okay. But by what process have we decided that they are really equivalent? And what we are asking somebody to do is go and do that, although we cannot articulate

it ourselves.

Do not get me wrong. I mean, I am in favor of the direction we are going here, but I think unless we do that, unless we are able to articulate it more clearly ourselves, what that process is going to be, it is hard to -- I ask myself, well, is it even really true, but because we can identify a few of these countries where we say, yes, they are equivalent, then I think maybe the road to that is saying how do we know they are equivalent? Why do we feel that way?

DR. SHAPIRO: Thank you. Yes?

DR. MESLIN: I do not know if it will be helpful, but we go to some length in whatever version of Chapter 5 you read, the one late last night, or the one that you had more time to read before, to stipulate the necessity for criteria being developed. We go out of our way to outline what I think is a reasonable set of criteria. Alta raised it earlier with respect to whether it is the USAID triple pillar approach, or something far more comprehensive.

I just, as a matter of strategy, would encourage you to maybe take a step back from proposing an actual process. This is an extremely complicated matter. We know from our own research that even OHRP in its effort to move towards what you are discussing

as equivalent protection declared not that Canada or India was itself a system of equivalent protection, but in the course of negotiating what were then Multiple Project Assurances, used the regulation to say that those guidelines essentially satisfied our requirements with respect to an MPA, and they were satisfactory to the Secretary, which is the language from the regs. It was not giving Canada or India the equivalent of an MPA. It was saying you still have an assurance, whichever the relevant institution is.

And the reality is, even for those developed countries with very sophisticated guidelines, it will probably be a political, in my view, a political and a policy decision as to whether the U.S. government wants to give up the ability to directly oversee another institution's process, which is what would happen by deeming another country's guidelines, or its system, to be equivalent. And that is why I think you were proposing that an equivalent protection determination, while aspirational, is a goal to be sought.

There are many steps in between. Some of us were at a meeting earlier this week with someone from the State Department who said they were reviewing a study, an international study, and had to decide

whether the guidelines being followed in another country were acceptable. I do not know whether they had had discussions with OHRP at all. I am just suggesting that this may be a time to be less specific about the process, because the hardest issue is going to be identifying the criteria, and we have given suggestions for what that should be, and are making recommendations that they be developed.

DR. SHAPIRO: David, then Alta.

DR. COX: So, Eric, I agree with you, but I have this little man in the back of my head that says this is great, we have our criteria, but that if really everyone sort of winks and nods because they are going to do it politically, not based on our criteria, then what the hell are we doing? So, I take your point, but I do not want for us to be able to put these things in really meaning it, but with full knowledge that no one is ever going to use them. So, I mean, we cannot force people to use them, but it just worries me.

DR. SHAPIRO: Alta.

PROFESSOR CHARO: I wanted to note that there seems to me to be a connection between this discussion and the discussion about recommendation -- about 1.3, and what to do with sub (c). And the version of sub (c) that I am thinking about is the

following situation: A private pharmaceutical company whose own people are doing work in another country. They are not affiliated with a U.S. research institution, and they are not receiving any federal monies in order to do their work. You see, if you have got somebody who is affiliated with a research institution, we could encourage, if we chose to, we could encourage OHRP to insist in its new federal-wide assurance process that each of those institutions make a pledge to having --to reviewing work by their own employees, even when it is done off campus, or off site.

PROFESSOR CAPRON: And not federally funded.

PROFESSOR CHARO: And not federally funded, right. And for federal agencies, they could impose on themselves, and we could recommend that they impose on themselves, a requirement that they review locally. That they review here in Washington, or wherever they are located, the work that they are sponsoring or conducting.

The only group of significant entities that can really elude those remedies that kind of make sure that there is going to be a U.S.-based review are the private companies who are doing work abroad.

Now, on the one hand, we are saying that we do not think that at this time there are many places that could meet the substantial equivalent system definition, and we are saying that there are many individual institutions in those countries that would have difficulty even if the system was in good shape in that country. For companies that are unaffiliated with research institutions, and not getting funded by the feds, unless we have some way of reaching them to say please do a U.S.-based IRB review, we are essentially throwing up our hands and going -- There is not necessarily going to be a U.S.-based review, and we have already expressed the view that there is not likely to be a very rigorous foreign review, and so, in no place is there likely to be a really excellent review. And so, the elimination of 1(c) as a subject of attention leaves, I think, an important gap.

DR. SHAPIRO: I agree with that. And I hope we can get some material for something like 1(c). I just had trouble articulating it in ways that did not in the end seem a little silly, and so I just was struggling with it. But if people have ideas around 1(c), I really could use the help.

Alex.

PROFESSOR CAPRON: A comment Larry made a

moment ago made me think I do not understand -- Or the understanding I expressed before, and with which Eric agreed, I mis-communicated because what Larry said was different, and I understand why Larry said it. It was the second sentence of 5.4. The language there says "unless the host country's system of human subjects protection". And I had suggested that I read that as meaning either the system at that institution, i.e., an assurance that they get, or the whole country-wide system getting the equivalent protection finding. Now, the actual language of the regulations talks about equivalent protection as though it applies to an institution as well. It is not necessarily country-wide.

Are we saying that if they get an assurance at that institution, that that is enough, or not?

PROFESSOR CHARO: The way I have been reading it, you actually have to have a country-wide system finding of equivalence, and although we have not gotten to the specific wording of 5.6 -- And by the way, every time I am criticizing this I have to note that I was involved in writing the very things I am critiquing now.

In 5.6, I think it is probably not clear

enough that what I think we are setting up there is a presumption that if the system is found to be substantially equivalent, then we can presume that the institutions within that system are capable of providing the protections outlined. But it is a presumption only, because you could have a nice system, and some lousy institutions. So, it is a presumption only.

PROFESSOR CAPRON: Well, if I may. If that is the reading, then I do not understand why we need 5.6, or conversely, I would turn 5.6 on its head, and say that a system should only be found to be a substantial equivalent if it is found to provide through its institutions protections outlined in this report. In other words, this would be advice to OHRP, et cetera, as to what kinds of criteria they should establish, which would be both substantive criteria, and enough assurance about the way the system works, for exactly the point you just made.

It is a different thing. It is rather than a statement which is like a conclusion that if this, then that; say only do this when that. And then, 5.6 to me has some real meaning, and it goes along with 5.7. It tells them what those criteria standards should be.

But also, now I understand 5.4 better. I want to ask -- So, that is point one. The second point is, I want to ask, in effect, what the version of the question Steve was pressing yesterday about why bother with a substantially equivalent system if you do not get off the hook of dual review. Why bother to get an assurance if you do not get off the hook of dual review? Because we are now saying that you could go through the whole process, and get an assurance, and you would still have to be reviewed by a --have the research reviewed by a U.S. institution.

So, if I am running the IRB in Uganda, why do I want to go through this paperwork blizzard? Why do I care? In other words, what is the encouragement to sort of make the natural progression so that I am part of what becomes a nationwide system that then meets equivalence? Isn't it sort of you have to walk before you can run type of thing? And do not we want to encourage people? But I guess there is no real payoff.

DR. SHAPIRO: Eric.

DR. MESLIN: I just wanted to remind people that we have both from our own research, and from testimony that we have received, there is not this international outcry by individual countries to not

have dual review. They are not chomping at the bit to have a U.S. IRB not review their research. In fact, we have heard testimony, and we have research data that show they find that it is helpful and it is useful.

The idea of equivalent protection is not meant to solve the entire burden of IRB review problems. It is meant to make a principle statement, and to move, or as is being proposed here, to move towards a situation where the kinds of burdensome duplication of effort can be avoided. But the substantive need for dual review described by a number of people, and in our work, for local context as well as expertise remains.

We did not hear in our survey that an overwhelming number of countries wished that the best way to achieve equal partnership is that the U.S. would grant them equivalent protections status. So, I do not want you to mistakenly believe that the only goal of an assurance, or the goal of equivalent protection, is to not have to go through double IRB review. It is one of the benefits that might arise. Those countries who want to negotiate an assurance do so both because they are required to, and those who get IRB review believe that it is helpful to them --U.S. IRB review believe that it is helpful to them.

DR. : (Not at microphone.)

DR. MESLIN: Yes. Except for countries who have those what we believe to be the substantially equivalent systems. I mean, the Canadas, and the UKs, and the Australias believe that it is an imposition of a burden to require the procedural minutiae that the assurance negotiation requires.

DR. SHAPIRO: Larry, then Bette.

DR. MIIKE: What Alex just said has just puzzled me. I thought it is pretty clear in these things that what we are talking about in 5.4 is that one of the pillars that we are under in terms of this whole report is reflected in this in the sense that local IRBs -- We are talking about autonomy, equal partnership, so local IRBs must review the research. And until such time as the country system is found to be substantially equivalent, U.S. IRBs also must review the research. If they are found substantially equivalent, the U.S. institution can still insist, and say we are partners, we are still going to review it. There is nothing prohibiting that.

But that is not what you said, Alex. I thought you just said that there was no incentive to get substantial review because there was always going to be double --substantial equivalence, because there

was always going to be double review.

PROFESSOR CAPRON: No, I am sorry; I was not clear. What I was saying was I had first read this to say that you could get --you could qualify for the second sentence and avoid U.S. review, particularly if you find it not just burdensome but kind of insulting, by either having your whole --be part of a system which has been found substantially equivalent, or if you went through the assurance process. That is to say, you were found to --your own institution was found to provide --to achieve all of the substantive protections outlined in this report.

I took the word system to mean could include the unit in the system. And your question made me look at it again, and then I looked at 5.6, and I thought, I think Larry has read it correctly, and I have read it incorrectly. And although I was getting a yes to my previous question, I think I must not have gotten the right answer.

So, I agree with what you just said. My second question then was, well, what incentive is there if that is the case, if you are in a country which has not been found substantially equivalent? What is the incentive to get your IRB to have an assurance? And I gather the answer is there. The incentive is if the

money is going to go directly to you, you have to have an assurance. If the money is being brought in by a U.S. team, and you are not getting a grant from the federal government, you do not need an assurance, do you? Is not that right?

DR. MESLIN: Yes, you do.

PROFESSOR CAPRON: You have to have an IR -- This recommendation would say --

DR. MESLIN: If you are from an institution that is receiving federal funds, you have to have an assurance.

PROFESSOR CAPRON: I know. That is what I am saying. If your institution -- Wait a second. I mean, if I am running a project at USC, and I purchase things from people, if I purchase a service from someone, they do not have to have an IRB if the research is being run by me. Isn't that right? If I have a collaborator to whom money directly goes from the federal government, if I have a subcontract where the money is going to go from the federal government directly to them. But I can imagine going into a country where the U.S. --most all of the money is being expended for U.S. personnel, U.S. equipment, U.S. drugs, et cetera, et cetera.

And likewise, it is true under the FDA

system, isn't it, that if an American company comes in, they do not need an IRB that has an assurance to work with them. Isn't that true? Well, what about the former? How do you read it?

DR. MESLIN: Well, it is not, because when you talked about collaborative -- I am sorry. When you talked about collaborative research, this is where that section 114 from the regs comes in from yesterday. Well, you have the text in front of you. So, if you are receiving those funds, then -- When you said you are paying for services, where did you get the money from? If you got the money from a U.S. federal --if you got it from a grant, then your IRB is going to have to review it.

Isn't that what you are --

PROFESSOR CAPRON: Suppose the money goes from the CDC, not the CDC, NIH to Harvard, give them a million dollars. And they are spending 950,000 of that million dollars for Harvard faculty, U.S. equipment, drugs, transportation costs, and they get there with $50,000 and they hire some nurses in the local community, and they have a local professor who is the professor of medicine who works with them, but they are not giving any money to the University of XYZ there. They are hiring people there.

The University of XYZ may decide that because its personnel is involved, it should be involved, right? And maybe the local IRB will be involved. But the local IRB in that case, do they need an assurance? I mean, after all, the federal government on the other hand says if you buy stem cells, you are just buying something. So, I mean, there must be times when it is just a purchase arrangement, where the federal money does not flow directly to that other institution. Remember?

DR. MESLIN: I confess I am a little confused. I would have to --

DR. SHAPIRO: Yes, I think they do not require an assurance.

PROFESSOR CAPRON: I mean, that is different from a collaborative arrangement where you have a mutual collaboration from the University of -- and Harvard, and they both directly get federal dollars. They get overhead with it. I mean, in other words, it is an institutional arrangement.

Now, I understand there you have to. The incentive to have an assurance is if you do not have an assurance, they will not send you the money. I understand that. But if you are in the arrangement that I described, or you are in the arrangement that

Alta described before, where a U.S. company which is not using federal dollars goes over there, and they get an IRB review, but the IRB does not have to go through all the rigmarole of getting an assurance.

DR. SHAPIRO: That is correct.

PROFESSOR CAPRON: And they do not gain anything by it. I just want to be clear. They do not gain anything. They do not come out --

DR. SHAPIRO: Yes, that is right.

PROFESSOR CAPRON: --under the second sentence --

DR. SHAPIRO: But what is the problem with that?

PROFESSOR CAPRON: I just want to be clear that that is what we are saying.

DR. SHAPIRO: I think that is a description of the situation. I agree. But to me, there does not seem to be any problem with that.

Alta?

PROFESSOR CHARO: Bette? I think Bette was ahead of me.

DR. SHAPIRO: I am sorry.

MS. KRAMER: Two things, all right. One is a confusion of my own, and I am sure that it is answered somewhere in the material, but I wish somebody

would point it out to me, because I do not understand why an individual institution within a country could not be certified to have an equivalent IRB process, why it would need to be country-wide as opposed to institution. Just thinking in terms of, say, some of these underdeveloped countries where there may be, you know, there may be a center, and it is --

PROFESSOR CAPRON: Which is excellent.

MS. KRAMER: Pardon?

PROFESSOR CAPRON: Which is excellent.

MS. KRAMER: Right, exactly. And why, if that is the institution with whom you are going to do business, if they have an adequate IRB, why that would not be sufficient. Now, if it is -- It is probably covered somewhere in the material and I just do not know where. I would like a reference.

DR. SHAPIRO: It is not covered.

MS. KRAMER: It is not.

DR. SHAPIRO: I mean, this is -- I mean, it is not covered in the sense that you suggest. That is, the way it is currently structured, that that local institution's IRB could get a Project Assurance, and so on and so forth, but it could not be exempt from the dual review.

MS. KRAMER: So, they could not -- An

individual institution cannot on its own attain equivalency.

DR. SHAPIRO: That is correct.

MS. KRAMER: It has to be country-wide.

DR. SHAPIRO: Right.

MS. KRAMER: And do we have a reason for that?

DR. SHAPIRO: Well, I do not know if we have a reason. I have a sense in my own head in that the kind of confidence I have in the protection of human subjects depends more on a single institution. And I mean, I am much more comfortable when this is something which is backed up by a system which is country-wide, and has some authority, and so on. I do not have to rely only on that institution, and the particular officers that are there at a particular moment in time, and so on. That is just my view.

MS. KRAMER: One more point. I would like to go back to something that Alta said before on a different point altogether, and that was how to capture (c) from the notes yesterday. If you go back to the way number 1 was written yesterday, where it is written in terms of "people should not be enrolled", could that language be used, and then expanded to say "by any agencies in any trials" et cetera? Could that -- Is

that more general language that could capture the concerns about --

DR. SHAPIRO: About (c)?

MS. KRAMER: Pardon?

DR. SHAPIRO: About (c)?

MS. KRAMER: Yes, right, exactly.

DR. SHAPIRO: I am open to all considerations here. That is a job not -- We have not done that job yet. Any suggestions you have, I would really very much appreciate it.

Alex, before we go on, you had a suggestion about 5.6 which, when you mentioned it, seemed useful to me.

PROFESSOR CAPRON: To repeat what I was saying was, in effect, flip it over. That is to say, say that OHRP, or whoever is going to be the U.S. government in identifying the criteria for substantial equivalence, should make sure that a system will ensure, procedurally and substantively, the protections outlined in this report. In other words, because if you look at the present description of substantial equivalence, Bette is correct in that under the federal rules, all substantial equivalence means is that the procedures prescribed in the country are equivalent, you know. But it is an institutional judgment. And

so, since that emphasis is procedural, and ours is substantive, it was simply a suggestion that rather than making it a --which was really not a recommendation, but was a conclusion. Recommendation 5.6 is really a conclusion, that if X, then that is presumed to be the case, and instead say, only X when that is the case.

DR. COX: That solves my problem completely, Harold, because -- I was not able to articulate it, but that is exactly what I was getting to, and when you flipped it over, Alex, it completely solved my problem, because it basically says there cannot be other ways, you know, of doing this. You have to show that, and then, it is equivalent.

DR. SHAPIRO: Alta.

PROFESSOR CHARO: I am returning, I guess, to the earlier discussion about the role of having an assurance, if there is any at this point. I think Alex is correct, that we have made the business of getting an assurance irrelevant if it has no effect on how research is conducted and reviewed at a particular institution. If that is what we want to say, and we could say it. It is a legitimate position to take. Express skepticism about the ability to issue assurances for foreign institutions where there is no

real capacity to inspect and monitor, and say there should be no such assurances, and that dual review can be foregone only when an entire nation's system has come up to snuff. I think we should say it. Let's be very explicit about it.

Of course, when you get that explicit, you get nervous about what it is that you are doing here, right? Do we really want to do something that dramatic? And knowing that in many of these countries the central government could be in complete disarray at any moment, while individual institutions manage rather miraculously to continue working, because there is this immense compartmentalization that has taken place as a survival skill, do you really want to take away the ability to somehow certify, accredit, assure, or whatever, on an individual, institutional basis?

Keeping in mind Eric's point that what we are talking about here is not whether or not research can be done in those places, but only whether or not it can be done without any U.S. review to supplement, right? I think either position, actually, is defensible, but we should say which one we want to take very clearly. No more assurances, let's get out of this business. It does not work; it cannot work; it is illusory. Or, let's continue it; let's speak in 5.4

about U.S. IRB review, you know, should supplement the local review unless the host country system has been determined to achieve all the substantive --unless the host country system, or the specific research site has been determined to achieve all the substantive protections outlined in this report. And a determination that a site has achieved these protections could be made via the current assurance process, or any new accreditation process that might be developed in the future.

But I think we would be better off stating it clearly one way or the other, because right now I think it is buried. Alex uncovered it, but it is buried.

PROFESSOR CAPRON: Alta, could I add just one thing? I think that is a very helpful putting together of what we might do. I am comfortable with everything except the statement "through the current assurance system". I mean, I think that the point of it would be to say "through an improved assurance system". But the current one would not give us the confidence that it really is working.

PROFESSOR CHARO: I have got to say I am a little bit nervous about that, because I share with Harold the sense that institutions that are not backed

up by a national system are considerably weakened. I mean, fine, they can have all the right people with the right expertise and the right intentions, but the fact is, without a system that has, for example, enforcement powers, penalties if you fail on the job, things are likely to go wrong more frequently.

But it is an imperfect world. I am able to live with either solution.

DR. SHAPIRO: I understand the point very well, and it is a matter we should discuss, because it could be written either way without great difficulty. I guess I am just reiterating what I said before, and what Alta just said at the end of her remarks.

I think the integrity of this individual institution cannot be separated in my own mind from the integrity of the system within which it operates on issues like this. It has to do with how individuals are treated, what happens to you if you do not treat them right, and so on and so forth. And that is just my view.

This is not a big, huge thing from my perspective. I think from the point of view of what we are doing, we could go either way, and you know, I could live with it. It is not a matter of huge principle to me. But that is just my view.

So, I associate myself with the latter, but this is not a matter for me to decide. I could go either way with this. That is just my view. How do people feel about that?

We run into what is at stake here. What is at stake here is single IRB review versus double IRB review. That is what is at stake here. It is not like, you know, the whole shooting match is at stake here.

David.

DR. COX: Harold, philosophically I agree with you, but in this situation, I want to be practical, and so, I come down where Alta is, because -- And what Bette brought up. Because I really would not want to preclude, you know, a group of people who can really do this correctly, even if they are in a messy situation. That is all.

Although, you know, whether that is ever going to be possible to do, which is your point, you know. I take your point. I would like to write it with the presumption that would at least give people a chance.

DR. SHAPIRO: Okay. How do other people feel about that? Bette?

MS. KRAMER: Well, I actually am going to

change my position, because what you -- I hate to do it, but the thing is that what you would not have, if you did not have a country-wide system, you would lose that policing function, so that if the individual institution which had at one point been found to have an equivalent system were ever to lose that, what basis would you -- You would not have any way of knowing that, that I can think of. So that seems to me to weigh in favor of making it be country-wide, because the policing function is important.

DR. SHAPIRO: Other views on this particular issue? Arturo?

DR. BRITO: But what about the situation where you have an institution that has a history of doing ethical research in a country, and the policing function from the country itself does not exist just because they do not have the infrastructure? What you are really doing is penalizing that individual institution. So, I would favor, with a little nervousness here, but I would favor the institutional approval, you know, for single IRB review if there is a history there, and there is equivalent protection within that institution. Because I think there are situations where, in the developing world, that the infrastructure just may not be there. So, more at the

individual institution in that country.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I agree that some institutions may be more stable than their government, or the broader governmental systems, and I would agree with Arturo that the institution might be more stable, have more stable personnel, more stable policies and practices.

DR. CHILDRESS: I would go in that direction also.

DR. SHAPIRO: Okay, other people's views of that. Trish?

PROFESSOR BACKLAR: I would go in that direction with trepidation.

DR. SHAPIRO: With trepidation.

PROFESSOR CAPRON: I would be willing to do that only if we are very clear that the U.S. side of that, that is to say, OHRP or whoever is doing this, has to be able, initially and on some ongoing basis, to be more informed than they are in the present arrangements. I mean, it is bad enough that U.S. institutions -- I mean, what is our enforcement --

(Simultaneous discussion.)

PROFESSOR CAPRON: I mean, we have an assurance system, and then in recent years, we have had

a few eruptions of problems that have led to closures, and so forth. But if you had three years ago said name five distinguished medical schools, and you had said, well, I do not know, Yale, Harvard, Penn, Duke, UCLA. Now, a few of those I just mentioned have been in the news. And we did not know that. I mean, a reporter who came to you and asked you to name ones, and said, well, are those good places or bad places. Those are good places, I guess. Why not?

I mean, you could apply Cox's rule about follow the money, and assume that if there is a lot of money, they are -- but short of that, we do not know.

So, who are we to say that if you do not have a country-wide enforcement mechanism it does not work? But it does mean that OPRR, whoever, OHRP, has got to play a different role than they do in the present system.

DR. SHAPIRO: Alta.

PROFESSOR CHARO: Well, I think it is too late in the game to make the suggestion that this be a recommendation. We certainly have not had time to think about it, or test it out. It is the kind of thing that might appropriately still be put in the text as an idea that is worth exploring.

The current quote unquote "assurance

process" needs to be transformed, I suspect, in ways Alex is describing, into something much more akin to an accreditation process in which a U.S. government agency --let's call it OHRP for the moment, but it is not necessarily going to be them -- has the role of looking out over all non-U.S. institutions, or in the case of this report, at least all non-U.S. institutions in developing countries, and saying we are willing to accredit you, and we will accredit you if you meet certain criteria having to do with both the substantive rules that you apply, and the practical ways in which you go about applying the rules. And accreditation processes come with a whole panoply of things that we are familiar with. They come with periodic reaccreditation, they come with means for testing competency, and essentially, it is licensing institutions to be able to carry out research without any kind of supplemental review back in the United States, and have the research be usable in the United States for various purposes.

It gives them an economic edge. They can sell their services to companies that need to do research at that site by saying look at us, we are accredited. Come here, it is easier, it is faster. We give you a reason to come to us instead of going to

Makerere across the border, whatever it is.

And that is an approach that does, I think, what Alex is suggesting. It transforms the assurance process into something. It still lacks the system-wide kind of enforcement from their own national government, but because of the periodic interventions of the U.S. accreditation, or licensing body, it provides an alternative policing mechanism.

That is something that might be workable, but there are so many pitfalls, and details, and difficulties, that I would not suggest this be made into a recommendation, lest we look naive, and this be too simplistic. But it is an approach that could be explored.

DR. SHAPIRO: In a system where you are going to accredit or otherwise, you know, rate some other institution as adequate in these respects, what is the purpose of worrying about the country-wide system?

PROFESSOR CHARO: In my opinion, in general, if you have a country-wide system that has been found to be substantially equivalent, could in essence accredit all of the country's institutions in one fell swoop.

So, if we found that in South Africa the

government had put into place a system that was similar enough to ours in terms of the substantive goals for human subjects protection, and also, we had over discussions and such become confident had the policing powers to actually make sure every institution in the country that they are willing to let research be done at could do it properly, we could then essentially be deferring all of that accreditation and policing to the South African government, or to one of the South African provincial governments.

But if you cannot do that, and I think we have all decided that that is not going to happen often, since we are nervous about doing it even with research partners with whom we have much more frequent contact like the Canadians, that it would continue to be much more common that we would have some degree of deference to individual institutions, and that is where a more stringent and responsible kind of licensing or accreditation system would help.

I mean, the current assurance system -- and actually, even the word is kind of confusing -- it is an accreditation system. It is just a bad one. It is an accreditation system that basically says if you look like you have got all the right things, then you are accredited. But it does not go the full distance.

It will continue probably to be the more frequent way in which these arrangements are set up to try to ease the review process.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: Alta's point about South Africa is an important one, but there are other countries that would not have the same number of institutions as South Africa that would be doing the research. So, in those countries, the notion of a country-wide system is less meaningful than in the example of South Africa. So, from country to country, what would work best may be different.

DR. SHAPIRO: As I understand what is going on here, we ought to not carry the discussion on. I mean, obviously, the sentiment of the commission is to allow for the institution-by-institution accreditation, to use that word for a moment. So, we ought to write this in that context.

But I mean, what we are saying, to turn from the general perspective to the perhaps what we are -- What we are insisting on is unlikely to be accomplished anytime soon. Which means that we are, for practical purposes, we are into dual IRB review, period. And that is what the issue is.

And the other is a framework which may be

in the long sweep of things, because we cannot provide that kind of assurance for our own institutions, as Alex and others have pointed out, obviously, and we are not even close to being able to provide it. That is, here in the U.S.. And so, to think about us being able to reach out and make these decisions in cultures we do not completely understand, and so on, it seems to me a long, long way off.

But that is fine. All it means is we have dual IRB review.

PROFESSOR CHARO: But pertinent to that, and something that I noted on the text when I was going through it, something that we have probably not emphasized a lot in the recommendations is that since dual IRB review is going to be the future, and since there is often multiple centers in the United States involved in the trans-national research, a key thing in the world of dual IRB review might be to try to get the U.S. side of that review simplified down to a lead IRB. Because I suspect the problem with the dual review is not so much just the two reviews, it is that it is two, or three, or four. or five U.S. IRBs all going in circles, and driving the Haitian, or Thai, or Ugandan IRB out of its mind at the same time.

So, maybe we need to somehow more visibly

signal that we need to straighten up our own house for the U.S. side of that dual review to make this manageable.

DR. SHAPIRO: Yes, and that whole issue will come up in the Oversight --is dealt with, or at least discussed.

PROFESSOR CHARO: Right. And it is mentioned --

DR. SHAPIRO: In the Oversight Report.

PROFESSOR CHARO: --in the text. It comes up in the text, but I do not think it has been emphasized, and it certainly has not come up for a recommendation.

DR. SHAPIRO: Right. Larry?

DR. MIIKE: That last statement you made, I would not agree with, in the sense that I can buy into substantial equivalence for individual institutions only because I think it is more realistic that they can get it, rather than a country-wide system. It is much more focused, and it seems if OHRP, or whichever the U.S. government agency is going to do it --

DR. SHAPIRO: Just a forecast, that's all I have.

DR. MIIKE: But if it is an aspiration

that we are never going to reach, then I would say why bother with the individual institution. I think it is doable.

DR. SHAPIRO: Okay. All right. Let me make a suggestion right now. One, we have -- I know some members have to leave very shortly. We have the first part of rewritten Chapter 4, I think, which has been handed out --

PROFESSOR CAPRON: And the very end.

DR. SHAPIRO: And the very end. I will let Alex speak to that after we break for a few minutes.

But what we will do, I want to break. For those of you --maybe you will take a chance to read this, and I will let Alex say a word about it in a minute. But before we break, you might want to take a look at this. And I will get two or three people together to take another stab at some of these recommendations to reflect the conversations we have had this morning.

David?

DR. COX: One point that I was not clear about, was 5.6 going to be flipped around?

DR. SHAPIRO: Yes. As a matter of fact, I am going to ask Alex to give us some wording on 5.6,

because I thought that was a good suggestion.

Okay, Alex, do you want to say a word about this before some people start reading it, or should --

DISCUSSION OF DRAFT REPORT: CHAPTER 4 (CONT.)

PROFESSOR CAPRON: Well, what you, I think, will find is the organization follows the first few pages, makes use whenever possible of text with which you are familiar, although I think it has all been edited, brings in some arguments which I heard described, which I did not see fully reflected. This is entirely an effort, although I am sure it has not been fully successful in these pages, to reflect what I have heard people say that they liked about the previous draft, they did not like about the previous draft. I did not intend substantively to put any conclusions here that you had not already seen.

DR. SHAPIRO: And you recall, yesterday we did decide to put the recommendations of 4 all at the end, and Alex has also provided that.

PROFESSOR CAPRON: Yes. Unfortunately, the conversion between WordPerfect and Word in getting this out meant that somehow 4.2 runs into the end of -- I guess there is just no space. That is all it is. So it looks like one long recommendation, but it is --

Anyway.

MS. KRAMER: What would go between pages 11 and 37?

PROFESSOR CAPRON: Well, if you have the old draft, there is a heading as the one on page 11, "What Should Be Provided to Communities and Countries", and I just had not gotten beyond that in the rewrite. I was not trying to move everything around in the chapter.

I mean, one of the discussions we had yesterday after Jim suggested changing the order of 4.2 and 4.3, which is done here, was how difficult it would be at this point to totally reorganize the flow of the chapter, and one of the reasons for moving them to the end was you could switch them without switching the text as well. So, Bette, it is just more of the rewrite.

This is slightly shorter, you will be amazed to know since it comes from me; it is slightly shorter than the text from which it is derived.

DR. SHAPIRO: Jim?

DR. CHILDRESS: There were a few other changes suggested in the wording of the recommendations that are not reflected here, and I assume those got in.

PROFESSOR CAPRON: Yes, I --

(Simultaneous discussion.)

DR. CHILDRESS: No, that is fine.

DR. SHAPIRO: I have got a note of those.

All right, let's break for 15 minutes.

(Whereupon a brief recess was taken.)

DR. SHAPIRO: Okay. Eric will be back in a moment, and I think we just have a few mop-up moments here before we adjourn. We do not have a quorum, but let's just see where we are. I will tell you what the plans are.

My plan right now is to distribute a completely revised --I mean, a clean draft incorporating all the various changes that have been made, thought about, suggestions, to Commissioners in approximately two weeks from now. And I would like to hear back from Commissioners within the following week.

So, that means that we should know exactly where we are three weeks from now. I do not intend to have this on the agenda again at another meeting. It is time for us to part with this report in as best shape as we can put it in, and we will make every effort to do that.

We will be working a lot during this coming week, and if any of you have additional

suggestions on any part of this, it would be extremely helpful to us to get any ideas you have. It really makes a very big difference if you share your ideas with us, because in almost all cases, it really helps us improve on what we do. Not all cases. We do have some discernment.

And so, I really hope you will continue as you -- If you have a chance to think about our discussions we have had today and yesterday, and other ideas that maybe you have not come up with that you would like to express, and see incorporated in the report, this is the best week to get them in, this week, because we really are going at it, so to speak, in a very serious and comprehensive way. But we probably will not finish until approximately two weeks from now.

So, you can expect to get by whatever scheme -- We seem to have fallen into both e-mail and Federal Express, just to help you with a little extra paper. You will be getting that, hopefully, on Friday or Saturday, two weeks from now. And then, if we could agree that if you have any comments, concerns, whatever, that we should really have them the following week, so then we can take those into account as appropriate.

As is always the case, if there is any particular position which is really --you take serious objection to, there is always the opportunity in the report to state that. That is fully available to every member of the Commission, as always.

So, that is the plan. So, we are going to begin this afternoon, and let's hear from you if you think there are other things you would want to say.

Bette?

MS. KRAMER: Are we not going to discuss this revised 4?

DR. SHAPIRO: Yes, I am going to come to that next.

MS. KRAMER: Okay. I am sorry.

DR. SHAPIRO: So, I just wanted to -- That is what the plan is.

So, let's turn now -- And the discussion this morning, I found extremely helpful. I think we got a number of things straightened out that were really quite important. I think if I were to make a prediction now -- I do not want to -- We will talk about 4 in a minute. I think Chapter 5 will be substantially different. Not in its recommendations, but in its structure and in the text. That is, I think, where the biggest difference will be. Well, it

will be in 4 and 5.

And of course, 1 is now going to be supplemented by the first part of that scenario we worked out yesterday, and that will make 1, in fact, a lot more substantive chapter than it currently is now. It will not change it in any major way, but there will really be something that we are really saying there. Because the other recommendations in 1 are recommendations we have all been making for years, and so, there was really nothing else there. But now we have something a little more substantive. So, that, actually, is very helpful.

So, why do not I just turn to Alex for a second. He may wish to say something about how he has tried to go about this.

PROFESSOR CAPRON: I do not really.

DR. SHAPIRO: Do not really. Have you had a chance --have members had a chance to look at this? Well, let's see if there are any questions you have, and so I am going to begin a discussion of this.

We have, if we need it, three-quarters of an hour now. If we do not need it, we will adjourn sooner.

Alta, did you have something you

wanted to --

PROFESSOR CHARO: I had a question to start, and it has to do with the meaning of recommendation 4.1. And I do apologize. Yesterday, I got caught up in a call, and missed the early discussion on Chapter 4.

I was not completely clear reading 4.1 if the recommendation is that all participants in a trial, control or active arm, would, you know, should be given access, if possible, to any successful interventions post-trial. Or if 4.1 is saying that only those who actually got an experimental intervention during the trial, were in the active arm, and did well on it, would continue to have access after the trial, if possible. And terrible to say, I cannot remember what the Commission decided on this in the last meeting.

DR. SHAPIRO: Again, I do not know that my memory is any better than yours, probably not as good as yours. My recollection is, and if you look at the argument in the chapter, at least as I recall it now, the examples really talk about the participant more than --the active arm, as opposed to the control arm. But my recollection of our discussion was that we thought at the end of the trial, all participants would be eligible. Now, I cannot really quite construct it,

but that was my -- Because, you know, they did not know which arm they were going to be in, and in some sense, they all took the same set of risks. They did not have the same experience. That is the difference between these two. But they were part of the whole effort. That was my recollection of where we were.

PROFESSOR CHARO: If that is the case, then just adding one word in 4.1 would get rid of the ambiguity that plagued me, and that is to say that you should make reasonable good faith efforts before the initiation of the trial to secure for all participants continued access at the conclusion of such trial. That would take care of it.

DR. SHAPIRO: What line is that, just to make sure I get it?

PROFESSOR CAPRON: Line 21?

PROFESSOR CHARO: Right. It is on --

DR. SHAPIRO: Yes, I see it. Thank you. It is on page 37 on this -- Okay, thank you.

DR. COX: Harold, that would really make it very consistent with the new text that Alex has put in, too, because you nicely showed, Alex, how depending on what the outcome of the trial is, in one case you may want the control arm, and in another case you may want the experimental arm.

DR. SHAPIRO: Right. That is correct.

Any other comments on this aspect of Chapter 4? If you recall, we did -- I have not looked at what Alex has just handed out. I do not know if it has some of the other changes we made. We made some small, editorial changes in some of these.

PROFESSOR CAPRON: Not in the recommendations.

DR. SHAPIRO: Okay.

PROFESSOR CAPRON: All I did was to rewrite on page 37, as it is, rewrite the language of the conclusion, and then, just cut and paste the existing recommendations in here. And I need to get, if I am going to continue to work in the next day on this, from somebody, all the corrections that have been made, and I will put them into the recommendations.

DR. SHAPIRO: I gave the corrections which I had noted down -- As a matter of fact, I just gave it to Kathi, I think. But yes, we will get them to you. They were helpful, but they were not at the heart of the recommendations.

Other comments or questions about anything here? David?

DR. COX: I have a comment. I think, Alex, you really captured nicely our discussion about

justice as reciprocity, and really captured that whole discussion in just a few sentences. So, I think it is very nice.

DR. SHAPIRO: Any other comments or questions? Okay, I mean, I do not want to --

MS. KRAMER: Where is the material on prior agreements going? I have kind of lost everything in the shuffle.

PROFESSOR CAPRON: It comes later in the chapter, and it will still be later in the chapter.

MS. KRAMER: But prior to the conclusion.

PROFESSOR CAPRON: Yes. This is jumping from page 11. I just did not have them duplicate the pages I had not worked on yet, because I thought it was a waste of paper.

DR. SHAPIRO: So, all that material may be altered, as a lot of the text will be, but will be there.

Any other question? Yes, Arturo.

DR. BRITO: So, Alex, what are you considering doing with the remainder of the chapter? And you are going to do that over the next week or so, you think?

PROFESSOR CAPRON: Yes, I will try to get it in the next few days.

DR. BRITO: Can you give us general concepts of what you are going to do with the remainder of it, just when we go back and review it again?

PROFESSOR CAPRON: I would be happy to have any instructions from anyone who has gone over that. The problems that I had with the chapter were principally in the first part of it. Because I did not think that in posing the issue, why are we looking at this, it was as clear. I also did not think that certain things like what has happened abroad were being marshalled as sort of part of the reason that we are going in this direction. I mean, in other words, we in part look to others and say is this persuasive to others, and then, partly, the justifications.

And the justice as reciprocity thing I worked on very extensively, because it did not seem to me that it captured as many of the doubts about how that concept would apply, and how it relates to other concepts. But if you have, if anybody has, marked up copies of the rest of the chapter that they would like to leave with me, I would be enormously grateful.

DR. SHAPIRO: I would like to look at it first.

DR. BRITO: The reason I ask is, as I recollect, most of the problems were at the beginning,

so I do not think there are significant changes.

DR. SHAPIRO: Well, it certainly would be terrific, Alex, if you could work on the rest over the next few days, because -- And what we will do here is turn our attention to Chapter 5, and some of the earlier chapters, until you have done that, and then we will try to work that in. So, that is really extremely helpful to us.

Any other comments or questions?

Okay, let me repeat what our plans are then. First of all, we will leave with you, although I do not propose that we discuss them any further right now -- we have done at least an initial stab at redrafting the recommendations in 5 along the lines of our discussion this morning. You can read those. I have not read them yet. I do not know if we have captured it quite correctly, but we did not want to forget the issues, at least. And so, if you have any views on those, please let us know.

As I said, we will try to get a new draft of everything to Commissioners on two weeks from today, and ask you if we could impose upon you to please give us any responses, suggestions, views, corrections, et cetera, et cetera within the following week. We will incorporate those as appropriate, and then enquire to

you, obviously, if it is satisfactory to you for us to release the report.

I do not expect any major changes in the recommendations other than editorial changes, but something may come up. If it is convincing enough to us, we will certainly incorporate it.

Thank you all very much.

PROFESSOR CAPRON: There was a minor request for a Happy Birthday song for Trish, who just walked out. Bye, Trish!

DR. SHAPIRO: Well, have you got another song? I do not want to give up a song.

PROFESSOR CAPRON: I gather we stand adjourned.

DR. SHAPIRO: Well, could we get a song off the record?

DR. COX: And is it clear that our next meeting for sure is in Atlanta as opposed to some other place?

DR. MESLIN: It is for sure in Atlanta.

DR. COX: For sure in Atlanta. Okay.

DR. SHAPIRO: Life does not always work out the way it should, David.

We are adjourned.

(Whereupon, at 10:31 a.m. the meeting was

adjourned.)

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