46th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

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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 call our meeting to order. Let me say before turning to Eric to give us an update on where are our various projects are, let me address the nature of our meeting today and tomorrow because this will be our last and final review of the International Report.

It will, of course -- the final report itself will be responsive to whatever issues come up today. And Commissioners, of course, will have the opportunity to review the final report: (1) to give any suggestions or (2) if they feel strongly about any issue, to be able to express themselves. That is just the typical procedure we followed with all our other reports but this will be the last meeting where we discuss it and I hope that we can do so effectively and efficiently in the next little while.

I would like to say something about our discussions today, that is there are substantive issues which we want to focus on principally surrounding the recommendations but there might be substantive issues in the text which we want to focus on and we certainly should focus -- that should be the focus of our

discussion.

What I will call the small but not unimportant editorial type comments should be handed in, in writing, to myself or Eric so that we can incorporate them into the draft. The larger items having to do with substance and approach, of course, are perfectly open for discussion as well as the recommendations themselves.

I do want to change with your permission the order of the agenda, that is I would like to deal first this morning with Chapters 1 through 3. I would like to go in that order and I really think that we are going to need to complete our discussion no later than noon on those chapters. We may decide to complete our discussion a lot earlier than that. We are not compelled to use up all this time but I -- and then this afternoon -- would like to go to Chapters 4 and 5, probably in reverse order since there seemed to be a somewhat larger number of issues in 5 than 4 at least judging from the comments and so on.

And that would leave us tomorrow morning to come back and review where we are. There might be issues we want to think about and work on overnight and come back and think about this again. That is the rough order of the agenda I would like to be able to

proceed along.

We will finish tomorrow somewhere between 11:00 and 11:15. So for those of you who may wish to make other kinds of transportation arrangements, we will not go beyond 11:15 or 11:00 o'clock, somewhere like that because at that time we are going to lose our quorum and so we will just have to keep our discussions now. If past experience is any guide we will be finished by then anyway. We will be exhausted by then and it is probably a good idea to finish a little earlier than we had anticipated.

So that is where we are today and tomorrow, to have our final or penultimate review of this and then produce a final draft, which Commissioners will then comment on if they have any objections or anything they want to say that is not adequately handled in that, they will, of course, as I have said before have an opportunity to do so.

So why don't I turn now to Eric to give you an update on the work of the Commission not only in this area but in other areas and then we will return immediately to dealing with Chapters 1 through 3 in that order.

ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH: CLINICAL TRIALS IN

DEVELOPING COUNTRIES

OVERVIEW OF WORK TO DATE

ERIC M. MESLIN, Ph.D.

DR. MESLIN: Thanks. Just very briefly, although we are not discussing our report on the Protection of Human Subjects Domestically, known as our Oversight Report, I did want to give Commissioners and the public a very quick update. That report is out for public comment at this point. The public comment period will close on February the 17th. At that time staff will be reviewing and analyzing all the comments and sharing them with Commissioners as needed.

We do have a meeting scheduled for May -- excuse me, for March the 15th and 16th in Atlanta, Georgia. The details will, if they are not already on our website, will be available on our website as to the location of that meeting in Atlanta. We are hopeful that the Commission will be able to review a revised draft of the Oversight Report that takes into account all of the public comments that have been received. Our staff, hopefully, having been liberated from the International Report will be able to devote their time to assisting Marjorie in the analysis of those comments, which we encourage the public to provide.

And if a draft can be provided to

Commissioners that is of sufficient quality and standard then we hope we will be able to sign off on the report at that time. If that is not possible then, of course, a meeting will be scheduled a month or so later in April. The date has not been firmly set where a revised draft would be provided and you would go through the process again. That is all I will say about the Oversight Report.

I just want to make a couple of quick points about the International Report for you before we begin discussing the report in its entirety. This report went out for public comment in September, on September the 29th, for 45 days and I asked our staff, Kerry Jo Lee and Liza Dawson to compile a brief summary of the data from those comments, and I did want to share it with Commissioners and the public very briefly.

We received 183 comments on the International Report between the 29th of September and the 17th of November when the comment period closed and we, in fact, accepted and continued to review comments even after the comment period closed. We tried to make a good faith effort to review all of them.

There were about 160 of those comments that were quite substantive. By substantive, they had something to say about the report as opposed to either

congratulating the Commission or not congratulating the Commission, or simply asking for further information. And I found that 160 was a very good number, more than we received for other reports where we had public comments.

But the most, I think, telling and useful piece of data that I want to share with you is we did receive 87 comments from U.S. sources and 50 from developing country sources. So of the 160 or so, we received a very good number of comments that were quite substantive from countries, alphabetically, from Argentina to Zimbabwe, and that included Bangladesh, Bonin, Bolivia, Brazil, China, Columbia, Dominican Republic, Estonia, Ghana, Grenada, India, Indonesia, Kenya, Mexico, Nambia, Nepal, Nigeria, Pakistan, Peru, Philippines, South Africa, Tanzania, Turkey, Uruguay, Venezuela, Zambia and Zimbabwe. I say that for the public record because I think it is important to know -- for the Commissioners to know that there was a good amount of interest.

DR. SHAPIRO: Are you intending to visit all these places?

DR. MESLIN: Just as a follow-up that would be very useful to speak with those directly.

So I did want to make that point. I will not

waste the Commission's time but can make available to the Commission and the public, if needed, how many of the recommendations -- the comments were broken down with respect to recommendations and the like but I think you will see both in the materials that we have provided to you that there has been a very good faith effort to try and respond to or deal with many of these comments, both in the recommendations and in the text.

The only other thing I will mention, Harold, is that we have a number of materials on your table. One of which, just through an accident of photocopying, is an extra page 1 and 2 from Chapter 2. The public should get access to this. We had a photocopying glitch and one of the pages was not completely photocopied and I apologize. That is available to you.

And if you have any questions about anything else that has occurred or about the legislative update that Ellen Gadbois has provided as she always does, please feel free to ask.

Thank you.

DISCUSSION OF DRAFT REPORT: CHAPTER 1

DR. SHAPIRO: Okay. Let's just go directly to our review of the chapters and see what comments there

are on Chapter 1. I guess we can start in that area. And since I sent an e-mail to all Commissioners on some changes, or you might consider modest or immodest changes depending on how you interpret it, to the -- in Chapter 1, perhaps I could start with that. I have not received any comments back from Commissioners on that e-mail. I do not know whether that -- to interpret that as disinterest, hopelessness, fatigue or completely agreement and enthusiasm, or none of the above and additional possibilities but let me just try to explain again what I had in mind in the e-mail.

And that was a question -- it focuses -- it does not change our proposal. In fact, it does not change any of the recommendations we make but at least for me it makes the recommendations something I am more comfortable with and I just speak for myself in that regard. And that is the question of "established effective treatment."

Now the text did read "we adopt the phrase 'established effective treatment' to refer to a treatment that is 'established...'" and then we explain what we mean by "established" "...'and effective.'" Okay. And then in the original text it says, or the way I would -- there was another parenthetical expression explaining what is "effective," and I guess

this is on page -- excuse me. It is on page 16, I think. Yes. It is page 16. Excuse me. I should have addressed you to that immediately. On line 15 where it says, "And effective." That is it is successful in treating the disease or condition.

I changed or propose to change to that parenthetical expression, which was that it is "as successful as any in treating the particular disease." So what I have in mind is an established effective treatment may refer to a constellation of treatments over which there is no compelling evidence that one is better than the other. And in choosing an established effective treatment means you are choosing from that set.

That seemed to make more sense to me. It seemed that the recommendations that come up later at least in my view make more sense. That way you do not have to worry about the issue of best, is there a best, isn't there a best, and it is in some sense equivalent to the issue of equipoise, that is there is a set of treatment in which, you know, people might differ but there is no professional opinion which says one clearly dominates the other. So that is a change I made. It comes up in Chapter 1 but it also has an echo in Chapter 2, which we will come to later.

So the question is, is that change agreeable or disagreeable to the Commission? I do not know if anyone wants to comment on that.

I am taking silence this time to mean agreeable.

Larry?

DR. MIIKE: Just a minor concern but you had added "as any".

DR. SHAPIRO: Yes.

DR. MIIKE: It then becomes sort of a competition between various --

DR. SHAPIRO: Right.

DR. MIIKE: -- it implies -- it implies that it is as good as any other. I do not know if that helps or hinders.

DR. SHAPIRO: I am not sure either, frankly, but to me -- I was just looking for a -- the right language and I guess if we agree on the principle we can worry about the language separately, that there is a set of treatments in principle -- could be a set. Could be -- a set could have one in it but it could also have many, which we are in equipoise over so which is the better.

So -- but I will be willing to accept any other language that is more -- I understand it is not -

- I may not have gotten the right language here but I am primarily concerned with whether we agree with the principle and then we can work on the language.

David?

DR. COX: So, Harold, to me the statement right after what is in parentheses, which is a clarification statement, which is "it is not intended to refer to a single best treatment."

DR. SHAPIRO: Right.

DR. COX: It is very helpful.

DR. SHAPIRO: Right.

DR. COX: Because what that does is that expands what the definition is and so the question for me is, is it better to have a really simple definition than with things that expand upon it or a broader definition that includes things. That is really what your recommendation is.

DR. SHAPIRO: Yes.

DR. COX: And I have got to tell you that I do not know.

DR. SHAPIRO: Yes. Well, to just jump ahead a little bit, I had a problem with some of the recommendations later, which arose, I have to say, when we had some criticism about the established effective treatment. And, although, I thought the criticism was

well taken, I was, I think, alone amongst the Commissioners who thought that or at least of the people I heard who responded. And this just seems to me to be -- to clarify the things that come later. We can come back and see if it fails to clarify it.

Alta, did you want to make a comment?

PROFESSOR CHARO: Well, I was only -- first, I apologize. I am one of the people who did not respond and I was busy fighting off a computer virus.

I am thinking that at this point in the Commission's life what we explain in the text may be just as important as what the recommendations say because we are in no position to expect our recommendation language is going to be adopted wholesale by anybody at any time soon because of the other topics on the table in Washington that are far more urgent.

And so I am -- I would suggest maybe that we not worry so much about the finest of wordsmithing in the recs because so long as the text clearly explains the intent, that is about as much as we can get.

DR. SHAPIRO: Okay. We will still continue to deal with language and if anyone has any issues with it, please let us know if we can improve it. I am certain there are possibilities.

Arturo?

DR. BRITO: Harold, I am in agreement with the principle of what you are trying to do here but, of course, any changes provokes new thinking and new ideas for me at least. Two things. One is minor and the other one -- on the recommendation 2.2 I think then it becomes a little confusing with this change in language because you talk about the justification for alternative design and I am not sure when you have multiple effective treatments that can be substantial, that language needs to be somehow altered to make it clear that that alternative design is something other than the effective treatment. So I think that is a minor point because it does not change the principle.

The other one is that what occurred to me is as I was rereading this and going back to the chapters that when we talk about effective treatments we really do not spell out -- as a physician, to me an effective treatment is something that has been scientifically proven to work and in medicine we use a lot of things that are anecdotally -- or anecdotally -- they are not scientifically proven necessarily but we use them just because of a history of being used, et cetera.

So I am not sure how this fits in but I think that some explanation in the text needs to expand on

the fact that when I think we are talking about effective treatment it is something that has been studied vigorously and I think there is some language missing here so that is the other part of this.

DR. SHAPIRO: All right. We will try to add something in the text that deals with that.

DR. BRITO: That explains it a little bit.

DR. SHAPIRO: Yes. Thank you.

Okay. Well, let's see if there are other comments on Chapter 1 and, in particularly, of course there are -- in Chapter 1 there are two, I think. Two recommendations. These have never been controversial. They are just helping to set the stage and they are really a matter of record more than anything else but I would really like to see if there are any further comments on Chapter 1 in either Recommendations 1.1 or 1.2.

Yes, Bette? Excuse me, Trish.

PROFESSOR BACKLAR: (Not at microphone.)

DR. SHAPIRO: Yes, that is right. I cannot get used to you on my left actually.

PROFESSOR BACKLAR: Okay. Actually there is something in Recommendation 1.1 that I brought up a little while ago and I think has gone off the radar screen, and that was line 24(e), "Individual informed

consent from all competent adult participants." And my concern is not with the recommendation itself but with the fact that we do not address in this report anywhere, and I have looked through the text, I must say there are a few pages in Chapter 4 that I have not looked at and a few pages in Chapter 3, so it possibly is somewhere in there.

But we had discussed, I thought, referring in some way to our report on --

DR. SHAPIRO: It is page 4.

PROFESSOR BACKLAR: Are you --

DR. SHAPIRO: Yes.

PROFESSOR BACKLAR: Okay.

DR. SHAPIRO: It is 4. It is page 4.

PROFESSOR BACKLAR: Oh, page 4. Sorry.

There is nothing in this report that addresses if you do research with people who do not have capacity for decision making.

DR. SHAPIRO: Right.

PROFESSOR BACKLAR: And we make a lot about the fact in other recommendations and so forth and in the text about competent -- people must be competent or that we would get informed consent from competent participants.

DR. SHAPIRO: Yes.

PROFESSOR BACKLAR: And all I am saying is that it seems to me somewhere in the text we have to address the fact that if people -- what we would do, what we are recommending for people who may not have capacity for decision making. And if you just want to refer back to our Capacity Report, that may be a way of doing it.

DR. SHAPIRO: Well, I think it would -- just to respond to you, I thank you for raising the question again, I think when we talk about the scope of the report, perhaps in Chapter 1, we can deal with the issue as to what we have not done because, I mean, your description is absolutely correct.

And does that seem useful to you, Eric?

DR. MESLIN: Well, it is and we do address that in Chapter 3 but your point is whether we should raise it also earlier in 1. I think is what you are asking because Jim had made some similar suggestions about that in an earlier set of comments.

DR. SHAPIRO: Or at the very least we can refer to that point and I think --

PROFESSOR BACKLAR: I may have missed that.

DR. SHAPIRO: -- no, I think acknowledging it somewhere early on is probably an important issue. I agree with Trish. And so why don't we make sure that

we do that in Chapter 1. I think that is a good point.

PROFESSOR BACKLAR: And, also, there is the issue of children, too.

DR. SHAPIRO: Yes. No, people are vulnerable in all kinds of ways.

PROFESSOR BACKLAR: Right.

DR. SHAPIRO: Of which those are two good examples, yes. Okay.

Okay. Any other comments or questions with respect to Chapter 1?

Okay. Then let's go on then to ask similar questions about Chapter 2.

Do people just want to take a brief --

DISCUSSION OF DRAFT REPORT: CHAPTER 2

PROFESSOR BACKLAR: I am presuming, Harold, you did not want us to talk about spellings and grammar.

DR. SHAPIRO: No, no. Please hand that in. I have given a marked up copy to Eric, which has a lot of things on it, and so -- but those are very valuable for us to receive because, you know, we have read this so many times and looking at the same mistake again and you do not see it the eighth or ninth time you look at it. And so that is extremely valuable and I want to reemphasize, those of you who have marked up copies of

any or part of odd pages, please we could really use them.

Jim?

DR. CHILDRESS: In looking at the recommendations and especially looking at 2.2 in relation to 2.3, in 2.3 we begin with "wherever possible, researchers and sponsors should involve..." et cetera. In 2.2 we just say "researchers and sponsors should design clinical trials..." and we are setting out a presumption or an ideal, and then come back and say, as we do in 2.3, that of course there could be exceptional cases.

And I guess -- I think it is not merely a matter of parallelism but whether it would be better to say "wherever possible, researchers and sponsors should design clinical trials..." and make 2.2. parallel to 2.3 in that regard since we do end up coming back to the exception. I do not feel strongly about it but that might be worth considering.

DR. SHAPIRO: How do other people feel about that suggestion, which is on 2.2? It is also -- we have all got a list of these recommendations in front of us but it would also be helpful to mention the page because people may have marked up their copy. This is on page, I think, 18 is where 2.2 is in case you want

to look at it. 2.3 follows on page 21. But I think Jim's point was very clear.

Carol?

DR. GREIDER: I would like to agree with Jim. I think both for the parallelism of language as well as for the substance I would agree to adding the "wherever possible" to the 2.2.

DR. SHAPIRO: Other comments, questions on this particular issue? Anyone have any objection to changing the language in that way?

Alex?

PROFESSOR CAPRON: Well, I think that the text and the discussion of the point about established effective treatments and the point about community representatives is slightly different and I do not favor adding "whenever possible" in the beginning. I suppose Jim is right that with the statement that follows in the next sentence there is an implicit suggestion of whenever possible but thinking about this particular recommendation and the controversy that has swirled around the topic generally, it seems to me that while our discussion of the community representatives recognizes that there are all sorts of situations where simply for practical reasons or the type of study, the type of community and so forth that one is dealing

with, there will not be representative of the community and that sort of gentle way of leading into that saying this would be a nice idea, which is what whenever possible seems to me to say, is appropriate there.

The notion of at a minimum an established effective treatment -- I mean, this is after all the issue on which hours of our time have been spent and reams of paper have been received from the public. The notion of beginning that with this, well, it would be a nice idea, which is what whenever possible means to me, it just seems to me to get us off on the wrong foot. And so I would not favor that addition.

DR. SHAPIRO: Jim?

DR. CHILDRESS: And as I mentioned, I do not feel strongly about it. On the other hand, one could say if you look at 2.2 and see a first sentence that seems to state the kind of categorical demand and then you immediately come in and recognize the possibility of justifying alternative, that internal tension, not a contradiction but internal tension, could be as problematic as having the wherever possible but I do not feel strongly about it.

DR. SHAPIRO: Larry?

DR. MIIKE: I suggest we remove wherever possible from Recommendation 2.3 because it does give

an out at the end just like the first one does and to me "should" is implicit. If it said "must" then it would be, you know, mandatory but this "should" seems to take care of wherever possible if we are looking for parallels.

DR. SHAPIRO: Parallels, yes.

Other comments or questions about that?

PROFESSOR CAPRON: I would certainly second Larry's recommendation.

DR. SHAPIRO: To achieve the parallelism, I also think that Larry's suggestion is to my taste somewhat better and, therefore, to alter 2.3 as opposed to 2.2, recognizing we have no perfect way to say this and so why don't we -- if there is no objection we will proceed in that way.

Okay.

Other issues regarding recommendations in 2 or other aspects of this chapter?

Hearing none, let's proceed to Chapter 3.

DISCUSSION OF DRAFT REPORT: CHAPTER 3

DR. SHAPIRO: And I will not start with any e-mails since I did not send any e-mail on Chapter 3 but are there comments, questions, concerns with respect to Chapter 3 and the recommendations that are there?

DR. MESLIN: Bernie had some e-mails.

DR. SHAPIRO: Well, why don't I mention that? As you all know, Bernie sent e-mail with respect to whether we had treated the issue of "undue influence, coercion," et cetera, that set of issues adequately and I do not know, Eric, if you want to say any more than that. Bernie was going to join us. I guess he is going to join us a little later. We could always come back to this if he feels strongly about it.

I think myself that the material on undue influence, coercion and so on needs some modest reorganization. That is I would like to deal with undue influence and coercion in a single subsection and recognize the fact that there is a whole spectrum of issues here and what we are really trying to do is to get IRBs and researchers to focus on this issue. And there is no way of articulating a completely, you know, easy rule on this but it is something they have to be concerned with as they look at research designs. And I do not think we have it quite right. This would not impact the recommendations themselves but we will work a little harder on that section and perhaps Bernie will help us with that. That does not impact our recommendations as far as I am aware of.

Other issues? Yes, Jim?

DR. CHILDRESS: Modest ones. On page 14 of

Recommendation 3.4, I would propose since we have developed processes, consent process, describe those processes that we change "researchers should develop processes to procedures or means or something," I think the sentence would read a lot better and the same for the last processes since we have the consent process.

DR. MESLIN: Procedures.

DR. SHAPIRO: Procedures. That is to replace the last process.

DR. CHILDRESS: Both of them. The first processes and then the last processes.

DR. SHAPIRO: Okay.

DR. CHILDRESS: So it would be "researchers should develop procedures to ensure that --"

DR. SHAPIRO: Okay.

DR. CHILDRESS: Et cetera. And then should describe those procedures in the research protocol.

DR. SHAPIRO: Any -- does that seem acceptable to everyone? Thank you very much, Jim.

DR. CHILDRESS: And then another -- a very minor one. This would be in 3.5 on the same page. I think for consistency where we have the next to the last line of 3.5 it should be ethics review committee, and that is actually also true for 2.3. We are pretty consistent throughout. Is that correct?

DR. SHAPIRO: What is that?

DR. MESLIN: Ethics review committee.

DR. SHAPIRO: Oh, okay. Okay.

Alex?

PROFESSOR CAPRON: This is going to be the most minor of things but would the word "means" work as well as the word "procedures?"

DR. CHILDRESS: I would suggest "procedures" before "means."

PROFESSOR CAPRON: Yes. We then jump down to procedures because it seems to me that certainly what we are talking about there could include forms of pretesting and so forth which many people would not think of as a procedure but a means. So where we just put the word "procedures" put the word "means". The smallest of things but I think it is --

DR. SHAPIRO: Yes. Now, Jim, you still want us to put ethics review committee in some other recommendation back in 2.

DR. CHILDRESS: Back in 2.3.

DR. SHAPIRO: 2.3.

DR. CHILDRESS: Just the same omissions.

DR. SHAPIRO: Okay. Let me -- okay.

Alta?

PROFESSOR CHARO: My comment concerns

Recommendation 3.11 if it is not inappropriate to jump that far forward.

DR. SHAPIRO: No, not inappropriate at all once the train passes.

PROFESSOR CHARO: Many of you may have caught the Washington Post follow-up article to the series on international research in which there was reporting about a fraudulent practice regarding consent forms in a trial taking place in Nigeria in which consent forms essentially were manufactured after the fact in order to comply with various requirements.

Now 3.11 in the text on page 28 and 29 and then in the recommendation itself notes our willingness to see the formalities associated with consent documents in the United States waived so long as some alternative is provided according to the recommendation that allows researchers (or others) to be able to verify that the research participants have given their voluntary informed consent.

Now I actually sense that there is a slight substantive debate here about the degree of procedure versus the ease of facilitating research. I mean, most of the IRBs in the United States that have been upset by their visits from OPRR and now OHRP have been upset because of the emphasis on complying with the kinds of

rules about consent forms that require that they be stamped and that they be filed and that they be signed this way and that way, et cetera.

And those rules exist not just to torment these IRBs but to provide a mechanism by which a regulator can come in and easily audit the process. So nobody has ever suggested those forms exist to substantively further the goal of consent. They exist only to permit an audit that allows some third party to check that the substantive goals at least have been attempted in the past.

I do not sense in the text here that we have completely spelled out what we want and if what we want to be saying is that consent documents or signatures on consent documents can be waived only if there is an alternative that allows third party auditors to come in and efficiently determine whether or not informed consent had been obtained from the participants, I think we should say it more clearly because it actually will impose some burdens. It is not easy to think about ways to do that other than the ways that are currently being done.

It might make sense for us if we possibly can in the short time we have here to at least mention some alternatives that have ever been used in terms of

contemporaneous witnessing and a signature by somebody other than the subject, for example, but signatures of the other investigators or the recruiters or somebody present at the time, et cetera. And then perhaps in the recommendation a very slightly emendation in which it says grant such waivers only if the research protocol specifies how -- I am not sure -- others in general or how regulators or how government reviewers -- I am not sure exactly to whom we should direct the action -- will be able to verify that the research participants have given their voluntary consent because it is not usually going to be the research collaborators who need to be able to verify the consent. That is one group but its purpose is also to permit this kind of oversight but that is a regulatory burden and it is a substantive debate whether or not we want to impose that burden.

Sorry to go on so long.

DR. SHAPIRO: No, thank you very much and I think with respect to the text itself I very much -- I mean, I think we should do something further than we have got there and I quite agree with you. Now if I understand your suggestion, Alta, with respect to Recommendation 3.11 itself, quite aside from what we do in the text, it is -- and I also respond positively to

that, frankly, that rather than having researchers bracket "or others" as if that is the after thought here, that that is really the main thought in some sense and so we have to do something or find some appropriate language that takes "or others" out of parentheses and somehow makes that more prominent in that part of the recommendation.

Do I understand that correctly?

PROFESSOR CHARO: Yes, completely. And I apologize I did not come ready with any other language because it did not really occur to me until I put together the Washington Post article and then my own review of these documents for the meeting so it is all still percolating.

DR. SHAPIRO: Okay. Do you want to work a little bit on the language here this morning and make some specific suggestions because I think at least my reaction is that is a very helpful change here because I quite agree with you.

Larry?

DR. MIIKE: Alta, you do not find adequate that statement on the top of page 29 that refers to process about which they could be audited by a competent body?

PROFESSOR CHARO: You know, again I am torn

between wanting to just get the report out and wanting to continue tweaking it. Yes, it is there but it is not as strong as I would like in an ideal world. It does not spell out in as much detail as I would like in an ideal world why such audits are important and why they are not merely a regulatory burden. Ways that they can be done. How it is that they create a deterrent effect to the kind of fraud that we saw here and occasionally have seen in the United States, frankly, despite all these kinds of protections. So that none of the protections we are advocating are going to be completely foolproof.

DR. MIIKE: In the recommendation there should be some reference to some independent person because this one -- the way it is written now that the researchers -- but then again I want to throw it back to hear what you just said when we began was that people are going to look at the body of the report and not just the recommendations.

PROFESSOR CHARO: I know.

DR. SHAPIRO: Well, I think -- let's see what we can come up with in terms of language. I think the language on 29, which Larry has just pointed to, which says, "Encourage a process by which these waivers are audited by a competent body," I think that is the

sentence you were referring to. It is a question of whether -- it would read differently if we said, "It is important that these be able to be audited by..." That would be different than simply we encourage that and it is small changes like that which I think we ought to at least think carefully about and try to see if we can strengthen a little and also then figure out the appropriate language for 3:11.

Other comments or questions on Chapter 3? Any of the recommendations, text, et cetera? I mean, again we are not going through small editorial issues but this was -- the issue that Alta raised is a substantive issue.

Well, let me just suggest -- I am sorry, Arturo. I apologize.

DR. BRITO: I am sorry. I missed my mark here. On Chapter 2 I had a comment in the text that is more than editorial.

DR. SHAPIRO: Okay.

DR. BRITO: Is it okay to go back before you go on to --

DR. SHAPIRO: Certainly. Certainly.

DISCUSSION OF DRAFT REPORT:

CHAPTER 2 (continued)

DR. BRITO: Okay. On page 16 there is -- the

last paragraph where it talks about the critics of the best proven method.

DR. SHAPIRO: Yes.

DR. BRITO: At the end of the paragraph I was left hanging as the reader here and it goes on to the next paragraph without giving a counter argument about this -- the best proven -- the critics of the best proven method. It almost leaves -- it leaves the reader thinking about potentially -- not realizing that the effective treatments are really going to be used in the control groups and that they are being compared to what may be more practical for the host country and I have written some language here and I would be glad to give that text.

DR. SHAPIRO: All right.

DR. BRITO: And I just think the counter argument is needed here if nobody is opposed to that.

DR. SHAPIRO: Sure. Arturo, why don't you just give us the text, I mean, when you are ready to.

DR. BRITO: Okay.

DR. SHAPIRO: Because actually I felt that sentence right on 31 ended abruptly myself and I have got some language which I suggested to Eric to complete the sentence.

DR. BRITO: Okay.

DR. SHAPIRO: Why don't you hand -- give your's in also and we will take a look at both and try to find the right solution.

DR. BRITO: It is consistent obviously with our recommendations.

DR. SHAPIRO: Yes. Okay.

Back on Chapter 3. Any other comments, questions, et cetera?

Well, those have been very helpful. Thank you very much.

We will now move on to the last two chapters where, in fact, most of our discussion has taken place in recent meetings. And despite my view that we ought to go through these from one through 5, Eric convinced me this morning that there are enough issues in five that we ought to go to 5 before 4 so we will do so.

Eric, do you want to get us started on this -- on Chapter 5 before we come back to 4?

DISCUSSION OF DRAFT REPORT: CHAPTER 5

DR. MESLIN: I think the only points to be raised, and the public has the side by side version of how recommendations have changed from the public comment draft, is I think we were very mindful of the fact that in earlier discussions that centered around the IRB issue that we wanted to make clear what the

arguments were in support of IRB review in the United States and ethics review committee review in the other country. That recommendation has been discussed and there have been many public comments. There were some public comments on it so that is one of the items and that is Recommendation 5.6.

The other points just to flag them for you relate to -- and I am sorry I am taking these slightly out of order -- relate to Recommendation 5.5 where the discussion around equivalent protection occurs. And here we were aware of the situation that exists of an inconsistency even in the United States where, for example, the FDA does not make determinations of equivalent protection and yet the recommendations as they evolved, particularly recommendations 5.8 and 5.9, which relate to the FDA, needed to in some way be acknowledged or mentioned.

So the issue that you need to ensure that you are focused on is whether Recommendation 5.5 adequately does the job of referring -- by only referring to research that is sponsored or conducted. And in that way in a sense leaves out the FDA explicitly but knowing full well that three recommendations later, as well as the text that follows later, you are making recommendations about what you would like the FDA to be

doing with respect to making its own regulations more consistent with the principles of the report.

I think those are the two, in a sense, major issues that have elicited a comment both by Commissioners on e-mail and by others.

DR. SHAPIRO: All right. Let's turn our attention to Chapter 5. Either those issues or other issues which are on people's minds, issues that you just wish to deal with in Chapter 5.

Now let me just start by saying in Recommendation 5.5 it is my judgment that the -- if we take the recommendation as it is written and as it appears on page 25 in our text on lines 10 through 16, I think that is exactly what is reproduced in the document here, the text following that is not quite consistent with the recommendation because the text following that immediately deals with the FDA.

And it seems to me that that set of sentences needs to be rethought some because it is from a time when perhaps the FDA was in the Recommendation 5.5 where we used not only sponsor and conduct but regulated, and that would of course bring the FDA in. That is a small issue but I just wanted to point out that we will have to change some of the text that is below 5.5 if we end up with Recommendation 5.5 as

currently articulated.

Jim?

DR. CHILDRESS: I am just commenting about the text, in reading over this whole document, the chapters have been worked over very thoroughly earlier, I think still hold up well. This one is in a more primitive state of development and I have not provided any comments on the text but will do so and I think the first few pages just are jumbled as well as being very wordy so I think that the text here needs some help.

Could I just make a few minor suggestions about the recommendations before we hit the substantive ones?

DR. SHAPIRO: Certainly.

DR. CHILDRESS: Recommendation 5.3, which is one page 19, as it reads it sounded as though that -- well, after a suitable period, it sounds like will be implemented by the Office for Human Research Protections after a suitable period. I would propose we begin with "after a suitable period of time an independent body should examine..." et cetera.

DR. SHAPIRO: Any objection to that change of structure sentence? I think in a helpful way actually but any other comments on that?

Thank you, Jim.

DR. CHILDRESS: Then the other minor on 5.4. We should -- and I have not been using the summary ones on this so I do not even know what page it is on but at the end --

DR. SHAPIRO: 5.4 is on 22 for anyone who wants to consult.

DR. CHILDRESS: In the last part of this, provide -- we should either say provide protections equivalent to those found in the U.S. Common Rule or as we are often doing using protection in the singular, we could say provide protection equivalent to what the U.S. Common Rule provides or equivalent to that found in the U.S. Common Rule. Very minor.

DR. SHAPIRO: Okay, Eric. Do you have a note of that?

Any comments or questions?

Carol?

DR. GREIDER: I have both a question and a comment.

DR. SHAPIRO: Okay.

DR. GREIDER: On page 20 in the text beginning on line 15 or line 16 it states that OHRP has not yet determined what constitutes equivalent protections. My recollection was neither did OPRR. And since OHRP has not been around for very long I thought it would be --

if that is, in fact, true then it should be stated there. I did not see that anywhere. The other places where it came up in the text it always said OHRP.

DR. SHAPIRO: So you would just like the text to be --

DR. GREIDER: Yes.

DR. SHAPIRO: -- to indicate its predecessor agency did not do that.

DR. GREIDER: Also did not do this, right.

DR. SHAPIRO: Okay. Do you have those, Eric? This is on page 20, line 15, as Carol noted.

DR. GREIDER: And also on page 23, line 4.

DR. SHAPIRO: 23.

DR. GREIDER: And maybe elsewhere.

DR. SHAPIRO: Okay. That gives it historical context and I think it is useful.

Alta?

PROFESSOR CHARO: This is a place in the report where I would be helped if I better understood what is currently happening in OHRP and Ellen Gadbois's legislative update makes reference to the new FWA, the Federal-Wide Assurance, that substitutes for the old single and multiple project assurances. But in its reference to the fact that different FWAs for domestic and international will still be required, I was getting

a little bit confused about how this is going to work on the international level or how far along they are in specifying how it is going to work, and I was just wondering if there are any further details available beyond what is in the briefing because that certainly affects how it is that we discuss this in the text even keeping in mind that the situation is very fluid now at HHS. Nobody really knows exactly how it all will pan out.

DR. SHAPIRO: Eric?

DR. MESLIN: The short answer is when they release their new assurance process they also stated that for three months they would be, in a sense, trying it out, that they would be receiving comments. So the -- what you see in our text is about as explicit as their website description of what they are doing is and what they have previously reported to us. The three months obviously expires a month from now. I have no knowledge of what they plan to do at the end of February, if anything, to the process is the short answer. If they plan to change or amend it based on comments that they have received from people who are trying to implement this.

There is going to be a huge changeover, for example, of the single project and multiple project

assurance system to put them into -- as well as the other assurance mechanisms -- put them into the slots now designated domestic and international.

And that is what we know.

PROFESSOR CHARO: Thanks.

DR. SHAPIRO: Other comments?

Jim?

DR. CHILDRESS: On page 34, Recommendations 5.6 and 5.7, we repeat the -- each of these is only two sentences long and we repeat the second sentence of the first one in 5.7. And I am not sure that is needed especially since they follow one another here but if we do feel that some reference is needed back to it in terms of what is stated and not simply "see Recommendation 5.6" then I think we ought to put in parenthesis something like that. I am not sure it is needed at all.

DR. SHAPIRO: Excuse me, Jim. I really could not quite follow your suggestion.

DR. MESLIN: You are proposing deleting the last sentence of Recommendation 5.7.

DR. CHILDRESS: Right. Which it repeats the second sentence of 5.6.

DR. MESLIN: Yes.

DR. SHAPIRO: Okay.

Larry?

DR. MIIKE: I am still having some problems with the language that follows 5.5 as opposed to the language that follows 5.6 and 5.7. I am still -- the -- if you read the language in the text following 5.5 it seems to be still in contradiction to the recommendation.

DR. SHAPIRO: Right. No, that is what I noted. I think that is. I think that text has to be altered. We are going to have to work on that, hopefully, some time today. I agree it is not consistent with the recommendation.

DR. MIIKE: I mean, there is some language in 5.5 in the beginning that we recognize is an aspiration at the moment so maybe that is the hook we can hang it on.

DR. SHAPIRO: I think -- Steve? I better start making a list here so anyone who had their hand up, please let me know.

Okay. Steve, Trish, Alta and then Alex. Thank you.

MR. HOLTZMAN: I do not know if I am confused or we are confused so let me assume I am confused when I try to read all of these recommendations from 5.5, so to speak, forward together. So I would kindly ask for

clarification on what we are trying to do here.

So in 5.5 we say we want a process by which we look at other countries and say are you similar to us in terms of your overall approach and institutions in protection.

If so, treat the IRBs like they are U.S. IRBs. However, by the logic of the following ones there is one way in which you should not treat them like a U.S. IRB, that is they are not sufficient in their approval of a study to -- in order to be able to allow the study to go ahead. There has to be a U.S. IRB as well in the case of federally sponsored research.

We then turn our attention to the FDA, which is now we are talking about for simplicity privately sponsored research, and we say do the same. We really think you ought to do the same. Therefore, by implication you should not be accepting studies if there has only been a local but not a U.S. IRB approval.

And then in 5.9 we say, however, a U.S. IRB or -- and I think that is a disjunctive "or" -- all right -- a local one if the local one is in a country where it was found to be substantially equivalent.

Someone please help me because I do not understand the logical consistency of that set of

recommendations.

DR. SHAPIRO: I cannot help you. I think you are actually right about that but anyhow I do not know if anyone else -- but I think we should focus on what we want to happen, right, that is the issue. So let's focus on this precise issue. I think one of the reasons we got ourselves into trouble here, because I think you pointed out a logical inconsistency here, is that we have gone back and forth and mixed ourselves up a number of times about whether and how we want to deal with issues of international trials regulated by the FDA somehow falls under their regulations one way or another. And going back and forth, we have not always carried it -- but I think -- let's ask ourselves what we want to happen and then we will worry about the -- just how to get the language of the recommendations here.

Steve?

MR. HOLTZMAN: So the logic tree I go through is I start with this assurance process first --

DR. SHAPIRO: Right.

MR. HOLTZMAN: Another country you look over and say they are like -- they are sufficiently like us. Then I say what do we want, if anything, of the pragmatic implication of that.

Specifically, is that sufficient to say that a local IRB is fully empowered or fully empowered or not in some but not all instances? That is the first question to ask.

We seem to have -- through the dialogue -- said it is not sufficient to be unto itself at least with respect to federally sponsored stuff.

DR. SHAPIRO: Right.

MR. HOLTZMAN: So why -- if we ask ourselves what is the basis of that determination, and if the basis of that determination is a concern about the protection of human subjects, I for one would be hard pressed to say why it should be different if it is a privately sponsored study.

DR. SHAPIRO: I agree with you.

MR. HOLTZMAN: All right.

DR. SHAPIRO: I agree with that.

MR. HOLTZMAN: On the other hand, I would still then come back and say so what -- where did the rubber hit the road? Now that I have said you, this country, you are just like us, what is the content of that? What is the pragmatic -- what is the operational content of that statement? We talk about it as aspirational and I still do not know what am I aspiring to when I then turned around and said, oh, by the way,

even if they were just like us, I still would not be satisfied without a U.S. IRB.

So if someone could answer that question I think we could make progress.

DR. SHAPIRO: Okay.

Larry?

DR. MIIKE: Well, I was with you on this before obviously.

DR. SHAPIRO: Larry, just hold it a second.

The list I had -- Trish, do you want to deal with this issue or is it another issue?

Let's deal with questions on this issue. Okay. Larry and Alex.

DR. MIIKE: Well, you know, we were in agreement on this several meetings ago. It seems to me the way this is now being tried is that we were dealing -- in Recommendation, was it, 5.9 that says either/or. We were dealing with situations where there were not people from the United States involved in this study and that is what we are trying to deal with. But I think there is somewhere in the language following some of these or before some of these recommendations that says that the Common Rule now requires that a U.S. IRB -- if a researcher is from a U.S. institution that that institution's IRB must review their research even if it

is in another country. I thought I just saw something like that but anyway there is an inconsistency.

PROFESSOR CHARO: It depends on the institution's MPA.

DR. SHAPIRO: Yes.

DR. MIIKE: It is in the report. Anyway, there is an inconsistency and that is why I was suggesting that maybe what we are talking about the equivalency is an aspiration at the moment. And so just pragmatically speaking we still do a double review. When you are faced with a situation of private industry not having a -- being covered by U.S. sponsored research or U.S. based researcher then one must make an exception if we are going to still allow those kinds of studies to be approved by the FDA and there is no way -- there does not seem to be any way around making that distinction.

DR. SHAPIRO: On this particular subject, Alta, and then Alex.

PROFESSOR CHARO: First, Steve, thank you for more precisely spelling out exactly what our dilemma is because all of us have been kind of reading these things going there is something wrong but I cannot figure out what it is.

I am having difficulty myself in figuring out

exactly which tack I want to take and which basic direction I want to go and so I am actually looking for discussion on that point. I see two things, two different directions that one could take.

One is to acknowledge, I think -- I do not want to speak for anybody else here because we are on the record but I think what is fairly widely shared, which is a skepticism about the capacity for many developing countries to actually undergo a rigorous review and a continuing monitoring of studies that may involve substantial risk or discomfort or inconvenience to participants.

And in that sense wanting a direction in these recommendations that consistently heads towards having some kind of parallel or supplementary U.S. based review of the research.

A competing set of priorities and concerns is a kind of collection of wanting to demonstrate respect for colleagues in the medical and scientific professions in these countries, respect for their good intentions, confidence in the growing ability to do this on the ground and the number of international organizations that are beginning to commit people and time to developing those capacities to do it on the ground, respect for the fact that there is genuine

diversity in opinion about what constitutes acceptable risk, minimal risk, invasion of privacy, et cetera, in the substantive review, and coupled with all those concerns about respect and parody a desire to simplify and streamline the regulatory process to facilitate research that is badly needed and is already strained.

And all of that would head in the direction of trying to encourage as easy and rapid a recognition of foreign IRBs as possible as equivalent enough that they can run the show without any U.S. IRB involvement at all.

And I have to confess I am kind of open to discussion about which basic direction we want to take because I think we have to make the choice and let the shoe drop.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: Well, I think Alta and Larry have done a nice job of describing the issues. I thought that we had come to the conclusion that we were more comfortable for the moment with the former direction that Alta describes rather than the latter. And to me it is not a question only of developing country IRBs. I was just asked to join an IRB that meets four times a year and when you compare that with

the IRB in my own institution which meets -- of which there are several, looking at different things, which meet every few weeks.

My guess off hand is that the IRB that meets more frequently and has more experience, has more staff and so forth, is likely to do a job with which I would be happier. And if a researcher from USC were involved with the other institution I would be much more comfortable for the research and for the involvement of a colleague if it went through the USC IRB as well as through that other institution.

And so it is not a global question of saying are we kind of distrustful of the abilities of developing nations. It is just how much experience.

I thought that Larry had it just about right in saying that -- or maybe I was reading too much in but what I would take -- I am sure you were very clear but I do not want to assume that you reach the same conclusion that I reach, which is if we could we would say vis-a-vis the FDA's approval that the same dual review ought to occur but we recognize that these recommendations and the FDA's implementation of them would have to incorporate situations in which no U.S. IRB -- U.S. researcher was involved as well.

I mean, they can get data that comes from

anywhere that meets their standards. In which case, the insistence that there be a literal parallelism and that any research would have gone through a U.S. IRB -- well, which U.S. IRB? There was not a U.S. researcher involved. They did not know they were going to take it here. I mean, it just -- it just does not work the same way.

Whereas anything that comes with federal dollars attached, it is possible to say that that should happen and most of the time it would be possible for a -- because you know at the outset that it is going to be under U.S. regulations, it is under the Common Rule.

Now I recognize again that if the money went from the U.S. to the Karolinska and all research was done by foreign investigators, you face something of the same problem but it seems to me that the problem is less acute than it would be with saying to the FDA, well, you should not take the data unless a U.S. IRB was involved at the get go.

Now the question would be, well, where should the Karolinska go? Well, the Karolinska can go to an independent IRB in the United States and have the review occur. The number of situations in which there is -- there are U.S. research dollars and no U.S. based

investigators involved, I gather, is very small.

Now if that is wrong, if there is a lot of U.S. money going abroad, and we would be constructing something very difficult, I still would prefer to have us say what we say in the report and then note in the text that this may pose a little bit of a problem. But I would like to have that clarified because otherwise I am actually comfortable with the way we have it for the reason that Larry explained that we recognize that the FDA just is in a different situation procedurally and it would be extraordinarily burdensome to say they had to have an exactly parallel procedure.

DR. SHAPIRO: Steve and then Alta.

MR. HOLTZMAN: That is very, very pragmatic but we are an ethics Commission and if we believe that protection of human subjects in the current world requires that there also be a U.S. IRB involved then we should demand it across the board, not as a function of where the money came from. That is the -- that could be the only motivation we have for putting this. Not being disrespectful, just looking at the world as it is. All right.

So we are trading roles here, pragmatist and ethicist. But, you know, would industry be happy with it? I think there are all the pragmatic issues we need

to deal with when we continue to demand dual approval, all right. What if it is a protocol -- what are we asking of the U.S. IRB, which is a protocol, which in the U.S., for example, you would not approve but over there they would approve, all right, or it is the consent form which in the U.S. you would not approve but over there you would approve. What are we asking of the U.S. IRB? What standard are we asking them? Have we really been clear about that in the text? It is not clear to me that we have.

By having said that I do not buy your argument, Alex. I do not think we should be going down the pragmatic road on this. I think we ought to be pure one way or the other.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: In some ways I think it is possible that we have twisted ourselves in knots because we are being -- because we are allowing ourselves to get tied to the current regulations and their current -- and the current phraseology such as the phrase "equivalent protections" and the old assurance system and the amendments to the old assurance system.

And since I do not think anybody is about to adopt these for a rapid regulatory change, maybe we

should free ourselves from them. I mean, I advocated keeping very close to the existing regulations for the Human Biological Materials Report because I thought that it was at least possible given the timing of that report and the receptiveness or seeming receptiveness of the key institutes at NIH that it might actually get adopted but here I do not think that is the case.

Now if we free ourselves from that we actually might be able to accomplish both Alex and Steve's goals simultaneously. I do not think they are completely incompatible. I agree with Steve that making distinctions based on funding source is not a great idea because it simply replicates the problem in the domestic system that we are advocating we get rid of in the oversight report, which is the artificial distinction of protection levels or protection styles, depending on funding source.

And we certainly could say that we think that there are certain basic substantive protections that all human subjects deserve and we could certainly say that we do not think that anybody from the United States should participate in research that fails to meet those standards.

We can certainly say that we do not at this time have the legal authority to enforce that over some

people and that that legal authority would have to be developed. It just does not exist right now so that is a way to on the one hand state what we think is the principled approach and second to go along and say here are the areas where that authority already exists by virtue of things like conditions on spending, direct authority of the Federal Government over its own actions, and here are the areas in which we do not really have that authority directly and where it can be got at partially through indirect action such as requirements that the FDA follow certain procedures when it is reviewing a drug and areas where it simply cannot be followed.

And that is all separate from the question of what we do with regard to looking at work that was done where there was no U.S. involvement at the time that the work was done.

And in this latter category I think we finally find the meaning -- a meaningful role for the notion of what has here been called substantially equivalent because up until now, as Steve has correctly pointed out, there is no role for the notion of substantial equivalent. If we have a process by which we try to anoint as many committees around the world as possible as substantially equivalent or countries as having

substantially equivalent protections but then we still do not defer to them then what is the point of the phrase? Right? I agree with Steve.

And yet I share with Alex the instinct that at this point it would be better to have a U.S. based review. Right?

DR. SHAPIRO: Let me --

PROFESSOR CHARO: Wait. Let me -- let me --

DR. SHAPIRO: I am sorry.

PROFESSOR CHARO: Just one sentence.

DR. SHAPIRO: I thought you were through. I am sorry.

PROFESSOR CHARO: But when it comes to the FDA looking at research that was done without U.S. involvement at the time it was performed, right, a Ugandan collaborating with an Angolan, and now suddenly it turns out that the work that they are doing has some potential relevance in the U.S., and there is some interest in using that data as part of the presentation to the FDA. That is the point at which we could say to the FDA feel free to use this foreign data if it meets your other scientific standards and if it was done under conditions that would meet our definition of substantial equivalent. If it does not then please do not use that data. All right. It is a way of --

essentially it is the Nazi data problem and what we are doing is saying, FDA, you can use the foreign data if there was a substantially equivalent procedure at the time it was developed.

So that is one way to reconcile these two positions. Sorry.

DR. SHAPIRO: Let me -- Larry and Alex want to speak also but I wanted to say a few words and then just ask a question just in view of some -- try to get myself to free associate here.

When we started down this road to equivalent protections we -- the first recommendation we came to, which we rejected incidently, was that if a place had equivalent protections then it was equivalent, you did not need these two IRB reviews. That was the first spot we were in. That made sense at that time by itself. I mean, it was a sensible idea even -- it may be a bad idea but it is a sort of coherent idea. And then we stepped back from that for reasons I think Alta and maybe others have articulated here. That is we really did not have the confidence that anyone would really have an equivalent system or that most would have an equivalent system. Okay. And I think that may be a fair description of the focus of the kind of trials we are focusing on in this report and that the

chances of people having equivalent systems right now are very small.

That seems, as Steve has pointed out, to sort of make no sense out of 5.5. You could also imagine dropping 5.5. All right. Simply it is another alternative. Supposing you dropped 5.5 out of this list. Okay. And you went to 5.6 and it just says that -- it says what it says about two IRB reviews being necessary for the -- it is the U.S. sponsored and conducted and then 5.6 says -- that would be 5.6. 5.7 is an encouragement. I mean, that is something for people to think about. We might have to change that in some way. It is just an encouragement. It is not a requirement.

So I think that whatever we do here we are going to have to decide whether we want to -- I guess Steve used the word rubber hits the road or people use other language -- whether really we -- this equivalence is -- although called for in the regulations as they currently stand -- really is something around which we want to hang any recommendations right now because of this -- of the ambiguity of the situation out there.

I think it is clear from the Commission's previous discussion that we are dissatisfied on the whole. We wanted two IRBs. I guess the argument,

Alex, you may have used the last time we were together, you wanted something that was somewhat parallel to the U.S. situation if I remember correctly what you said where we have people collaborate and each IRB takes a look at it.

So I think we are going to have to decide whether we really want to say something about equivalence that we mean or not but let's -- I have got David, also, but it is Larry and then Alex, David and Bette.

DR. MIIKE: In response to Alex saying that I agreed with him, we actually came down in a different place. If you recall, I was not -- well, first of all, I said if we are going -- first of all, I think we are being tied to the current situation and we are getting worried about substantial equivalence. That is an aspiration down the road.

But if you recall a few meetings back I was in support of the notion of 5.5, substantial equivalence. I was not in support of if we -- if we agree with that about still having double IRB review. And my point was that if you are an institution such as Alex's and you are worried about the collaboration you can always impose it. You can always say we are going to insist on a review. It does not have to be required but any

particular institution could say that because our researchers are involved we are going to insist on reviewing it.

So that is why when we came out in our recommendations that said there had to be -- that there had to be IRB review by the U.S. institution as well as the host country when I was in disagreement but I eventually caved in because it was not my worthwhile to write a dissent about what I considered not that big a deal.

We all recognize the inconsistency of those two positions so I think the way I would -- I would still stick to an aspiration of substantial equivalence but knowing full well that that is going to be a very difficult process to implement. But I think we still have to say -- if it is going to make any sense, once we determine a substantial equivalence, we should treat that host country or IRB just as we treat a U.S. IRB.

And the dual review should then be optional based on the institution involved or -- I just checked with Eric and there does seem to be a requirement in the Common Rule that if you are a researcher from an institution that institution's IRB must also review it.

I would like a clarification on the last point

because it seems to me it would take care of much of the inconsistency that we are currently having between aspiring to have substantial equivalence and still insisting on double IRB review.

DR. SHAPIRO: Eric, do you want to clarify that issue before we turn to Alex?

PROFESSOR CAPRON: I think we should. I was not looking at that issue.

DR. MESLIN: No, it was just the point of receiving federal funds if you are at an institution. That is the obligation to obtain IRB review. That is clear.

DR. SPEERS: In the regulations it speaks specifically about cooperative research, which is what is relevant here, which is any institution that is engaged in cooperative research is obliged to follow the Common Rule. It is actually Part 114 in the regulations.

So if you have --

DR. MIIKE: Excuse me. But, Marjorie, they could waive that, right, because if we are talking about multi-institutional clinical trials there is a move towards designating or deferring to one.

MR. HOLTZMAN: Reflects that accurately.

DR. SPEERS: Correct.

MR. HOLTZMAN: It is the issue of waiving. The question is whether they may defer to another.

DR. SPEERS: That is right. That is what I was going on to say that in that it says that you have to follow the Common Rule or make other arrangements, which is where one can then defer to another IRB.

PROFESSOR CAPRON: Shall I simply read the language then? Okay. After saying that each institution is responsible for safeguarding the rights and welfare and for complying with the policy, it says, "With the approval of the Department or Agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB or make similar arrangements for avoiding duplication of effort."

So, in effect, as Alta said a little while ago, if your assurance says you can do this, you can do it.

May I comment on the other?

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: The other issue here. I took our comments and what I wanted to look at was the language of 101(h), which is about the equivalency. And there it says -- it begins by saying, "When research covered by this policy takes place in foreign

countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy," and then it goes on to say that the agency may make a determination of substantial equivalence.

And I thought about three years ago when we started on this that we were surprised to discover that there was no set of criteria by which such determinations would be made and consequently they had apparently never been made. And it seems surprising to us that around the world, starting with our neighbor to the north, with all the elaborate procedures and which we have in the process learned we believe in some countries are in some respects superior to our's, with all of that, this had never happened.

The purpose I took of our Recommendation 5.5 was to say that if a country has established a set of requirements and processes by which a determinence that those requirements are being met, which would provide substantially equivalent protection to what we give, we think there should be criteria by which that can be judged and it should then be judged.

That then merely says, as I understand, that an institution meeting those other criteria, that Canada or the U.K. or whoever has said your committee

meets our national requirements would not have to go through an SPA process because we thought this -- that is what is redundant.

Now having said that they are equivalent then Larry is right, I think, that they are back in the same position as two U.S. IRBs which meet our requirements but as to which an institution might decide or an agency might decide that an institution should decide that they should both review it nevertheless.

And then we looked at FDA regulated research and said, well, that research does not necessarily go through double review. The drug company does not have an IRB because some of its people are involved in the research and the institution has an IRB, it is just the institution has an IRB. There is only one U.S. IRB that looks at that research.

That being the case we thought equivalent treatment -- I do not mean not -- okay. Similar treatment, I should not use the word "equivalent" because that confuses it back to 101(h). But similar treatment of the two situations would say as to FDA regulated research in the U.S. that only gets one IRB review, the foreign would get one IRB review.

Now Larry may be right to say what we ought to do is back off of our recommendation that insists on

dual IRB review if what we really mean to say is that that dual review should occur if the institution would do dual review if they were in the -- if they were operating in the U.S. But that then would bring us to Alta's dichotomy between whether we are more on the side of a little skepticism about how adequate it is even if it is -- even if the procedure is deemed equivalent or has gotten an SPA.

But I do not think 5.5 is particularly in play in all of this. I think what is really just in play is the question of the two reviews because the second country review can be a qualified review either because they have gotten an SPA or because the whole system of that country has been found to offer equivalent protection and we would still face the question of whether we think it would be more prudent and more likely to lead to ethical results if there were a U.S. IRB involved as well. And that seems to me -- so we -- I am just saying I do not think 5.5 is the nub of this.

DR. SHAPIRO: Well, it is either 5.5 or 5.6 has to be somehow dealt with here.

PROFESSOR CAPRON: Well, maybe --

DR. SHAPIRO: At least the way I think about it.

PROFESSOR CAPRON: I just do not think that

that is -- I mean, the host country IRB mentioned in 5.6 could be one which has gotten an SPA or could be one whether the whole system after this process of setting criteria and using the criteria has been judged to offer equivalent protection. In any case we could still say despite that we think it would be at this time more prudent to have a U.S. IRB look at it if U.S. researchers are there. In effect, your multiple project assurance or whatever it is now going to be called, your federal assurance, ought not to -- ought not to allow you to waive that. That is what 5.6 says. You should not be able to waive that.

DR. SHAPIRO: Okay. David?

DR. COX: I make this comment with great trepidation because I hope to be a clarifier and not a turbidifier, and I am not sure that I will achieve that with this comment.

You helped, Harold, clarify this whole report for me many moons ago by the following statement: And I attribute it to you and if it is not true then I am sorry.

DR. SHAPIRO: I take all praise justified and unjustified.

(Laughter.)

DR. COX: Which is that, look, that not

everybody does things the way we do in the U.S. but the reason why we are doing this report is because it is U.S. money and that if it violates what we think are ethical principles in the U.S. then there are some things we simply cannot do.

So from my point of view, yes, I think it can be substantially equivalent but as Steve points out when the rubber hits the road, substantial may not be enough in a particular case, right, because that is where -- exactly the situation where people may differ about what is acceptable or what is not acceptable.

So I do not see how you can meet that first criteria, which is saying, so, is this something that we, you know, go for in the U.S. or not if we do not have a U.S. IRB.

Now on the other hand I do really respect the other countries and I do really respect and want to have them involved just like we have multiple IRBs involved in the U.S. because what it does is it leads to better protection of human subjects. What you want to do is you want to minimize redundancy and minimize cost but the whole reason for doing this in multiple ways is to make sure that this whole process we are going through is really protecting people. Multiple ways of looking at and dealing with it.

So for my point of view is that I would be very uncomfortable if we did not have a human -- or a U.S. IRB squarely involved in the process because I think it is the fundamental place by which the whole report comes from in the beginning.

DR. SHAPIRO: Let me try to -- I mean, Bette wants to -- I think wants -- let's go there first.

MS. KRAMER: I have been sitting here and trying to ask myself why -- you know, where my problem is in all of this and I think for myself that a part of it is that with the IRB -- the institution with the IRB in the United States there is a long, long history. And that when I think about the International Report there are some countries out there who have an equally long history like our neighbor to the north, and there I personally would be very comfortable if we said, "Fine," you know, then we do not need an additional IRB review.

But when we are talking about developing countries where we are talking about helping them to initiate or to begin to develop or to augment their already incipient efforts, there is not the tradition, there is not the background. You know, you do not have that same assurance that you can say, yes, I am really comfortable that there is an equivalent in those

countries. It may turn out that at one time there is and then before research goes into another study something dramatically has changed or has changed dramatically and it is no longer the case.

So I think that is where, you know -- that is where I am ambivalent, where my ambivalence is coming from. I do not know if that clarifies anything or not.

DR. SHAPIRO: Here is a question -- Alta, I will turn to you in just a second. I know that you want to speak.

Let me try something else. Take 5.5 as it stands. It just says to get equivalent protection, the IRBs are the same, that is all that says. It is pretty -- that is straight forward by itself.

Now we go to 5.6 and it talks about things that we should not do. That is we should not sponsor or conduct trials in developing countries unless such -- and then the option unless, okay, and then we go to the two IRB reviews. That is, as I take it, as it stands the gut requirement out of 5.6.

Now quite aside from the issue of our own individual assessments of how many countries could get equivalent status, put that aside for a moment, that is not what we are trying to do. We have not done that

study. We have nothing to say on that except some guess is it is probably a small number right now, maybe a zero, I do not know what it is but it is a small number.

So what happens if they are not equivalent? Now it seems to me the most straight forward thing to do is to say -- is to deal with that in 5.6. Now if they are not equivalent, okay, then we want -- then -- because what do we want? It seems to me if they are equivalent they are equivalent and we just treat them that way. Whatever a U.S. institution needs, that is what you need over there. That seems to be straight forward.

And so somehow I still feel a need -- to me 5.6 is now the one that is the least understandable and where we should devote some time and attention.

Alta?

PROFESSOR CHARO: I am not sure I am coming out to a different place than you, Harold, but I am beginning -- this is terribly risky. I am beginning to think that it may make sense to scrap a collection of these and try to start fresh. It is a terrible notion. Because I think that it might be possible to funnel them down a little bit differently in the following way: To start by saying that as a general matter we

think that dual review is necessary for any research that is conducted by the U.S. Government, by U.S. entity or any -- for any research that is going to be regulated by the U.S. Government. That is kind of catching it on both ends. That there are going to be some exceptions and the exceptions are: And then we list them.

One exception would be if the work was being done under the auspices of the group, under the auspices of a committee that had been accredited. And I think this is an opportunity to actually reach across to the Oversight Report and actually make some kind of recommendation that accreditation processes be developed not only at the national level but to encourage the U.S. Government to collaborate with international entities like WHO potentially in the development of an international accreditation system, which may be one way to handle this.

Because the second would be this whole substantial equivalence thing but I have less confidence in that because it is a kind of single -- it is a one time only determination and the dilemma that we are facing here really is not that other places cannot come up with a nice piece of paper that sets out a lot of principles and a lot of theoretical

procedures. I think in some ways Alex got at it when he talked about the IRBs that meet infrequently.

It is that the actual implementation of it is a far cry from what it looks like on paper and that is a much tougher thing to do and the accreditation processes are the kind that actually allow for kind of a continual monitoring and checking that people have the ability to follow through on their plans. I mean the CLIA laboratory stuff does exactly that and that is why you can actually have enough confidence to be able to then say, okay, here we do not need the dual review.

Another exception might be that, you know, nobody from the U.S. was actually involved.

But, I mean, funneling it this way, I think, might help. You start with a general notion that the dual review is required and then there are some narrow exceptions that might grow over time. And not try to link it to specific things that used to exist like the SPA, which no longer exists, or even to the phrase "substantial equivalence" because nobody knows what will happen to that phrase but to just spell out what we want.

And then in the text acknowledge that we -- like I said before, we do not have the legal authority

to do this right now. We would actually -- this is the kind of thing that would actually require some legislative action. There is no authority over some of these entities at this point.

You know, a U.S. investigator who is unaffiliated with an institution has voluntarily pledged to do all this, who is not presenting this stuff to the FDA, it is just a regular citizen who wants to go around doing research, there are not very many of them, and they are actually beyond our reach right now under current law.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: I certainly agree with the latter statement. In fact, you and I had an exchange because at one time a draft was going around that would even reach those people.

I wanted to come back to a point you made before, however, which suggested that maybe the FDA does not have authority to insist on that and I would be happy to have that addressed by someone who knows the FDA law better than I do but I do not see anything on its face under the FDA statutes that would say that if they wanted to say you had to have review or you had to submit everything on pink paper or whatever that they do not have the statutory authority to do that. I

mean, they would face a lot of head wind if they tried to.

PROFESSOR CHARO: No. I was only suggesting that they cannot force people to do something. They can certainly give them a carrot and they can use a stick.

PROFESSOR CAPRON: Yes.

PROFESSOR CHARO: But they cannot force them.

PROFESSOR CAPRON: Fine. But the carrot being if you want us to use this data in the approval process it has to meet certain criteria.

PROFESSOR CHARO: Right.

PROFESSOR CAPRON: And the fact that a U.S. investigator was not involved would not seem to me to mean that they could not make one of those criteria a U.S. IRB review.

We come back to the nub of the question which is whether something has gotten recognized because the individual institution has gotten a -- the federal-wide, is that the new phrase for the assurances? -- a federal-wide assurance, which simply means that if it does agriculture work or HHS work it is approved. Is that what the federal-wide language is going to mean?

Or because they develop -- OHRP develops a -- in line with what is now 5.4 and 5.5 -- a process for

giving a judgment of equivalency. The fact that the institution is in a developing country even if it is nominally in line and it has that, do we want to say that that is enough? Should that be one of your exceptions the way you are conceiving the policy?

And I am not comfortable going there yet. I would still say that for -- clearly, Mr. Chairman, the example you give in which the IRB in the other country does not have any of that, it does not have an assurance and it is not in a country where it meets that country's guidelines, which have been certified as equivalent, obviously it has never been through any approved IRB. It has to go through the U.S. IRB. But it seems to me that even when it has gone through that country's IRB, which can contribute a lot -- they will know more about local customs and so forth. They may not have the experience and the sensitivity to some issues which a U.S. IRB, which has looked at a lot of research over the years would have.

And I would still want to say if an American investigator using U.S. money is over there that the U.S. institution should not be allowed to waive its own review. The procedures in 114 for cooperative agreements ought not to apply at the moment for such work in developing countries.

DR. SHAPIRO: Could I just ask a question precisely on that issue? I understand the issue that -- the assessment that not many people, if any, would get equivalent status. Therefore, we need two IRB reviews. What I was trying to ask myself is a question, I think, Steve raised -- again I am forgetting who raised which question but I will attribute it to Steve -- that what is the purpose of equivalent protection.

What function does it play in the way we have -- now if it does not play any function, that is we are not going to treat them as if they are equivalent, we are just going to declare them equivalent as a kind of badge but we do not change any action, what -- I am having a hard time understanding the --

PROFESSOR CAPRON: Well, it seems to me that the equivalent protection language applies to any foreign country and I thought we were simply taking the occasion -- it goes -- in other words, it goes slightly beyond the scope of a report that focuses on clinical trials in developing countries.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: But it certainly says that as to 101(h), which has had this language all this time --

DR. SHAPIRO: Correct.

PROFESSOR CAPRON: -- they ought to take a step to implement it. Now what about developing countries? Well, we are talking about a process which I think we see as evolving over time. If that process -- if the equivalent protection process has been spelled out and implemented as to countries which really do have the kind of history that Bette was just describing, then at some point in the future one would come back and perhaps the recommendation spelled out the way Alta described it where we have exceptions, would say at the present time subject to review in five or ten years or something, then we could begin to say, well, in countries that meet these criteria, then we would be on the equivalent ground as a U.S. institution collaborating with some institution in the United Kingdom or in Canada where the U.S. institution under 114 could say we are going to work out a joint review or we are going to work out a system in which we defer to your review, and that would really work.

And they could then say in Nigeria they have been doing this long enough and well enough that we are going to do the same thing there.

DR. SHAPIRO: Would --

PROFESSOR CAPRON: So for the moment the

equivalence protection is kind of like the first step in that process for Nigeria. I mean, if they could get a system running which got that stamp of approval where we would say we are not going to worry about doing federal-wide assurances with your individual institutions because we believe you have a system internally in your country that has standards and procedures that are equivalent so we are going to treat them as though they have an assurance.

And now the time has come to say some developing countries would be on a list of among those who have risen to that level who are now also going to be treated as not requiring dual review. So it is -- so that is the role. Does that make sense?

DR. SHAPIRO: It does make sense to me but if I were to follow that logic just as I am thinking about it, and we are going to have to try to recess and get some language together here, if you thought of 5.6 -- I do not have the language but looking at Recommendation 5.6 given your comments right now, where it said that we should not sponsor or conduct research unless there is dual review. And then say unless. Okay. And then you could list declared equivalent, have equivalence or whatever -- or have an SPA or something.

That would make sense to me because it says --

I understand and agree with you regarding your assessment regarding how many people are going to get equivalence right now. And if it was only a question of official papers, they all have equivalence right now. But what we talk about is not equivalent paper. The language here is provides equivalent protections to human participants. That is the key. So that requires a whole system and so on.

And so it seems to me that if we are going to keep 5.5, which is fine, I do not think I object to anything in 5.5, it seems that 5.6 would have to spell out those exceptions to requiring dual review.

I am just -- now all I am asking is if that would go along with what your thinking is as you just articulated.

PROFESSOR CAPRON: It would but what I am saying is you have the equivalent protection or you have the assurance mechanism there as an aspiration because you want --

DR. SHAPIRO: I understand.

PROFESSOR CAPRON: Yes. You want them to try to get that. That is good if they get it but still for the moment even having gotten that we want to say we want a dual review. That is what I am saying.

DR. SHAPIRO: Well, that is where I do not

understand. It is the last item that I do not understand.

PROFESSOR CAPRON: Well, you see there is -- I thought that was the point that Alta made. There is formal -- formally having assurance or formally having equivalent protection and then there is how well it really operates. And, you know, Alta, I think the idea of worldwide accreditation is wonderful. We have not even gotten to the point yet of accreditation system in the U.S. So that is really aspirational but sure, we could say that would be a much better way of knowing that the assurance or the equivalent protection is real.

DR. SHAPIRO: I understand what you are saying. Okay.

I have three people here and then we are going to go off on a new tact.

Bette, I will add you on to this list.

Alta.

And then -- David, did you have your hand up? Okay.

Alta, and then David, and Larry. Larry is on the list.

PROFESSOR CHARO: I think we are at a point where we just simply have to decide at what level we

are writing this. Are we writing it in the expectation that it is going to be implemented tomorrow? Are we writing it in the expectation it is going to be something that is really over the very long-term?

If it is the latter I think we can afford to take the tact that Harold has just outlined. We recommend dual review unless, and then we have a specific list of exceptions, and the exceptions include that the country or the individual IRB of the individual institution where the work is going to take place have been found to meet essential criteria and that can be through a worldwide accreditation process -- it does not even come close to existing yet -- or a substantial equivalence finding -- it would be nice if we would set up some criteria for it -- and a procedure by which we would make those determinations, and if that ever happens in the United States then this would also become operational with the caveat that we would want to make sure that it was real and not illusory, you know, practical and not simply on paper, that there was true substantial equivalence.

And, therefore, the moment in the text we can say we expect the dual review is going to be the rule and we anticipate that this should be applied both to research that is conducted by U.S. entities as well as

to any research that is having its data used by a federal regulatory agency for the approval of a new drug, et cetera.

With regard to what the U.S. IRB should do because some people here were suggesting that it is not clear what they should do, I would suggest that, in fact, it is very clear what they should do. They should be following the rest of the recommendations in this report.

In a sense I would suggest that this report has laid out what constitutes substantial equivalence from the substantive end because the collection of its recommendations sets forth our notion of what the minimum standards are for participation in research.

It does not begin to lay out the procedural kind of practical implementation things that go into that -- you know, what constitutes true independence in a committee and, you know, how do you document things and what kind of staffing do you need, and all the kind of stuff that typically goes along with accreditation.

But from a substantive level I would say that these recommendations form both the standard by which the U.S. IRB should review this and also form the basis of the criteria by which either a substantial equivalence finding or an accreditation process might

move forward.

And as a final note I think that something that dropped off the radar screen but may be appropriate here is to return to the idea that in the U.S. few IRBs in the U.S. have the capability to do this kind of review themselves. It comes before them too infrequently. The issues are too novel. And, therefore, that we should again make a cross over reference to the oversight report and endorse the idea that the use of a regional or national IRB, on a voluntary basis for the moment, that individual IRBs can defer to or any kind of -- or an independent IRB that individual institutional IRBs can defer to is appropriate so that there are some groups of reviewers who develop some collective expertise.

And I think under those circumstances we might actually have some kind of solution here. I mean, slowly over time we will be able to actually recognize the reality, which is that there are -- there are ethics review committees in South Africa, in Thailand, in Haiti that have been doing this stuff since the year dot with us and know how to do it as well as anybody here, and then there are places that have only been doing it for the last two years, and really cannot handle it. And I think we can accommodate both.

DR. SHAPIRO: Okay. Bette?

MS. KRAMER: I am sitting here finding myself becoming more and more skeptical about the whole idea of the equivalence because thinking back just over the past year or year-and-a-half how established institutions with long time functioning IRBs here in the United States have been closed down for infractions and that is with -- so -- because here in part of our system is the fact that there is an organization that provides an ongoing review.

So how -- you know, unless you were to say accredited by an international accreditation system, et cetera, and that system had its own built in ongoing sort of police or monitoring agency, I find myself becoming very, very uncomfortable as to what equivalence would really comprehend in terms of supervision. I do not think that is very clear but it is my -- I am getting paranoid here about the whole possibility.

DR. SHAPIRO: Do not get too discouraged.

David, and then Larry.

DR. COX: So very precisely I am -- I think that the beef is in 5.6 and that is where -- from my point of view -- most of the action should be right now because the rest of the discussion is a theoretical

discussion about equivalence. And that when you make something that is theoretical, okay, part of you present substance, people can drive a truck through it to obfuscate what you were trying to do in the first place.

So I really like 5.6 as being the primary thing. I really like what Alta said, which is, look -- is that right now that there is really no operative way for dealing for equivalence but we wrote this report and so that can be the substance of what equivalence is. We would like to see a process by which that really works.

When such a process works, okay, then let's put it in place and let's operationalize it but if we have something that does not exist right now and we are having that be part of our recommendations it just does not seem to pass the red face test.

DR. SHAPIRO: Larry?

DR. MIIKE: I guess I will have to change my mind in the sense that everybody seems to think that equivalence in our IRBs in these countries are not an attainable goal and it sounds to me like even in the future for some of the other people here. So I would suggest a pragmatic solution. If you look at 5.2 that talks about capacity building of IRBs, it seems to me

that one can put specific language in there about the substantial equivalence or in a text discussion about what Alex had summarized as the stake of the implementation of the substantial equivalence provision and the difficulty with that.

And sort of relate the -- because this is a report and a chapter on helping developing countries increase the capacity so they are supposed to be equal partners with us. So one can think in terms of the ideal state would be to have IRBs that would be an equivalent of the U.S. so that they can be partners or independent reviews but given the state of the current regulation of substantial equivalence it does not seem -- it seems a remote possibility but that is an aspiration.

So in the mean time one works towards helping to build that and I guess you can look at a dual review as also helping the host country IRB develop capacity because if they are working with the U.S. IRB then they should gain the experience of that.

I do not know what one does about the non-U.S. sponsored research that comes to the FDA though unless one deals with it the way Alta talked about with exceptions.

So I can be persuaded that we should focus

more on the assurances of good ethical reviews in the dual system but I do not want to lose sight of the fact that we ultimately do want the host country IRBs to be our substantial equivalence and perhaps that goes more towards 5.2 and the capacity building.

DR. SHAPIRO: Let me make a suggestion here and then we are going to recess and do some writing. The -- I think it is important to distinguish views that we have regarding the current state of play. That is how many people are in what state of preparedness to do this well vis-a-vis our own aspirations and what we believe is ethically appropriate.

Those are important issues. Do not misunderstand me but those can be handled in my view in the text that is to explain what aspirations we are working towards, what we believe the current state of play is, et cetera, et cetera. All those issues can and need to be handled in the text.

When it comes to the recommendations, however, I think we are entitled to set down the recommendations that we think appropriate, even though the surrounding text may have all kinds of issues regarding how much time it is going to take, what the current state of issues are, et cetera, et cetera.

And so I just think that we cannot in the

recommendations themselves easily merge these two things together, both our understanding of the current state of play and the actual recommendations we are going to make. But the recommendations obviously have to take account of the current state of affairs so it has to allow for the fact that there is a large variety of situations out there and they will have to be handled in some kind of way that is suitable to the situations that actually exist.

So I am going to recommend we recess now and see if we cannot help appoint a small group of people who are willing to work with Eric over the next, let's say, hour on this particular set of issues to see if we cannot get language that is better understood by all of us and more acceptable to all of us. Anyone who wants to is welcome to participate but if the following members do not mind making a small group with Eric so we can work this out, I would ask Steve and Alta and Alex, and anyone else who wants to work with them, to work on this and anyone else who would like to work with them please feel free to do so.

And the rest of us can work also obviously informally on other aspects of the report but I think it is important that we not just leave this and come back to it tomorrow. I want to work it out today so

that we can leave here with some idea of where we are.

So why don't we recess now.

Alta, is that all right with you?

Steve?

Alex?

Okay. Alex is working on another assignment so -- well, let's have Alta, and Steve, and Eric, and anyone else who feels they would like to work on it. I do not want to exclude anyone so anyone who wants to be a part of that, that is just fine.

And let's recess right now. Thank you.

We will try to reassemble approximately an hour from now because I want to allow some time to do this thoughtfully.

(Whereupon, a recess was taken from 10:40 a.m. until 12:00 p.m.)

DR. SHAPIRO: Colleagues, it is not necessary to sit down but if I can just have your attention for a moment. We have to have a formal announcement that we are going to break for lunch now and to remind you that we have made some considerable progress, I should say, in the last more than an hour now but the -- and I think that we will come back and talk about that later on this afternoon but we do have public comment at 1:00. That is why I want to make sure we are all here

for 1:00 o'clock. So those of you who want to eat, you should do so now and make sure that we are all back here for 1:00 o'clock to be here for public comment so I do not want to shift us around until public comment is over.

Okay. Thank you very much.

(Whereupon, a luncheon recess was taken at 12:01 p.m.)

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

DR. SHAPIRO: We will compete this afternoon with the UU Net or whatever it is sales meeting which is going on next door. That is a real meeting. I mean they have video and lights and laser beams and so on. That is -- we might have some that next time.

(Laughter.)

We ought to jazz up this meeting a little bit and get a little. Maybe they are preparing for it, I do not know.

Well, I want to now move to our public comment session and I want to apologize to those who will be speaking us today that we are starting, despite our best efforts, approximately 10 minutes late and I apologize. But we have two people who have signed up for public comments. Both may be known to you. Dr. Sid Wolfe from Public Citizen and Kate Louise Gottfried, Executive Director of National Human Research Protection Advisory Committee, who will be accompanied by Mary Faith Marshall, who is chair of that committee.

So why don't we start with Mr. Wolfe. Thank you very much for coming again.

PUBLIC COMMENT

DR. SIDNEY WOLFE

DR. WOLFE: Thank you once again. I think it has been about three years ago since Jim Childress, when I called him concerning the issues that we were working on then, said, "Why don't you try and bring these issues to the National Bioethics Advisory Commission?"

And I met -- I was at a meeting for about five minutes or so and suggested, I am sure with 100 percent certainty, that whether I had appeared or not these issues would have been taken care up by you but I think there has been a lot of thought put into it. There has been some incredibly well done research that was farmed out to Hopkins and other places which has brought some data and facts to bear on some issues that probably need more research but it was a very important start.

I just want to start by saying that I believe that for economic reasons that people in developing countries are really vulnerable populations in a very similar way and in some different ways than the vulnerable populations that you have previously studied in other reports.

They are in a sense economic prisoners, not just the patients or potential patients for the human trials, but the people on the IRBs or the ethical review bodies. As the Hopkins research showed,

economic considerations can have an enormous effect on the extent to which an IRB in a foreign country will say yes as opposed to say no, not that we do not have that problem here but I think it is exaggerated.

So that if we look upon this whole issue in developing countries as something with extraordinarily vulnerable populations, both the researchers and the patients, most importantly the patients, we have to then say is there even after all these deliberations any evidence of a double standard wherein things that we would not do here we are doing in developing countries. And I think that some of these issues, particularly with the thoughtful discussion this morning, have at least begun to get addressed. There are others that do not -- that have not gotten addressed and I would just like to spend several minutes talking about those.

They include the possible double standard in the design or the ethics review, the ethics review as I just mentioned is moving in a better direction of not having a double standard. The possible, and I think still existing double standard of informed consent and finally post trial availability. I will focus mostly, if not entirely, on the post-trial availability for the people in the experiments.

Going back to the issue of the research design, we have previously raised this issue and the current draft still uses the phrase "effective therapy" as opposed to "best available effective therapy." The reasons that are stated are twofold.

One, the idea that in a developing country you could not afford bypass surgery or expensive complicated systems. We agree with that and I do not think we ever intended nor did anyone else intend to impose those kinds of things which just are not feasible after the experiment would be done or even possibly during the experiment.

On the other hand, the Helsinki rejection of this kind of language, namely saying "effective" as opposed to "best effective," I think is instructive because somewhere between the placebo, which I think that the issue of placebo you have taken care of very well. I do not think it would be possible for the kinds of uncomfortable life-threatening terrible circumstances for which you should never do placebo to do one in a developing country, at least I do not think so. But you have not taken care of it by retaining the language of "effective" as opposed to "best effective" the possibility for the control subjects of using something that really is not as good as it should be.

Remember part of the other argument you used other than the technical feasibility of complicated super structure or bypass surgery is whether it is feasible in that country for the control group.

Now the experimental group is the one being given the therapy that you hope to use and is feasible in the country and, therefore, if the control group, as opposed to the experimental group, is using something that is more expensive or more complicated but still affordable and reasonable within the context of the experiment, I do not see anything wrong with it.

So I do not think that either of those arguments wash very well. You think that generally this is closer to Helsinki but if it really is, there is no reason not to use the best as opposed to effective.

The issue that there may be several best effectives I do not have a problem with that. If someone is going to say it is a toss up as to whether A or B or C is the best effective, someone will figure that out but the standard as written now allows something that is significantly less than the best effective.

Moving into the issue of informed consent, your own research again farmed out and very well done,

recommended incorporating into the informed consent protocol or sheet a test of understanding. Three years ago Howard French, the New York Times reporter, showed pretty clearly by interviewing a number of people in the Cote d'Ivoire that they did not know what a placebo meant. I am told that as part of the investigation by the team from the Washington Post they found the same kind of thing in Thailand.

In other words, it is not enough to have the process in place without measuring the outcome and I think that what is missing in 3.4 is a firm statement that before you start an experiment there needs to be a small -- it does not need to be everyone who is ever going to participate -- you need to do a random selection of people who have already signed up for the trial and you need to determine whether they actually understand all the things that they have signed off on or have been told about that they are not able to read.

In the absence of that we continue, not just in other countries but here, subjecting vulnerable people to experiments that they really do not understand and the placebo one is the easiest one to understand why they do not understand it because most of the people thought that a placebo was just a different kind of medicine. As one person said, a

cheap medicine. But it is some kind of medicine as opposed to nothing.

The last category I am going to mention is the post-trial availability. Again a double standard exists if in this country a group of people who were part of an experiment did not get as the continued treatment for the problem that they entered the experiment for the medicines afterwards.

As it stands now not only for the country but even for those in the experiment there is really no strong statement saying they should be available. There are the loopholes that we pointed out before saying you should do it but if you do not want to, just discuss it and come up with a fairly good reason. I think that there is too much opportunity -- just to go back for a second to the issue of trial design.

Even aside from the difference between best effective and effective, there are even loopholes from the effective standard wherein if someone comes up with a good reason -- I do not have the reason right in front of me here but if someone comes up with what is thought to be a good reason -- here we go.

"In cases in which the only relevant and effective study design would not provide the control group with an established effective treatment, the

proposed research protocol should include a justification for using this alternative design. The IRB must assess the justification provided as well as the ethical appropriateness of the research design."

So even though it starts out with a lower standard than Helsinki, namely effective as opposed to best effective, there is even an out for that. I do not think that those two sentences really belong in there. They are an open invitation as are the comparable sentences in the post trial availability for someone to say, well, that is a good idea but we do not want to do it and we have thought about it and this is what we have thought.

In summary, I think that these documents and the recommendations have involved an enormous amount of thought. Some very creative ideas I think were brought forth this morning on the issue of the ethical review boards. If you are a patient in a developing country the ability to get harmed or killed does not depend on whether the drug you are being given is through a government funded trial or a drug company funded trial. I think that very clearly there needs to be a strong direction given to the FDA that they develop these regulations.

I agree with Alex. I do not think they need

any new statutory authority to do them. They should develop them as quickly as possible. Otherwise what you have read about, and Alta began talking about this morning, in the Washington Post on Tuesday will happen. This is an American based pharmaceutical company that clearly did not go to an IRB in this country and did not even require apparently that the IRB in the foreign country show them that they had met or done anything. The response by the Pfizer person was, "Oh, I did not know that they had not gone through an IRB," which means their process in a foreign country does not require up front before the experiment starts showing of that and it is not the only example.

Dr. Lurie gave examples of how the studies he did in Africa were looked at by his own IRB at UCSF and found to have some important deficiencies which he remedied but the same set of protocols were sent to other countries where they said, "Oh, that is fine. It looks good to me."

Huge vulnerability of the foreign researchers and the IRB members.

Anyway, in closing, I hope you will -- as you have before -- take our suggestions very seriously. This is an important topic, and I do not need to tell you that, and I think it would be unfortunate if you

wind up coming up with some residual evidences of double standards and have the new president with all the embarrassments he already will be getting, and have yet another one in the form of something that really is not very defensible. I think that the rest of the world clearly looks to this country for a number of reasons for guidance on these aside from the Declaration of Helsinki.

It is critical to the rest of the world, particularly the topic of this report, that we eliminate all of the double standards and not just some of them. Thank you. I will be glad to try and answer any questions.

DR. SHAPIRO: I want to thank you very much and thank you and your colleagues for your continuing interest in our work. We very much appreciate the careful thought you have given to what we have had to say and we take your comments in the same spirit and we will certainly think about them carefully.

Alta?

PROFESSOR CHARO: Thank you again for all of the letters and background material.

I would like to walk through with you, perhaps with a specific example in mind, the question of whether there really is a double standard at play here.

I say this against the back drop of being somebody who has continually viewed the populations in these countries as being equivalent to vulnerable populations domestically in the sense that they are not as well situated to protect themselves as a highly educated, well-insured, upper middle-class person in the United States.

But let's just take a domestic example. Despite years of efforts and a number of limited successes I am still a cigarette smoker. Now from what I understand, the very best way to get somebody off cigarettes involves behavior modification, group meetings, and one or more of the various pharmacological aids on the market, whether it is Zyban or it is nicorette gum or other -- you know, nicotine substitutes, but it is a collection of things.

And yet busy people, people with annoying personalities, they do not do well with group meetings and behavior mod so they do not actually take advantage of the best available therapy.

So somebody wants to propose a study that looks at Zyban versus nicotine patches. Neither is the best available effective therapy. We know that because we have already got studies that have shown that the collection of interventions works better than any one

intervention alone. But what they want to see is whether or not for people that are simply not positioned to take advantage of the best therapy, which of the nonbest therapies is their best option.

My impression is that would be permissible even though cigarette smoking is a life threatening behavior. I am sure I could come up with an even more kind of pertinent example if I thought it through longer but my sense is that in the U.S. we do not insist on this and that we do not insist on it in part because there is valuable research to be done specifically on prioritization among nonbest therapies.

It worries me that we would be cutting off valuable lines of research if we were to adopt the position you advocate.

DR. WOLFE: Well, this is actually an issue we spent a lot of time on back 15 years ago. The issue when these studies were being done on nicotine patch and so forth. We made the point that there is a pharmacologic addiction which you take care of through various kinds of nicotine products or Zyban now, A and B. There is the psychological addiction, which needs either a group therapy setting or there actually are some interesting data on just the use of the primary

care doc -- forget the group and all the hassles of being in a group -- spending five or ten minutes every couple of weeks with the patient. So there actually is yet another alternative that for the group of people that you describe may be very, very preferable on the psychological addiction side to do.

But if it is in this country, the person we are talking about who can (a) afford cigarettes, can probably afford some of the other interventions. We and other employers insist that the employer pay for all of the pharmacologic help if there is anyone still smoking who works for our organization.

But I think it is very different again in this country because the idea of economic prisoner is really not quite as prevalent in this country. There are poor people to be sure. I do not know if you are positing whether it would be okay to do an experiment like this in a developing country or what.

See I do not know yet of an instance where in a developing country -- let's assume your experimental -- I mean, because other parts of your recommendations have been followed -- that this is something that is feasible in the country. We are not just using Africa to develop hepatitis B vaccine and then not making it available, something that is feasible. So the

experimental arm is feasible, affordable, do-able, and it is just the control arm for the sake of the equipoise experiment where you believe the less expensive experimental arm is as good as the control arm.

PROFESSOR CHARO: Right. Let me --

DR. WOLFE: So just for the purpose of that experiment do you use the fancier, more expensive control arm? But your hypothesis about equipoise is that the less expensive one is going to work just as well. I do not see how that retards progress at all and it protects as opposed to a placebo or the best as -- effective as opposed to best effective therapy. It protects the people in the control group. I do not know if that answers your question.

PROFESSOR CHARO: Take the example I gave you even though it may not be the best one and imagine you want to use it in China where the cigarette smoking rates are extremely high as I understand. Okay. If you were to test -- you already know that neither intervention, neither single intervention is as good as the collective effect --

DR. WOLFE: Right, they are additive or even synergistic possibly. Right.

PROFESSOR CHARO: Right. So would that then

suggest that it is impossible to compare the different components to one another for those portions of the population that for whatever reason are only going to use one intervention at a time?

DR. WOLFE: I guess my answer to that would be I do not believe there is any plausible biological hypothesis that would suggest that people in China or any developing country are going to have a different kind of response. Or the cultural differences in the psychological intervention are going to have any different kind of response.

So I would say the question is already answered. We know the answer that (a) the treatment of pharmacologic addiction works better than nothing and (b) psychological addiction works better than nothing, and that the combination will work better than either. I do not see why you need to do an experiment. I think that the answer to a lot of -- a number of these dilemmas, Phil Nyberger and I were talking about this before, the answer to a certain number of these dilemmas are to look back at the evidence sometimes from randomized control trials and sometimes just empirical evidence such as needle exchange.

No one has ever done a randomized placebo controlled trial or any kind of legitimate trial in a

needle exchange. If we already know what the answer is, why do an experiment?

PROFESSOR CHARO: I am not sure I agree with your premise that we know the answer here already. I have got colleagues at the University of Wisconsin who have demonstrated that rates of depression vary across national populations. There are biological precursors to depression. One can imagine, therefore, that one might find wide geographic variation across the globe in the characteristic neurotransmitter levels of various kinds of neurotransmitters that are associated with mood and mood elevation. I am not sure that the question is as answered as you think.

DR. WOLFE: Yes. Well --

PROFESSOR CHARO: Clearly they are related so I am not sure I agree with your premise that I am posing an experiment that need not be done in local environments in order to be sure of the local response.

DR. WOLFE: Well, I think it has been done other than in the United States. I do not know if it has been done in a developing country. Let's agree that there are some differences in mental health status, incidence of serious mental illness such as depression or schizophrenia. I do not think -- and we

also know from other studies that the instance of smoking is much higher in people with schizophrenia and I believe in bipolar illness too. But I just do not see what we would gain. It is highly unlikely in my view even given the differences culturally that we would come up with a qualitatively different answer as to whether the combination is not, in China as well as here, better than either of the single components and/or whether either of the single components is not better than doing nothing.

There is just an enormous amount of data to that and even allowing for possible cultural differences I just do not think it is an experiment that needs to be done at all. So we disagree on the extent to which there are cultural differences. I mean, certainly the cultural differences have been cited for a number of things ranging from Tuskegee, the cultural difference between this country and Scandinavia where the natural course of syphilis was already known or on some of these other things.

I think that more often than not, more often than not, not always but more often than not the alleged cultural differences or possible cultural differences that justify doing it again do not justify doing it again.

DR. SHAPIRO: Any other comments or questions? Steve?

MR. HOLTZMAN: Thank you very much but I think Alta asked a question which never got answered so I am going to try to restate it.

DR. WOLFE: Which was?

MR. HOLTZMAN: Suppose I develop a new drug, an alternative to the SSRIs which are used, such as Zyban, and I want to test whether they are efficacious in order to be able to control addiction to cigarettes. May I pursuant to your line of argument and Helsinki conduct a trial of that new pharmacological agent versus only Zyban, whether that trial is in the U.S. or in China or any developing nation? Or under Helsinki and your recommendation, must I conduct that trial of my new agent versus the best available therapy which consists of Zyban, patch and behavioral modification? That is the question. You have vetted -- you said to your understanding in the U.S. it would be perfectly ethical in order to be able to do simply Zyban versus my new agent so you did not think there was a double standard. That is what I took you to be saying.

So the question for some of us -- what you call a loop hole, all right, we do not think is a loop hole because we think that the best available therapy

is not always what is in the best interest of people. So why don't we just take the question. Is it illicit and unethical, whether in a developing nation or in the U.S. to conduct my trial of my new agent versus Zyban alone?

DR. WOLFE: Well, I am going to punt for about ten seconds just simply to say that for depression alone -- if the variable is depression --

MR. HOLTZMAN: I did not say depression. I said --

DR. WOLFE: No, no. Just let me punt for ten seconds. For depression alone, given the strong placebo response rate, as you know there are still studies being done in this country for mild depression or moderate, as opposed to serious DSM-IV or V, whatever we are on now, depression to use a placebo. But if now the stakes are smoking as opposed to just depression --

MR. HOLTZMAN: That is an interesting point you have just made there in terms of the mild because in order to get the effective result you do not have to give the best available therapy as the control.

DR. WOLFE: We have always taken the position -- we have always taken the position that there are exceptions to --

MR. HOLTZMAN: To Helsinki.

DR. WOLFE: To use a placebo, yes. And in Helsinki, we have stated this for about two-and-a-half years now. Bob Temple not withstanding. We have presented congressional testimony on this. We had a debate at the --

MR. HOLTZMAN: So you disagree with Helsinki?

DR. WOLFE: We disagree with Helsinki in the sense that we believe that there are generally accepted circumstances where not only can you but you must use a placebo. We would argue that you should use a third arm, for example, whether it is with --

MR. HOLTZMAN: So you would agree with our loophole about --

DR. WOLFE: Pardon?

MR. HOLTZMAN: You agree with our loophole then that the --

DR. WOLFE: Your loophole as far as what?

MR. HOLTZMAN: With respect to there can be circumstances --

DR. WOLFE: Only on the placebo issue. Only on the placebo issue. The way you have phrased that section, it almost implicitly is not referring to a placebo because the placebo can neither be the best available treatment nor the -- an effective treatment.

It is neither.

MR. HOLTZMAN: No, but what you have just said is you agree that there could be cases in which we depart from Helsinki, including giving placebo if that is what is necessary to do the experiment. That is what you just said.

DR. WOLFE: We have said in front of you at least a couple of times that we believe that Helsinki both in its past and current iterations should allow, despite the language, allow for very minimal number of circumstances, irritable --

MR. HOLTZMAN: For departure.

DR. WOLFE: -- bowel syndrome, a departure. But once you have done that -- once you have gone through that departure then we are talking about nonplacebo studies where we are talking about one effective therapy versus the new experimental one and all we are --

MR. HOLTZMAN: Your problem is not with our loophole because you have the same loophole. Your problem is that we have chosen as the starting point established effective as opposed to best because you --

DR. WOLFE: Which is what I said. I said during my statement that I thought you had taken care of the placebo thing in silence or otherwise but I am -

- the problem is exactly what you just said, which is the difference between best therapy and just an effective therapy.

MR. HOLTZMAN: Okay.

DR. WOLFE: Neither of which in my view are talking about placebos. Placebos are already set aside. We have already dealt with that.

MR. HOLTZMAN: All right.

DR. WOLFE: Does that answer your question?

MR. HOLTZMAN: So we will come back to the Zyban, my example.

DR. WOLFE: Right.

MR. HOLTZMAN: So, therefore, that would not be a morally acceptable experiment?

DR. WOLFE: Well, here we are not talking about a mild condition as in allergy or irritable bowel syndrome, mild pain or something. We are talking about, as Alta purposefully phrased it and framed it, we are talking about death dealing tobacco addiction, cigarettes. And, therefore, we depart from the treatment of mild depression or mild allergies and the stakes are much, much higher. And again I would say that you really -- either for reasons where we would have some disagreement slightly over whether there are sufficient cultural differences to have to do it again,

either do not do the experiment at all or you do it using the best available therapy. You use behavior plus drug A as opposed to behavior plus all drug, Zyban, Nicorette, nicotine patch, whatever else.

MR. HOLTZMAN: Okay.

DR. WOLFE: Okay.

MR. HOLTZMAN: But again then that is true in the U.S. If I have got this new drug, new candidate drug, and I want to do it just versus Zyban, all right, to see whether it is effective, you would say you need to do it versus Zyban plus patch plus --

DR. WOLFE: Yes, the fight, occasionally called pissing match, that we got into with the FDA was exactly over this issue. We said that when these patches and so forth came out initially there was nothing really on the label saying this does not work as well as it should unless you also do this where either Smoke Enders or more realistically and better, I think, for most people just your family doc, and there is all sorts of data showing that an important determinant as to whether people stop smoking is whether their family doctor is part of their team, talking with them for five minutes every month or so.

PROFESSOR CHARO: Assuming they have a family doctor.

DR. WOLFE: Assuming they have a family doctor. I think most smokers should have a family doctor. Most nonsmokers should also.

DR. SHAPIRO: Any other questions from members of the Commission?

Again thank you very much. We very much appreciate your --

DR. WOLFE: Thank you for allowing us to participate in this process.

DR. SHAPIRO: -- presence here today.

DR. WOLFE: We will eagerly look for the output.

DR. SHAPIRO: We will send it to you as soon as we can.

Ms. Gottfried is next. If you would like to both come up, you are welcome to. We could -- I guess someone has to pick up a chair and bring it forward. I apologize for that but I would like to extend a welcome to you both. Thank you both very much for being here.

KATE LOUISE GOTTFRIED

MS. GOTTFRIED: Well, thank you very much. I am Kate Gottfried, the Executive Director of the National Human Research Protections Advisory Committee. And, as you know, this is Mary Faith Marshall, chairperson of our newly developed committee.

I really want to thank you for the opportunity to share some information today about NHRPAC and I expect that this is only the beginning of a hopefully complementary and fruitful relationship between NHRPAC and NBAC.

Most of you probably know something about NHRPAC but to just give you a quick update, let me start by saying that the first meeting was held on December 20th and 21st. The group was charted in June of 2000 and the origin of this committee, I think, is very important because what transpired really was the interest -- an awareness of an interest among the public, among the Hill of issues with respect to human subject protection. There had been several incidents in the news that everyone is familiar with, Jesse Gelsinger, the issues with respect to Duke and its research, et cetera. And so that really I think -- I do not know if I want to say catapulted but it really brought some of the issues to the surface for the public and for Congress people.

And so the Secretary of the Department of Health and Human Services was aware of some of these concerns and really thought that the interest generated was such that it warranted the development of the National Human Research Protections Advisory Committee

or what I fondly call NHRPAC.

She seized that opportunity and basically has invited these experts both to review on a short-term and a long-term basis issues revolving around a variety of areas such as IRBs, human subject protection, protection of vulnerable populations, children, emotionally compromised individuals, decisionally impaired people, elderly people, et cetera. In addition, issues of financial relationships in clinical research and so on. I mean, the list -- it could be endless.

I think that this committee will be a very important step for not just HHS and the Secretary but for the government as a whole and I think that having this advisory committee will be something that will endure over many, many years to come.

Presently the committee is constituted of 12 members. I am happy to say that today it is 12 and tomorrow we expect it will be 17. Hopefully by COB the Secretary will sign and approve an amended charter to increase the number of members. That increase reflects a prior awareness, and I should say it is almost by really administrative oversight or error that we did not have a larger membership to begin with so we were very aware that there were aspects or disciplines

missing from the membership. We have now proposed a pediatrician, an IRB administrator, another social scientist, and somebody who is a strong consumer advocate.

I just want to touch on a couple of issues with respect to the charter. In our charter the purpose and the functions are laid out and basically it talks about providing expert advice and recommendations to both the Secretary of HHS, the Assistant Secretary of HHS, the Director of the Office for Human Research Protections, and other departmental officials on a broad range of issues pertaining to or associated with protection of human research subjects.

The function also indicates that the committee is to provide advice on the continuous improvement of human subject protection functions within the authority of HHS and the committee will provide advice on the development and management of collaborations and communications between HHS and its operating and staff divisions and other pertinent elements of the Federal Government, et cetera. The biomedical communities, et cetera, et cetera.

And that the committee will provide counsel on opportunities to improve public awareness of the function and importance of human subjects protection

activities. I think that is a very key sentence there that the Secretary is aware of the concerns that the public has. She wants the public to be engaged in a dialogue as well and understand what is occurring.

I think that our first meeting was a very solid meeting. We got right into the heart of several issues and we had, I think, some very good exchange, both among the committee and with the public. It was a collegial meeting. It was, I think, ultimately very productive and a meaningful start.

The Secretary of HHS then followed by Senator Edward Kennedy who opened up the meeting, and the public gave us very positive feedback as well.

With respect to the substance of the meeting, the issues we focused on were the -- were as follows: Social science and its relationship to human subject protection, financial relationships in clinical research, the Declaration of Helsinki, and children's issues. Many of these are fairly broad topics but I think they will be followed up in the future. But what we have done from the outset is created some action steps and most of those action steps really focus on working groups.

So in the social and behavioral area we have determined that we should have formal outreach to the

social science community. The social science community is very concerned about the area of human subject protection. They feel somewhat like a stepchild. They have not been as engaged in the issues and they feel as though we should focus more attention on their concerns. And we understand that concern and we invite and are inviting the social science community to create a work group and provide us with some guidance on how to proceed in this area. How and what to do relative to the nonbiomedical research.

We then moved on to issues of financial relationships in clinical research. There was a paper that really arose in advance of the committee meeting and that was a paper that was drafted in conjunction with NIH, FDA, CDC, OHRP, Office of Human Research Protection, ASPE, the Assistant Secretary of Planning and Evaluation.

That paper was disseminated to the committee in advance of the meeting and discussed at length and the outcome from that discussion was the creation of a working group which is headed by one of the committee members and has about four or five other committee members to participate.

Stuart Nightingale, formerly of the FDA, now downtown in the HHS Assistant Secretary of Planning and

Evaluations office, has been an incredibly valuable resource and has worked along since the beginning with this paper and will continue to be a resource in this particular area.

The third area we focused on was the Declaration of Helsinki. That issue certainly is on the minds of many, many people and it particularly is of concern not only in HHS, I think, but government-wide. And CDC, FDA, NIH, all were concerned about this issue and wanted a balanced presentation at our meeting and so we had Dixie Snyder of the CDC come and talk about the Declaration. And from the generous assistance of Glen Drew from your group, he provided us with a copy of the comparison charts that he drafted so we were able to use those as a basis from which to start our discussion.

At the end of the meeting I think there was a general consensus among the NHRPAC committee members that there were some very positive and important areas focused on in the Declaration, both from the original declaration and the revision in 2000. There was also a recognition that there are some problem areas and the recognition that this is an issue much greater, broader, larger than the existing NHRPAC committee.

And so what they decided to do was basically

turn the Declaration of Helsinki discussion and analysis over to what is now finally chartered as the Human Research Subcommittee of the Office of Science Technology and Policy, what was formerly called the Human Subject Research Subcommittee so now is HRS. We actually presented there as well and talked with the committee members. That is a government-wide subcommittee. And they will in turn form a working group within their committee to analyze and draft a response to the Declaration of Helsinki.

The expectation is that there will be some kind of formal response developed and vetted through both HHS and all the government agencies prior to determining how to then approach the WMA or however -- whatever the process turns out to be.

The last area we focused on at the meeting was children's research and we had a guest presentation by Alan Fleischman, who many of you know. We also decided in that instance to create a working group and have Alan be a valuable resource to that group. And I can say safely that at the next committee meeting children's issues will be followed up on and discussed in greater depth and then determine what areas of focus should be -- what areas should be focused on.

The committee, I think, will meet quarterly.

I think I talked now about the substance of it. I want to just mention a few things that I think is important with respect to emphasis by the committee, and that has to do with process.

I think the process is very attuned to having an open, very transparent conduct of proceedings throughout -- from its inception basically throughout the next several years and its entire tenure.

I think the -- again we have got to deal with all of the sophisticated research issues and there are many complicated issues around cloning and stem cells, et cetera, all these ground breaking research areas within genetics. And we need to capitalize on that opportunity right now with the bipartisan support that we expect is out there. That is the sense now.

The Office for Human Research Protections got a -- which was formerly the Office of Protection from Research Risk got a tremendous increase in its budget in order to focus on a variety of issues. NHRPAC is not part of OHRP but it is related or advises OHRP and the director of OHRP, Dr. Greg Koski, who is also the executive secretary of the NHRPAC.

So I think that this is really a critical time with respect to taking up a lot of these issues and in

demonstrating to the new administration that, in fact, these issues are not controversial with respect to Democrats versus Republicans. They are just generally controversial.

DR. SHAPIRO: Excuse me. Are you nearly finished with your remarks?

MS. GOTTFRIED: Yes. I am almost done.

The last thing I want to say actually has to do with our material. All of the material is on the NHRPAC website and I want to say that the NHRPAC website is as follows, but do not quote me because I did not get a chance to double check it before I left, but it should be along the lines of www.ohrp.osophs.nhrpac/nhrpac/htm or .htm but I am not entirely certainly. I can tell you that if you go to --

DR. SHAPIRO: We will make sure that all committee members have the right address.

MS. GOTTFRIED: Great. And there is a direct link also to NHRPAC on the OHRP home page.

And finally the financial relationships paper that was distributed at the meeting, we are seeking public comment on that, and that is also on the website. It is in several locations. It currently states that we would like the comments by February

16th. That date has been changed to March 2nd and we very much would invite public comment and your comment on the draft document.

And the final fact that I have to provide you with is that we have scheduled the next meeting for April 9th and 10th.

Thank you.

DR. SHAPIRO: Thank you for that very comprehensive presentation.

I do not know if you have anything to add now that you would like to share with the committee if it is short.

MARY FAITH MARSHALL

PROFESSOR MARSHALL: It is. I will just say briefly thank you very much for being here and I just wanted to mention that I have had some questions in terms of the relationship between the NBAC and the NHRPAC. I am coming to realize that in government it is probably possible to have an entire conversation that consists merely of acronyms.

I think that there will be overlap. We certainly will learn from your guidance and your excellent scholarship. I see our committee as perhaps being more narrowly focused on human subjects protections but perhaps procedurally more widely based

in that we report directly not only to the Secretary but our charge is to a broader constituency in the sense of a responsibility to the public as well. So procedurally in our meetings when we have discussions about issues, our -- what I call our public members are afforded the same amount of time as the members of the committee and the ex officio members who represent the 17 federal agencies that come under the Common Rule.

So that in the future if there are any occasions when we need to have conversations back and forth then I would certainly welcome those and thank you for all the guidance that you have provided over the years.

DR. SHAPIRO: Thank you very much and thank you for taking the time and effort to be here this afternoon. I know there are a couple Commissioners who want to -- Alta and then Alex.

PROFESSOR CHARO: Thank you very much for coming and my sympathies. Your acronym is not the most mellifluous I have ever heard but it certainly works and your website address is longer than our's so you are up against a few obstacles already.

I am actually very interested in the relationship between the two groups. One of the difficulties with this particular Commission has been

that virtually all of its recommendations have been made in the area of human subjects research and would need to be implemented by the Department of Health and Human Services but there are a number of different agencies and institutes within that department and interagency coordination on a response is difficult and slow.

One of the reasons why OHRP was created was to help to centralize those functions within HHS. One of the reasons you were created was to help OHRP know what to do with that new centralized ability. And since our charter actually directs that there be a response formally made to our recommendations within 180 days of them having been made, I am wondering whether you anticipate that it will be your responsibility to make that response to the various reports that have already been issued on human subjects research with people with impaired capacities to make decisions, research with human biological materials, and now the reports on the domestic and international research systems.

PROFESSOR MARSHALL: I guess my perception is that that is not in our charter or our direct responsibility. You know, again I think that there are areas of overlap. Obviously if you look at the agenda for our first meeting then there is a great deal of

overlap. I would see us perhaps as in a more concrete and perhaps policy directed fashion implementing many of the recommendations that you have. But in terms of being positioned or required to make a response, that is not my current understanding. That is the best that I can say. I do not conceive that to be our charge.

DR. SHAPIRO: Thank you.

Alex, and then Larry.

PROFESSOR CAPRON: My question follows up from Alta's and in a way perhaps it is just asking for a clarification of what you just said because it seems to me that the best response that we could hope would be what you said is your charge, which is seeing that those recommendations are acted on.

We will be, one way or another, expiring soon. I gather that the expectation is that your charter will survive. And it is, therefore, the good fortune, I think, for us and I hope for those who would be benefited by our recommendations that there will be a body of citizens in the position that you hold to ask those who are able to take the steps that are necessary, when those steps will be taken, and if they are not going to be taken, why, because otherwise our Commission, like others in the past, who have the

ability to make recommendations and ask for response and then disappear before the responses are forthcoming would be less effective in the course of history on these subjects than we may be because you will be there. And I am delighted that you see your role as seeing that these things are acted on. Whether you send us a report about it or not is of little consequence.

PROFESSOR MARSHALL: If I can just briefly respond to that.

DR. SHAPIRO: Yes.

PROFESSOR MARSHALL: I could not agree with you more and I can tell you from my perspective as the chair of the committee, and I think the other committee members, and certainly Kate's and Greg Koski's perspective, we view this as a golden opportunity. Because of unfortunate events there is, I think, a confluence -- or a confluence of events, there is now the opportunity for a wholesale shift or wholesale reform perhaps in the way that human research subjects protections have been looked at and operationalized in this country. And if our committee throws away this opportunity it would be a real crime and I think that we see that burden and understand it and that we intend to make the most out of it.

DR. SHAPIRO: Thank you very much.

Larry?

DR. MIIKE: I am interested in exactly how you people will function and how your impact will be because unlike our group, which is sort of a general body, generally advising the Federal Government, your's is attached to a specific office who has a specific purpose. We do our influence by writing reports and to the extent that individual members can on a personal level influence policy.

What is your understanding of what you are going to be about? Are you going to be -- one can talk about an advisory group to an agency or to an office that advises them more on a personal informal level than by taking time and writing very nicely documented reports.

So generally I would like an answer in terms of which tack are you people taking and then secondarily what kind of resources are available to your committee to help you in your work.

PROFESSOR MARSHALL: Those are excellent questions and I guess that I have a couple of answers for them. We are a new committee. We are evolving. Some of this is yet to be discovered. But my sense is that the opportunity that has been provided us by our

charter allows us both to be advisory to a wide array of individuals, both within and outside of government.

Now you know as well as I do that someone can take that advice or leave it but that we also have the opportunity to engage directly the development and the management of HHS and OHRP and to make -- to be critical of its system of operations and I think that certainly the country and the government and the research community is galvanized around an opportunity to look at a much broader system of protecting human subjects than has ever existed before in that we are in the position not only to make advice about that system, provide advice about that system, but also to provide a critique about the response to that system. That is my understanding of what our charter is.

We are not perhaps more authoritative than that but I think that we do have the advantage of being able to say here is our advice and here is how we think you are doing or not doing your job or could be doing your job better.

My understanding is that there are -- if you look at the budget for the OHRP or for the committee that it has been greatly expanded and that there are people who as we speak are being hired in support functions to provide the resource to have -- the

resources to enable the committee to do its work and the OHRP to do its work.

DR. SHAPIRO: Thank you very much. Any other questions?

Well, again thank you both very much for being here. We very much appreciate your report and look forward to working with you and look forward to your own work in this area. Thank you very much.

Okay. I now want to return to the material we were dealing with in Chapter 5 and I will let Eric take us through some proposals for dealing with Chapter 5, particularly the latter part of the chapter, the chapter that -- the part of the chapter, really the first 17 or 18 pages or so of the chapter are unaffected by what we are about to deal with. But I think there is -- we have a new approach we want to recommend and discuss and see whether that is satisfactory to the committee, which will involve restructuring especially the last part but Eric will talk more specifically about that so let me turn to Eric now.

DISCUSSION OF DRAFT REPORT:

CHAPTER 5 (Continued)

DR. MESLIN: We passed out a two page document. I hope there are enough copies for the

public as well. It has no title, no page numbers, and no author attribution but it starts with "Point one, people should not be enrolled."

PROFESSOR CAPRON: Do we want to deny it?

DR. MESLIN: No.

I just want people to know what they pick up and that they have the right document. Every other document tends to be --

DR. SHAPIRO: Well, we want to leave that possibility open. First of all, I want to make sure every Commissioner has a copy.

DR. MESLIN: Right.

DR. SHAPIRO: Okay. Thank you.

DR. MESLIN: This document lists six points numbered in order, which are supposed to be representative of a logical flow of thinking that summarizes the answer to a couple of questions. The first question is how many ethics review committees are needed and the second question is are there any exceptions to that and, if so, how should we be thinking through that problem.

I will let people glance over them but I do think it is important to go over them one by one.

As we do this, the following proposal should be kept in mind: These are not identical to what

proposed recommendations might be but within them I think you will see an attempt to replace what is now in the chapter as Recommendations 5.5 to 5.9, inclusive.

Alta and Steve and Alice and Harold and others who worked on this during the break can come in and make suggestions as well but the logical flow -- and I will not read the text, which is meant to refer -- the words under the phrase "text" -- which is meant to refer to what would go in the body of the text as further explanation are as follows:

First, "People should not be enrolled as research participants in clinical trials in developing countries without the substantive ethical protections outlined in this report."

Secondly, "Clinical trials in developing countries that do not provide the substantive ethical protections outlined in this report: (a) should not be conducted or sponsored by the U.S. Government; (b) should not be used by federal regulatory agencies to approve drugs, devices or biologic for sale in the United States; (c) should not be conducted by U.S. citizens or by researchers affiliated with U.S. institutions."

Point three: "Substantive protection can best be assured by review by an ethics review committee."

Point four: "Host country ethics review is necessary to ensure that local issues are properly addressed, and therefore is always required. U.S. IRB review should supplement the local review, unless the host country system of human research protection has been determined to achieve all of the substantive protections outlined in this report."

Point five: "If the host country human research protections system has been determined to be substantially equivalent to the U.S. system, then it can be presumed to provide the protections outlined in this report."

And finally: "The U.S. Government should identify substantive and procedural criteria for determining whether a host country human research protection system is substantially equivalent to the U.S. system, and develop a process for issuing such determinations."

Now a couple of points and then I will turn it to Harold to lead this or Alta or Steve to make any other comments.

We do not name directly the FDA. We do not -- as has been mentioned in Recommendations 5.8 and 5.9. We do not put the issues of equivalent protection first for the reasons that I hope are self evident. We put

them towards the end. And, thirdly, this is meant to in some ways parallel what is going to appear or likely to appear in the oversight report with respect to issue such as irrespective of the source of funding.

The only other thing I would say, Harold, is if you have Chapter 5 in front of you, the easiest way to think about what would happen is pages 1 to the very top of 19, including Recommendation 5.3, would remain unaffected apart from editorial changes that are needed.

What I suspect would occur is that from pages 19 to approximately page 26 up to what is now the words "ethics review" would be lifted and moved all the way to page 36. Now the moving takes a lot of knitting together and the like. But what you would have then is the first set of discussions in Chapter 5 that talk about capacity building, both for research and for ethics review, and then we move directly to the ethics review section of the chapter following the flow of the argument that I have just outlined and then would close with a somewhat shorter description of the equivalent protection strategy.

Steve, Alta, Alice, Harold, did I misrepresent what I think is the --

DR. SHAPIRO: No, I do not think -- since all

of us were in and out of the discussion, I cannot speak for all parts of the discussion but I think that is a fair representation.

The key issue here is whether the sort of logical flow of thinking in these points seems reasonable to people and then we have to articulate it carefully obviously in the form of text and regulations and so on and do not ask -- that has not been done yet. We may yet have a chance to do that today or early tomorrow but it is no use doing that if the sort of flow of the thinking does not -- is not consistent with what the Commission would like to do so it is really that issue.

Larry, and then Alex.

DR. MIIKE: Just a minor point. When you move your wholesale, you have addressed it but basically you are also replacing 5.4 because 5.4 is the same thing as point 6 so this will be -- actually I like the flow. And I would still be interested to see how we handle the FDA issue and so on but I assume that that is going to be more in text than anything else.

DR. SHAPIRO: Right.

Alex?

PROFESSOR CAPRON: I think this is a very helpful approach and I do not know when you think it

would be appropriate to raise any substantive questions about it.

DR. SHAPIRO: Right now.

PROFESSOR CAPRON: Okay. Under point 2, as I looked these over, I found myself wanting to go back to the strategy that I recommended in an e-mail exchange with Alta in which we try, whenever possible, to name who we expect to do something for exactly the reason we were just discussing with -- and Alta was raising with Professor Marshall, and that is the action forcing power or at least the response getting power.

And I looked at 2 and I thought, well, what if we said there federal agencies should provide that or should make sure that clinical trials in developing countries that did not provide the substantive ethical protections outlined in this report: (a) are not conducted or sponsored by the U.S. Government; (b) are not used by federal agencies to approve drugs. And then I got to (c) because I do not know who would have the authority to say that a U.S. citizen should not engage in that.

I think because of that (c) it seems to me is more at the level of what would be good in the world rather than what we think can be mandated. It is aspirational rather than policy in other words. And I

wanted to get the sense of the drafters whether they would agree with that. We can put to one side whether you agree with my sense that we ought to try to state these in terms of the actor but just on this point (c).

Now (c) itself has two parts. One speaks of U.S. citizens who are just operating in some fashion, an independent researcher of some sort. And the other is researchers affiliated with U.S. institutions.

My understanding of the view of the Federal Government is that there are limits to the extent to which it can require actions by people simply because they receive federal funds, by institutions, let's say, simply because they receive federal funds. That is to say they can require actions related to those funds but they cannot require actions unrelated to the funds.

Now if that is wrong and it is a misreading of Grove City and so forth, then I stand to be corrected.

Therefore, as I understand it now, HHS does not believe that it can insist that all institutions that get federal funding must review all research which is conducted there, including privately sponsored research.

Most of the time that is the result that the

assurance provides but the assurance is nominally a voluntary agreement and most upstanding research institutions do take the view that they should review privately sponsored as well as government sponsored research by the same processes and they do not make that distinction.

But if it is the case that they cannot insist that that is the case then researchers affiliated with U.S. institutions but who are not in category (a) or (b), otherwise the research is not in category (a) or (b), again we are in a -- it seems to me even there -- in an aspirational rather than a mandatory policy mode. So that has laid out the issue for you.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I want to respond at a somewhat general level to something that I think is infused in this for me but I cannot speak for the other people who scratched down this. I do not think we need anything here that is tied to current law, current regulation, current agency configurations or current efforts to be action forcing. The reason is that although there have been times in this Commission's existence where that kind of focus was appropriate because there was the genuine possibility that the report would be received and used, and its results

could be measured by whether or not its recommendations were implemented. I think we are long past that point.

I think that in my mind we are now at a point where it does not make any sense to be trying to say what the FDA should do or what the NIH should do but we should be speaking more in terms of ethics rather than law, more about principle than regulation, that we should recognize the document for one that is exhorting rather than proposing specific policies because I do not think that we have any hope of the specific policies ever having a serious response.

Now we have heard from Professor Marshall that they plan to take up these very same topics, and I do not doubt that they will, but the fact is that since they are not required to respond to the specific recommendations we make and that none of the departments have chosen to do that, nor under the current administration has anybody in the White House asked them to do that, that really these documents stand only in my mind as documents that are about where we would like ourselves to be as a matter of ethical principle rather than as a matter of law.

So for that reason I am quite comfortable with a number of things that are tied together in your comment. First, comfortable in not identifying the

agency that has to implement something because it does not matter to me whether in two years somebody at a congressional hearing can ask FDA did you do this. It is quite clear what the goal is here and it is identified as a goal having to do with the entire U.S. Government and perhaps Professor Marshall's committee and perhaps some other place in the government will take that on as a goal that they will achieve in some fashion.

Second, it makes me comfortable with the statement made in 2(c) about the conduct of U.S. citizens or researchers affiliated with U.S. institutions because we acknowledge right away in the text that, number one, this goes beyond current legal authority and would require new legislation and that even if such legislation were enacted it would be subject to reasonable challenge on a constitutional level as to whether or not it interfered with individual rights but that as a statement of ethical principle this is how we think people ought to behave even if we do not have the current or even prospective legal authority to force them to behave that way.

So because I am approaching it from the point of view of ethics and basically what constitutes to me a decent way to behave rather than something that is a

real close road map of how to get there and a list of people that we can query to see if they are traveling that road, I am comfortable with this format rather than the one that you outlined.

DR. SHAPIRO: David, excuse me.

DR. COX: To be brief, for me this is in English and I understand what it says and it says what I believe.

DR. SHAPIRO: Thank you. I believe you.

Can I just respond a little bit to this conversation here? I think the impact of our reports, both then and now, is both unpredictable and in some sense not really easily knowable. That is as I have watched our reports go in the last --

PROFESSOR CHARO: Or discernible, Harold.

DR. SHAPIRO: Well, no, very often topics we have taken up, people have acted on before our reports and so it is just hard to trace down who is acting when and so on. And it really does not -- I think, Alta, it does not -- I do not have a strong feeling as to whether we phrase it the way Alex suggested or not. The idea stands on its own regardless of whether we address, you know, Ms. X and Mr. Y. The idea, I think, stands on its own and so it does not concern me. I do not have a strong feeling one way or another. It does

not concern me.

I think (c) is clearly in a different category than (a) and (b) and just how we handle that -- although I am not quite sure and I do not think it is a huge deal one way or another, it clearly has the characteristics that both Alex has said and you have repeated, and it is a matter somewhat of aesthetics and so on. It is just how we handle it in the report.

So that I think what I would like to focus on here is the logic -- what we are doing. I think Alex's suggestion is helpful. We have to give that some consideration. But as I understand it, you are supportive of the way this is going through although you have some suggestions about how it ought to be framed if I understand your comments.

PROFESSOR CAPRON: Just to -- I thought Alta's response was very helpful. It does leave me with a sense, however, that you actually have an odd mixture of principle and pragmatism because if you are talking at the level of principle, which is the way you have tried to pitch what you were saying, there is nothing about point (c) that is narrowly limited to U.S. citizens or U.S. institutions. And if we are going to speak about the way things ought to be and speak at the level of principle, it strikes me as very odd saying

U.S. citizens. I mean, it is equally true that clinical trials in developing countries should not be conducted by Brits or Russians or Chinese or anybody else or by Ugandans or whatever that do not comply with the substantive ethical principles here.

If we are not speaking in other words to U.S. policy makers and if we are speaking at the level of what we believe are deeply felt ethical principles, subjects should be no more harmed by or their rights no more abused by someone who is not a U.S. citizen than is. And it is an odd mixture of ethics and pragmatism.

DR. SHAPIRO: Yes, but I think we are giving advice to the U.S. Government. That is what we are here for. Other people may be impressed and convinced by what we have to say or not.

PROFESSOR CAPRON: But, Harold, if we are giving advice to the U.S. Government -- in other words, if we are complying with our charter which says that we are supposed to advise federal agencies --

DR. SHAPIRO: That is right.

PROFESSOR CAPRON: -- then we need to speak to federal agencies --

DR. SHAPIRO: I understand what you are saying.

PROFESSOR CAPRON: -- and then we should put (c) in terms of an additional ethical aspiration which is beyond the scope of any U.S. agency at the moment. Maybe we would recommend -- it is not even clear as the text underneath notes that legislation could be passed which would have a sufficient bite in terms of some federal authority to allow us to insist that a U.S. citizen who happens to be in China and does some research has violated a law if he does not comply with these requirements.

DR. SHAPIRO: That is right.

Steve and then Larry.

MR. HOLTZMAN: Let me speak as someone who is ignorant of the law, right, and constitutional law. I think what (c) is getting at, this mix of pragmatism and idealism, is reflecting a kind of view that says, you know, we cannot -- we are making a suggestion that there ought to be a law that says U.S. folk ought not do this and just out of pure innocence and ignorance it seems to me that the United States should be able to make a law that says U.S. citizens and the people in control of the U.S. law not violate other people's rights in these ways.

Now that may be totally naive and there may be a lack of a constitutional basis but I think that is

what (c) says and the reason it does not say no one should do it because it is trying to do more than just be a statement about how the world ought to be. Now it may be naive, all right, but I think Alta's text is saying, you know, it would take a law to do this and the law may not stand up to constitutional muster but that is what it is saying.

DR. SHAPIRO: Larry?

DR. MIIKE: In past reports we have addressed recommendations not just in the Federal Government but to outside organizations, et cetera. So I see that as happening here now. I do not think it is as starkly dichomatous as saying ideal versus pragmatic and I think what we have tried to do is find a middle ground. I would change (c), though, in a sense that to me U.S. citizens and researchers in U.S. institutions are too broad a category.

But if you direct it at institutions and you say that U.S. institutions, researchers in U.S. institutions, then many of these institutions will do what they already do which is IRB review of nonfederally funded research anyway. So it is a call for voluntary extension and it seems to me that that would sort of set aside Alex's approach of trying to identify targets.

The U.S. citizen thing is just too broad to me. There will always be individuals who we can affect.

As far as U.S. firms, I think that is covered by that second one about regulatory agencies. If you want to go ahead and do research and things in other countries, since our focus is on the U.S., I think the regulatory hook would take care of that side. So I would not extend (c) to include pharmaceutical firms, et cetera, but U.S. research institutions.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: But I think the intent here was to reach out to that other group. We thought of instances of a wealthy individual. And again maybe this is naive but it is basically saying a wealthy individual who can be within the reach of the United States law, it should be -- they should not be allowed to do certain things.

With respect to your example of the firm, because the FDA mechanism for the private firm is in retrospect, right, and it is very effective because 99.9 percent of the clinical trials you are going to undertake, you are hopeful of being able to submit them in support of an FDA registration.

But if you do not, if you wanted to take just

an experimental kind of study to get some information with no intent of going to the FDA, if you just have (a) and (b), you know, we have not said firms ought not do that.

And I think where we are coming from more than aspirationally is to say that human subjects research should only be conducted in a certain kind of way. And again it may be naive about whether one can have laws based on human rights but that is what we are trying to say. We ought to argue, therefore, about whether or not we want to be naive.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Two things. First, in one respect I do not share Alex's analysis about the generalizability of what is going on in (c), which certainly could be pulled out and made into a separate point so that it could be clearly discussed.

It is not my intent here to take on the entire argument about moral relativism on a global scale. It is not my intent here to say that the substantive principles we have laid out in this report apply to Ugandans who are doing research in South Africa.

It is my intent to say that these are principles that we think are nonnegotiable when it comes to how we Americans treat other Americans and how

we treat other people regardless of where they are. In other words, it governs us but it is not something that I am saying governs other people. It governs how we behave, whether here or abroad. So to that extent there is a distinction here and it is not a matter of saying that we might as well just say that it should not be conducted by anybody anywhere in violation of this report.

The second thing is that if you take a close look at what is going on in (b) it speaks only to things that are going to be put up for sale in the United States, and that is done -- in some ways, I guess, we are getting back to pragmatism because that is clearly the stick that the FDA can use. The threat that it will not use your data.

But the question is whether we want U.S. based pharmaceutical companies that are doing research in other countries in order to develop drugs that are not going to be put up for sale in the United States but are going to be sold elsewhere to be subject to the kinds of rules that are laid out in this report. If the answer to that is yes, then (a) and (b) does not get there yet. (a) and (b) does not say to a U.S. based company that is doing research in Equatorial Guinea on a drug that it plans to sell in West Africa

that it has to abide by these particular rules that we have laid out here. Right? At this point it is not planning to go to the U.S. FDA because it is not going to market the drug here. It is only subject to whatever rules apply in Equatorial Guinea and, by reference there, usually to WHO and other kinds of -- some international bodies but not to the rules that are laid out here.

So the question for me in (c) is whether or not we want such companies to be subject to these kinds of rules. And my answer is I am not sure that we can legally force them to be subject to them but I would like to say that I think that they ought to abide by them.

If we want to pull that out separately and discuss it more explicitly and spell it out more cleanly, sure. But that is what I would like to see come out of this.

PROFESSOR CAPRON: So by (c) you mean -- you do not mean U.S. citizens alone. You mean U.S. companies, U.S. resident aliens, U.S. citizens, people who are legal people as well as human individuals.

PROFESSOR CHARO: We can -- yes, I mean, in fact, we were struggling a little bit with the language and we had U.S. citizens versus U.S. nationals. We

deleted the entire thing and talked about only research affiliated with U.S. institutions. I would kind of like to cover the waterfront here because it does not matter if we are too general and we could not get away with it because, hell, we do not expect to get away with it. So why don't we just say what we believe, right, and leave it to others to worry about whether or not you could ever accomplish it.

DR. SHAPIRO: Bill?

PROFESSOR OLDAKER: I agree in part with what Alta is saying but I also would caution that U.S. citizens is not the exact phrase, I think, that we want to use because there are people here who are not U.S. citizens who are doing research but who hold green cards. On the other hand, you have U.S. citizens who may never have lived in the United States who may be born to U.S. parents who grew up in a different country and who are doing research under that country's laws. I do not think we want to reach that researcher who never has stepped in the United States at all but by fate happens to be a U.S. citizen and has held that citizenship for life.

PROFESSOR CAPRON: Does he have a passport? He has got to do it.

DR. MESLIN: They do have passports.

PROFESSOR OLDAKER: Right. I mean, look, we are creating -- we are -- by trying to be as broad as we are, I think in some ways we are causing ourselves problems. I think that you are getting I would say 99 percent of everything in (a) and (b) and trying to get to that last one percent may cause us problems which will make people depreciate their view of what our opinions are. And that is the only thing I am worried about, is trying to have our opinions held on the highest level that they could be held.

DR. SHAPIRO: I have a suggestion here so we can get on and see whether -- again I want to really focus on whether the logic of this is acceptable because this all has to be recast in certain ways so I do not want to focus too much on the detail.

But it seems to me a way to handle this is to come down to deal with (a) and (b) and then develop text that tries to express our feelings about the issues that are involved in (c) and see what language evolves out of that. And I really -- Bill's point is well taken. I mean, we went back and forth using citizens and, you know, we sort of -- then we forgot that we had a controversy there and it was just left in because we do recognize the issues that Bill has raised and others.

So what I will assume is that -- let's go back to just a general logical flow here and we will make some special effort to identify the difference between (c), however expressed, and (a) and (b), which are straight forward. But I have to say I do have a strong -- I share Alta's strong wish if I am correct in interpreting your feeling that we should try to reach out -- we may not be able to do it in a formal recommendation but at least anyone reading our report will know that that was really where we were aiming even though we might not have been able to articulate the exact recommendation. We will have to see. But I think that sentiment is probably pretty important.

Larry?

DR. MIIKE: While we are at it, I have just been looking at one and really one is a variation of two and if you just take one standing alone it is much, much broader than what we are talking about.

DR. SHAPIRO: Yes, sure. It covers all research.

DR. MIIKE: And it is redundant in a certain way because we are talking about research subjects in clinical trials.

DR. SHAPIRO: Yes. Okay. Let's try to proceed through this document a little more to see if

there are other comments you might have on items 3, 4, 5 and 6 because once we get satisfied with this we then have to turn to actually finding out how to incorporate this.

Alex?

PROFESSOR CAPRON: I would wonder if the drafters would be comfortable stating number one in positive rather than negative terms. "People enrolled as research participants in clinical trials in developing trials should be ensured or should be guaranteed the substantive ethical protections outlined in this report."

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Speaking as someone involved in the drafting, I think we were really trying to get at a logic flow, all right, so that when you ask a question like that if there is no substantive difference, I do not think this would -- we -- wordsmithing is not what we should be doing now because these are not even recommendations unless you want -- I think if I understand where we are in this process, Harold.

DR. SHAPIRO: That is right but I think that is another way to write it and it might even be a better way.

MR. HOLTZMAN: Right.

DR. SHAPIRO: That is a helpful suggestion and we ought to think about that.

PROFESSOR CAPRON: I thought we were now going to go over these and -- I mean, it seems to me that these are excellent. These are very nicely framed and if we are close -- I mean, one of the problems that we have as a Commission is having a discussion in which we agree on the generalities and do not nail down some of the specifics, and then we come back at the next meeting with a report that we have just received shortly before the meeting and we go over them and then we ended up in the same place.

So I think the drafting subcommittee has done a very nice job of putting forward not just a logic but very helpful language. And if we can push these to the next point so that we are ready to say here are recommendations to replace 5.5 to 5.9, terrific.

DR. SHAPIRO: That is our intention. We will come back to that in a second.

Jim?

DR. CHILDRESS: I just affirm what Alex said. I put my vote there, too.

DR. SHAPIRO: Eric, why don't you say what we would like to --

DR. MESLIN: Well, let me just give you the

running score card here. From what I just heard, I have a possible recommendation based on the conversation of item 2, which is the U.S. Government should ensure the clinical trials in developing countries that do not provide the substantive ethical protections outlined in this report, and then listing (a) and (b). That is a first crack at what I think I heard you saying.

The first point that you have just discussed would not in my view be a recommendation. There are only two or three of the items on this list, and we could flag them, that should be in the category of recommendation language but that is just -- I am doing what you are suggesting, Alex.

DR. SHAPIRO: Well, I think what the next task is -- I think the Commission is broadly sympathetic to just incorporating this structure into Chapter 5. Now we actually have to do it. We cannot do this sitting at the table. We have to actually do it and get it back to the Commission to look at and --

PROFESSOR CAPRON: Did the Executive Director just say that number one is not appropriate for a recommendation? I mean, is that what you were saying?

DR. MESLIN: That is exactly what I said and I will tell you why I said it. The idea to replace

Recommendations 5.4 to 5.9 came about because there were concerns about three major issues. The logic of items 1 to 6 were meant to express how to go about making recommendations to replace 5.4 to 5.9. If you think that this item 1 is appropriate for a recommendation, I would submit that it probably either goes into Chapter 1 or somewhere else but it does not fit into the logic of where we had suggested it would go in Chapter 5.

DR. SHAPIRO: If I may make a comment, that may be correct but I think until we actually work it in we do not know, which is the point that Jim and Alex made a few moments ago. So that we really have to take that next task on now and so I think we ought to -- we cannot turn to that around this table. We will have to get some people working on that to do some material as fast as we can.

DR. MIIKE: But, Harold, I also suggested that one is really a separate way of saying two so there really needs not be --

DR. SHAPIRO: Let's not try to settle that now. These are all issues which we can consider but let's not try to settle that now.

Steve?

MR. HOLTZMAN: I do not know if I am trying to

settle or just clarifying.

DR. SHAPIRO: Let's assume you are clarifying.

MR. HOLTZMAN: May I clarify. One is the animus, right, for this whole thing. People should be treated ethically, right, in these trials. Two then said how do we get at that. The discussion here has said we may have limitations on how we can get at that. We may be limited to cases A and B. We may not be able to achieve C. So if I am thinking of the logic or I -- I think it is very important to have one.

Now it may be that we simply reference earlier that we establish this as a principle and a recommendation. We are now turning to how do we make it real. All right. Well, we can make it real in the following to ways: 2(a) and (b). And we would wish -- but we are not satisfied. We would like to see how one could get to -- get it to all research. We are just not sure we can get it there. All right. But that is what -- we want to convey that. Okay. That sort of ends the chapter there on one and two, all right, is the way I would think about it.

Now whether one gets put into the affirmative, Alex, I think that is a matter of if it is more euphonious.

And the reset than just sort of spins out as

pretty straight forward looking.

DR. SHAPIRO: Let me make a recommendation. First of all, I am going to recommend that we take a ten minute recess now and then when we get back we -- those of us who -- we will turn to Chapter -- I want to turn to Chapter 4. Alex has been doing a lot of thinking on Chapter 4 and has some -- I think, although I have not seen what he is recommending, what I hope and believe will be some very useful suggestions about how that gets structured and what that may mean, or may not mean, with respect to the recommendations in Chapter 4.

In the meantime, while we are recessing, we will work out a mechanism to really start redrafting Chapter 5 and even with the possibility of getting that done sometime, say today or this evening.

So it is now 2:35. Let's reassemble at quarter to the hour, ten minutes from now. Thank you.

(Whereupon, a break was taken.)

DR. SHAPIRO: Colleagues, I would like to reassemble now. As Jim mentioned this morning, Chapters 4 and 5, just from the point of view of the quality of the writing and so on, needed more work than the first three chapters, a comment which I certainly agree with. And we are in the process of doing that.

Eric is not here right now. We have banished him to a room to begin re-incorporating and reworking Chapter 5. The objective is to have the last half of the chapter in your hands before you leave sometime this evening. That is the last, I do not know, 18 pages or whatever, the last half of the chapter roughly is, which is where the material that we have been discussing a good part of this afternoon comes from. So, it really is quite important. We will get it to you. Steve, I know you have to leave this evening; will try to get it to you before you leave so that you can -- What is your time? When do you --

MR. HOLTZMAN: (Not at microphone.)

DR. SHAPIRO: Yes, well, I think we can. I hope we will be able to get it to you before you leave. So, the rest of us can, perhaps, review it this evening, and be ready to discuss that aspect of Chapter 5 tomorrow, and see how far we get with that, because I would like to leave here with a pretty good understanding of exactly where we are, or close enough so we feel we can draft the appropriate documents.

DISCUSSION OF DRAFT REPORT: CHAPTER 4

DR. SHAPIRO: We will come to the recommendations in Chapter 4 in a moment, but Alex has taken the initiative to redraft a presentation in

Chapter 4. He has been working on that, more or less been working off and on it all day today, and then last night, and other times I am sure. And I hope we will have that in your hands by tomorrow morning also.

So, I want to take a look now at Chapter 4, but if we could structure our discussions around the particular recommendations, as opposed to the text and presentation, which are really going to be re-orientated in a sufficient way, so I do not think it is especially helpful, although after we get through the recommendations, if you have any thoughts you think might be helpful to Alex, that would be terrific. But Alex, do you want to say anything about what you are attempting to do now?

PROFESSOR CAPRON: I will just say very little. The staff had already begun, in response to comments I had made, to reorganize some of the first pages, where I felt that the presentation was not in good sequence. And then, Alice made an additional stab at Chapter 4, and sent that to me on Tuesday of this week, and I brought it with me on the plane, and in reading the rest of the report, got started last night.

I am really just trying to shorten and trying to make the structure of the argument what I hope will be clearer as to the sources from which we

would derive a sense of obligations to participants, and to other people in the country. And we will see whether it succeeds, once you have read it.

DR. SHAPIRO: Good. So, let's just proceed directly to the recommendations, and see what comments we have on the recommendations as they stand right now, recognizing that as we look at the revised text, that may cause us to alter, restructure, re-sculpt some of these in some way.

Jim, do you have some comments?

PROFESSOR CHILDRESS: First of all, let me ask a question about the authoritative text. Are we to assume, in terms of recommendations, that what is in the chapters as written, or what is in the summary of the recommendations is the -- There are some differences, not that they are major, but --

DR. SHAPIRO: Let's assume that it is in the text. I, myself, do not even have a list of the recommendations, but let's assume it is what is in the text.

PROFESSOR CHILDRESS: Okay, so the summary one has some omissions from what is in the recommendations. So, that is the first question.

Looking at recommendation 4.1 which is on page 13, I think it would be better at the end, first

of all, in the next to the last sentence, if we changed "address" to "describe". I have problems with "address" in that sentence, but especially in the next sentence, because in a protocol you could say, "My protocol does not address the issue." You could just address it by saying, "Well, we do not think it is important." I mean, "address" does not really help us as a term in discussing this.

What I would propose in that last sentence would be something like the following. "When no arrangements have been negotiated, the researcher should justify to the ethics review committee why no arrangements have been made, or alternatively, why this is the case." Why the protocol does not address the issue does not really tell us anything there, I think.

DR. SHAPIRO: So what are the -- I agree with that, but you had two alternatives, Jim.

PROFESSOR CHILDRESS: Why this is the case.

DR. SHAPIRO: Will you repeat the first one, just so I make sure that I --

PROFESSOR CAPRON: It is "describe", would be the first.

PROFESSOR CHILDRESS: That is right. It is "describe", rather than "address".

DR. SHAPIRO: Right.

PROFESSOR CHILDRESS: And then, in the last sentence, "When no arrangements have been negotiated, the researcher should justify to the ethics review committee why this is the case."

DR. SHAPIRO: I appreciate your recommendations. I had not thought about it that way, but I think "describe" is better than "address".

PROFESSOR CHILDRESS: And then, if I could just take a couple of more while we are on these --

DR. SHAPIRO: Sure. Yes.

PROFESSOR CHILDRESS: I think the order of 4.2 and 4.3 probably should be reversed, and here we are on pages 24 and 36, if we are using the text. At least as I understand it, 4.3 gets at the question of the process of negotiating the agreements in advance, whereas in recommendation 4.2, you start explaining in the protocols, and it seems to me that if we are thinking about it in terms of a step-wise fashion, it would be better to have, say, talk about the prior agreements being negotiated by the parties, and then, you move into the discussion in 4.2. So, I would propose that.

But that relates to the way we present

the recommendations in this chapter. We have gone through a process, and obviously, we are now revising that in Chapter 5, where we have tended to put the recommendations in a place in the chapter where it would sort of flow with the discussion. I would actually recommend for 4, that we put them at the end of the chapter. And again, thinking in terms of the flow of the steps. Because these recommendations, even though they will often be read in relation to the text, will often be pulled out, and treated as recommendations. And it is when they are presented as a set of recommendations that it seems to me you really want to make sure that when people are reading them, they can think in terms of the kinds of steps of action that they will be taking.

So, at least, that would be a proposal that I would make for your consideration.

And then, the last point that I would make on the recommendations would be on 4.3, where we have a redundancy. "Where possible, preceding the start of the research, prior agreements -- ". We should get rid of "prior", since "preceding" takes care of that.

DR. SHAPIRO: I understand, Jim, you have made two points. I want to make sure I understood them

both. One is that you think as we look at these recommendations together, 4.3 comes temporally before 4.2, I mean in the process, and therefore, should be laid out before.

But you then made a second suggestion, I believe, which was that in Chapter 4, that all the recommendations should appear at the end. Just lay out the arguments, followed by all the recommendations at the end of it.

PROFESSOR CHILDRESS: I am talking about three here, so it is quite --

DR. SHAPIRO: Yes, it is a small number.

PROFESSOR CHILDRESS: So, the other chapters --

DR. SHAPIRO: Larry?

DR. MIIKE: Perhaps the easiest way to deal with that is do that in all the chapters, just as a summation of the recommendations at the end, even though they are scattered in the --

DR. SHAPIRO: We will certainly have them all in the executive summary. That is not written yet, but they will certainly be there all together.

DR. MIIKE: I do not know if I could support putting them all at the end. It seems to me that they should be keyed to the text, and if we put it

all at the end --

DR. SHAPIRO: I do not have a strong feeling about it. If we do, changing the order of these has different implications depending whether you take the second recommendation or not. Because if you take the second recommendation, then changing 4.3 and 4.2 is just flipping paragraphs. If you do not, then we have to rearrange the text as well.

DR. MIIKE: Alex, your rewrite, is it going to affect this at all?

PROFESSOR CAPRON: I think I could accommodate whatever you all want. I do not think we have to do the same thing in this chapter as we do in other chapters, both because there are only a few recommendations, and because they are all closely related. And so, going through the arguments, and then coming to conclusions about them, is certainly feasible here.

Usually, I think Larry is right, that it works better, and in other chapters it would be very disruptive to hold them off, because they cover such a varied amount of ground. I am just --

DR. SHAPIRO: Let me make a suggestion. In this case, given where we are, my suggestion is that we take both of Jim's suggestions in the case of

Chapter 4. That is not a perfect solution, but that gives us, I think, an easier way to --

PROFESSOR CAPRON: It certainly is easier to do both of them because, otherwise, I can tell you, in the flow of what I have been writing, it makes more sense to go from obligations to participants, to a broader justice view of obligations to the country, and it would be very awkward to stick in the text relating to what is now 4.3 before you get to that. If you can go through all of that, then ordering 4.3 before 4.2 is easy, and I think that is the greatest argument in favor of Jim's approach, and I will do that.

DR. SHAPIRO: If there is no objection, let's assume that that is the way we will handle the recommendations in 4. We will flip .3 and .2, and just put them all at the end.

Well, let's proceed now to other issues that surround these things. Steve?

MR. HOLTZMAN: The first is a minor grammatical question, and that is in the first sentence of 4.1, is we are using the preposition "in" and we have got "researchers and sponsors", and it is supposed to be "sponsors of", but "researchers in". So, someone should figure out how to write it so that it is right. And I am indifferent as to how it is rewritten as long

as it is right.

The second is potentially substantive, and it is -- Let me just phrase it as a question. If you read the first sentence, "Research proposals submitted for IRB approval should include an explanation of how successful interventions will become available." Do we mean successful interventions, if such exist, wherever they came from? Or do we mean successful interventions resulting from the research?

DR. SHAPIRO: My understanding, it is the latter.

MR. HOLTZMAN: Okay. So, do we need to clarify that?

DR. SHAPIRO: Just let me make sure that everyone agrees with my reading of this, that that is what we are intending here. I mean, all the text does not make sense otherwise, as far as I can understand it. Okay.

Do you have any other -- Alex?

PROFESSOR CAPRON: Well, you know, Steve's point goes to the question of what is, from a viewpoint of fairness, the relationship between a research intervention which proves to be successful, and those people who participated at different stages in its becoming successful. And I was not clear,

Steve, whether you were suggesting that we, in clarifying this, narrow the sense of "successful" to people in the country. We are talking about 4.2, right? People in the country where the research is conducted. That is, the conclusive research showing that something is successful, as opposed to people who participated in some earlier part of the process.

MR. HOLTZMAN: Alex, no, I was not aiming at that. I think in the text we have tried to say that you have to look, case-by-case, at what is the relevant population. Well, that is actually more the people, the participants in the trial. This is everyone now. I just wanted to make clear, because there had been some discussion about whether there was an obligation to provide, on the basis of someone having participated, even if the trial failed, if there was something that could help them, did you have an obligation. Larry raised the problem that that would lead to undue inducement, and I was just clarifying we did come out there, and that we are specifically referencing effective treatments that result from the trial, as opposed to who gets -- what is the catchment.

DR. SHAPIRO: Other comments or questions on any of these? Arturo?

DR. BRITO: A comment on the suggestion

of rewording 4.2. I understand Steve's concern, and I think we are all in agreement on what we are trying to say, but in the rewording, the only concern I would have is that -- When I read this, it is implicit to me, and I do not know if implicit, because we have worked on this so long that I, you know, it becomes implicit, or if somebody off the street that reads this, if they are going to understand this quite clearly.

But we have to be really careful that what we are not talking about here is the control group, that we are comparing what we are trying to prove that is effective in a developing country and that would be more pragmatic. In other words, if we are comparing two different arms, and the control arm you know is not really what you are testing; you are testing the other arm. So, I just want to caution that when we reword it, not to -- So that a month from now we are not going back and saying, "Wait a minute, the way that this reads is that we are trying to make a control arm that is not pragmatic to implement in a developing country, which is what we are not trying to test now." We are saying that there should be a means for making that available. So --

DR. SHAPIRO: Arturo, I cannot say -- I

did not fully understand what you were trying to say. I apologize. Maybe you could restate it. I did not fully understand it.

DR. BRITO: Okay. What I am trying to say is that, if you are doing a study in a developing nation, and theoretically, you are doing a study of a -- you are comparing two different groups. You are comparing what you are trying to implement into that country, what is reasonable, and what can be useful to that host country. Sometimes you need to make a comparison to a control arm that -- For instance, the AZT drug trials that we have talked about before that you know cannot be implemented. What you are trying to prove is something that is more feasible, that is just as, if not more, effective. If at the end of the trial, you end up finding out that the new treatment is not as effective, or more effective, and therefore, what you end up proving is that the control arm, which is what you are not trying to implement, is actually more effective, then I am not sure from the wording of this --

It is almost like saying, now you have to find the means to make this available to the host country, or the host population. So, what I am saying is that it just would not -- I do not know if it is

rereading it more and more, and now with the rewording -- So, I agree with what Steve is suggesting, but what I am saying is that we have to be really careful when we reword this to make it very clear that we are not talking about this control arm. We are talking about new therapies that are trying to be proven to be useful, and just as effective as the control arm.

MR. HOLTZMAN: That is how -- If you just take the word "new" and insert it before "successful". So, it would read, third line, "how new, successful interventions resulting from the research", and then, everywhere else, you have "successful intervention", if you just insert the word "new", it will be clear that we are referring back to that.

DR. MIIKE: Or I would suggest just saying "if the experimental intervention is successful".

DR. SHAPIRO: Okay. I understand the point. I agree with it.

DR. MIIKE: But the text makes it clear what we are talking about.

DR. SHAPIRO: Any other comments on these recommendations? Okay, if there are no other comments, then we have no other official business here this afternoon, unless there are issues you want to raise.

We will not be receiving, I think, the new drafts of Chapter 5. I do not know when we will get it, but it is probably close to five. It is not going to be in the next ten minutes, or 15 minutes. And so, unless there is another issue that you would like to address right now, we will lend you some time, which we will reclaim at some other moment.

Steve?

MR. HOLTZMAN: Two issues. The first is a question. I have some problem with some of the logic of the argument in page 9 about where the blood example is.

DR. SHAPIRO: Now is the time to look at it.

MR. HOLTZMAN: Okay. So, my question is, is the author of the blood example -- what we had in an earlier version of this text -- am I directing this to Alex, who is doing the primary rewrite?

DR. SHAPIRO: To all of us. Let's all take a look at it.

MR. HOLTZMAN: Okay, the notion was that the justice as reciprocity argument was put forth, and in the initial versions, the notion was we had this whole Norman Daniels, I think, idea of primary goods, and you could only trade a primary good of a logical

type A with a primary good of a logical type B. And then, some of us said justice as reciprocity does not require they be of the same logical type, just of the same sort of value and level.

The point of the blood example was to make the point that there is an intrinsic connection between the action, both of which could be described as providing blood, that whether it is a gift, or donation, versus a sale -- In other words, the nature and meaning of the action has to do with the intrinsic connection of how it is treated, the cultural institution.

So, this is being used on page 9 to exemplify justice as reciprocity. It was introduced to say, no, this is not justice as reciprocity. This is the nature of the intrinsic connection. All right?

And then, the question becomes whether we should demand that the form of recompense be one where there is an intrinsic connection that supports a certain kind of social relationship, namely the gift relationship. Then the logic of the thought goes to the fact that while it is interesting, a culture can be broad enough to have different kinds of actions, and meanings, and relationships, as broad as giving blood and selling blood, and that you have to get into the

local context to understand whether or not it is ethical or unethical. But there is a presumption, I think we are making, that the form of recompense should take the form of health care, as opposed to the gift of a soccer stadium. Because if it is a gift of a soccer stadium, you have changed the nature of the act.

That is the logic of it all, and it is totally lost in the way this is written.

DR. SHAPIRO: Well, as I understand, as I look at this, I did not understand the very first premise you started with, Steve. You said that this example was given as illustration of justice as reciprocity.

MR. HOLTZMAN: No, it was to show -- It was in -- If you go back to when Alice and Ruth first wrote it, the argument was justice as reciprocity says that if you are involved in research, the recompense has to take the form of a health benefit, because of justice as reciprocity. And then, they went on to cite this notion that reciprocity demands things of equal value, and things of the same logical type. We cite, on the other hand, it is argued against that it just has -- Reciprocity demands equal value, not same logical type. And that there can be, for example -- If something is of a value of a primary good, there is

more than one logical type of primary good. So, that in itself cannot be a sufficient motivation for the argument that participants in research recompense has to take the form of a health care benefit. So, wherein comes that demand?

And then, they said, well, was there an intrinsic connection? This argument about the notion of donating blood was to show how there is an intrinsic connection, because the nature of the recompense, in fact, defines the meaning of the action.

DR. SHAPIRO: And?

MR. HOLTZMAN: Okay. So then, once you have seen that, right, you now can ask the question, do we believe the world should consist of giving providings of blood, to use my example, that are donations, or should it also allow for sales of blood? Should medical research, right, be ones where the recompense is medical care, which is like the giving, if you will, or should it also be broad enough to have where the recompense is building the soccer stadium?

DR. SHAPIRO: There is a lot of moral room between a health benefit and a soccer stadium.

(Simultaneous discussion.)

MR. HOLTZMAN: But that --

(Simultaneous discussion.)

MR. HOLTZMAN: -- reality and meaning as a continuum, and that is what we are being asked to think about.

DR. SHAPIRO: So that, at least as I think about it, and I will have to go back and read this carefully now, as I think about it, I think there ought to be moral room for different kinds of reciprocity, and there is a spectrum of things from health care to other kinds of things. But certainly, in terms of primary goods, and things like that, it would not be restricted to health care. It may not include soccer stadiums. That may be somewhere else on the spectrum, I do not know. But I would not, myself, confine it to health care.

MR. HOLTZMAN: Right. So, my point, Harold, is I thought the idea of the primary versus secondary is not the motivator here.

DR. SHAPIRO: Right.

MR. HOLTZMAN: The real motivator is the nature -- I hate to talk this way. It is the nature of the social world you are encouraging, and what are the nature of the actions, and what they do to us when you have a world with those. And I can imagine, and when we have this thing, the world is complex enough, that statement is meant to get at the fact that it need

not take the form of the medicine itself. It could be the building of a health care clinic. That is consonant with the spirit of a certain kind of social relationship, with an intrinsic connection.

On the other end of the spectrum is the here is a six-pack of beer and a soccer stadium. Well, it does not feel right. Why does not it feel right? Well, it is not just the symbolism; it has changed the nature of the social relationship. It can get to the point of being coercive and exploitive.

Okay. Now, there is a whole range of things in between, and what it requires you to do is get into the specifics of the context, all right? Which is why you end up having to invoke the participation of the local people who speak for their society to understand what its meaning is in that society. It is that simple.

DR. SHAPIRO: No, I understand that. Okay. Well, we will tend to it.

Other comments or questions? David.

DR. COX: Can I just make a comment about that? I am very much in favor of these extreme examples, like the six-pack and the soccer stadium, because it helps focus what the issue is. I will just make that as a -- Because I was having an extremely

difficult time figuring out what was going on. But with the extreme examples, then I think it brings into relief what the issue is. So, I mean, maybe you do not have to use the six-pack example --

DR. SHAPIRO: No, I understand. My own view on this is, in fact, there is a couple of different arguments which we mount here to help motivate this need for possible additional benefits, post-trial benefits.

I am not an expert on this, but from my view, the justice as reciprocity is the least of it, in my view. And in fact, every time you try to explain it, it is a stretch to explain. The other arguments, at least to me, are much more convincing.

DR. COX: I agree with that.

DR. SHAPIRO: Other comments, questions?

MS. KRAMER: But have we determined that we want to keep that in there?

DR. SHAPIRO: Well, I think what I have learned from this comment is that I do not see any reason to take it out. I think it is an interesting example, but we just have to explain it in a somewhat different way. That is my view of it.

Alex?

PROFESSOR CAPRON: For what it is worth,

I had reached the conclusion which was reinforced by comments from several Commissioners prior to Steve's intervention, that the blood example was confusing to people, and it was easier to stay within the context and do a range of examples from the very medical benefit, to alternative medical benefits, to something unconnected, like the soccer stadium, and that got the point about the intrinsic connection across, and that the blood example was just causing people to scratch their heads.

So, what you are going to see from me does not include it.

DR. SHAPIRO: I think the point made here is that there is moral room for different kinds of compensation here. Some seems inappropriate to us in a certain spectrum, but others, for various reasons, seem appropriate. And I think that is the intrinsic point we are making here.

Steve?

MR. HOLTZMAN: What I was trying to do was understand that. And the reason for the blood example, and I apologize for the confusion, is what struck me is, you know, again, put aside blood for the second and stick with -- Let me keep it in the U.S. You may not sell your blood, but you can sell your

plasma. All right? Well, I am continuously struck by that. Okay? That somehow, we do not feel the sale of plasma is unethical. That somehow, we do not feel we have bartered away our soul, that we have somehow imbrued ourselves. But when it comes to blood and organs, we find it morally reprehensible, the notion of selling them. Well, that is fascinating. All right? And so, one of the things it should set one up for is before one starts writing absolute moral rules about these things, is to start to appreciate the importance of the granularity and texture of social relationships.

So, that is why I agree, Alex. You can -- if you give the example, and you give the continuum, one of the striking things is that this one would seem to have been at the end of the continuum, selling plasma, that would be beyond the pale, and yet, it is not. Why not? What is it? But that is maybe not for this report.

DR. SHAPIRO: Yes, Jim?

PROFESSOR CHILDRESS: But Steve, in response, where it gets more complicated is that the we -- And there are many people who would agree with the prohibition. We do not have a prohibition on the sale of blood, by the way.

MR. HOLTZMAN: We do not have?

PROFESSOR CHILDRESS: No. We do not in practice, but we do not have a prohibition. It is not illegal to sell blood. It is illegal to sell organs.

But a lot of this really does not relate to the meaning of the practice. It really relates to the question of consequences. Many people would agree with the prohibition because they worry about people being exploited, abused, et cetera. So, I think we have to be very careful in talking about the meaning of a practice, when there may be a variety of different moral arguments that would be used by different people in a society to support it.

DR. SHAPIRO: Other comments or questions?

All right. We will try to put in your hands before tomorrow morning's meeting, both the new part of Chapter 5, and the new version of parts of Chapter 4, so we can discuss that tomorrow.

What time is our meeting scheduled to start tomorrow? Okay. I think it is important that we not follow our usual practice of calling it at eight and having it at 8:30, because we have to conclude approximately at 11 tomorrow, and to get through our business, we are going to need the Commissioners to come having read what we have provided to them. We

will try to put it in your hands one way or another, if we possibly can, and then see how far we can get tomorrow.

Okay, thank you very much. We are adjourned for this afternoon.

(Whereupon, at 3:38 p.m., the meeting was recessed, to resume the following morning.)

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