42nd MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

Hyatt Regency Bethesda
One Bethesda Metro Center
Wisconsin Ave. at Old Georgetown Rd.
Bethesda, Maryland

Volume I

July 11, 2000

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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 get started.

First of all, I want to thank Marjorie and a number of early birds who showed up for the video. Someone suggested if we started all our second day meetings with a video we would start promptly. I do not -- probably we are not going to test that proposition but, in any case, thank you all for being here.

Let me say a few words about where I --

PROFESSOR CAPRON: Could we also thank Robyn and her daughters and her husband?

DR. SHAPIRO: Very appropriate. Yes, for the wonderful time last evening. Thank you very much for mentioning that, Alex. Thank you. I hope you will convey to Robyn our appreciation. Thank you very much for mentioning it.

DR. MESLIN: Sure will.

DR. SHAPIRO: Let me tell you where I think we are now on the International Report since we only have an hour-and-a-half left. We are going to get everything done in an hour-and-a-half.

My proposal is as follows: We are going to

go through as promised some alternative recommendations coming from Chapter 4. Recall we were discussing about what the alternative recommendations we might make regarding what is owed to participants subsequent to a trial. You all have in front of you a document that looks -- which has these reformulated recommendations in front of them.

With respect to Chapter 4 Recommendation 2 there are four alternatives, which are just for purposes of our discussion to see where we really want to come out on this. That will be -- we will turn to that in a moment. And then there are some recommendations which we are struggling with on 7 from Chapter 2, Recommendation 7 or 7 and 8 depending on how we end up numbering these, where Ruth and Alice have some suggestions here based on their own conversations yesterday.

In a few moments I am going to turn to Ruth so we can go -- she will explain that and we can go through and make our -- at least some initial decisions on those issues.

We will then turn to Chapter 5 and get at least an initial set of comments with respect to Chapter 5, the current draft of Chapter 5, from commissioners.

Hopefully, we will then have some time left to at least get some initial reactions also to the

material that Alex left with us yesterday. I hope many people have had a chance to read that in the interim and I will certainly ask Alex to speak about that. That is alternative material to material we already have in Chapter 1.

But let me say before we turn to look at these recommendations, Chapter 5 and so on and so forth, let me say a word about where I think we are on the broad nature of this report.

I have just spoken to Ruth just a few moments ago this morning. I would like myself a chance to -- as I said to Ruth -- rethink in some global way just the whole structure of the report and its nature and what it is that we say. So I am going to take a stab at redrafting this report over the next month or so dealing with some issues which I have not fully -- there are some issues here which I have not fully thought out yet. There are some issues which I think are purely pedagogical issues as I explained to Ruth a few moments ago.

To take an example of a simple example, and I keep forgetting what is in what chapter but there is a -- on Chapter 3 there is a very long, and I think very useful description of clinical trials, alternative clinical trials, and I actually think it is extremely useful material. I am not sure, however, it belongs in the text as opposed to an

appendix with the text really focusing on why it is it is important to understand these things and sending people to an appendix. That is a purely pedagogical organizational issue.

But there are a series of issues like that which I think want to think through a little more carefully than I have had a chance to really think through so far with respect to again what it is that is owed, the recommendations we are going to talk about here in a moment.

Speaking now only for myself, I want to think through more deeply than I have what the real basis of that obligation is. I think I have a clear idea in my mind and I want to at least get a chance to put that more carefully before the commission before we move ahead, et cetera. I am not going to go through a long list of these things. There are not probably a very long list but they are nontrivial issues.

And so I am going to -- I want the opportunity if the commission agrees to take a stab at that. That means that we will probably delay -- not probably, definitely will delay the public comment period because I do not think that I am going to be able to get through that in less than a month and then provide a new chapter -- not a new chapter, a new draft perhaps or a new somewhat altered in some

way -- I do not want to predict right now -- for the commission to think about.

There are other kinds of issues, which I am not going to take time this morning because I really want us to focus on the recommendations which are still a little unresolved in my own mind and as I said to Ruth this morning I do not want to just come up with this on an ad hoc basis and always sending back someone else to write them out and take care of them.

I think that is not a stable process so that I am going to take a shot at incorporating all -- in my thinking of course -- all the comments and suggestions that have come up from various members of the commission, especially a lot of the material that has come over e-mail, which has been very helpful at least to my own thinking.

So I wanted to just mention that and tell you -- I now see that our schedule is going to probably move back about 30 days, something of that nature, something close to that, but at least I -- if the commission is willing to tolerate that, I think that at least speaking for myself I would just feel more comfortable with the nature of the arguments that we are putting forward.

Now whether -- the irony of all this is I might do all that deep and wonderful thinking and

change absolutely nothing regarding the recommendations. That is a clear possibility. As a matter of fact, it is a high probability but at least, speaking for myself, I want to have a chance to think through the arguments more carefully than perhaps I have and I may be the only one here in that position but I think that ought to be done.

So that is how we are going to proceed but that is not something we need to have a lot of discussion on this morning.

I want to turn directly to the recommendations. If any of you have any concerns about that change in the schedule, let's take it up at the break and so on. I do not want to take our valuable time this morning. There is flexibility in all that.

So let's turn now to the material you have in front of us, Chapter 4, Recommendation 2.

Ruth, would you like to just describe these various options here and then we can open it up for discussion?

ETHICAL ISSUES IN INTERNATIONAL RESEARCH
DISCUSSION OF DRAFT REPORT

DR. MACKLIN: Yes. There are now four options. This is apropos yesterday's discussion. There was some uncertainty both about the wording and the substance.

The current version is listed as option A and that is what currently appears as Recommendation 2 in Chapter 4. The other three are variations and we intentionally refrained from using the adjectives "strong and weak" because yesterday when we were discussing these there was -- those words were used but it is not entirely clear that they are useful in this discussion.

So let's just look at them. (A) is as it stands. The one we heard yesterday.

(B) is substantially changed. "After the trial is concluded sponsors should continue to provide the research, product or other effective treatment provided during the research to the participating subjects for as long as they need it and if they would not otherwise have access to an established effective treatment. The product should be provided free of charge or at an affordable cost to be negotiated by the relevant parties."

Now you see what this says, it actually -- I will use the word "strong." I mean it strongly here requires providing the effective treatment to the subject for as long as they need it so that that is not up for negotiation. What is up for negotiation is whether it is free of charge or at an affordable price and the price itself would be negotiated.

So that takes away some of what was in

version A, some of which is to be negotiated. Here it says clearly what they should get.

Version C begins with the presumption, as it says, "a presumption exists that after the trial is concluded sponsors should continue to provide the research product or other effective treatment provided during the research to the participating subjects if they would not otherwise have access to an established effective treatment."

The second sentence, "The length of time and the costs are to be negotiated among the relevant parties."

Now the difference between A and C is that A begins by saying "Sponsors should continue to provide it," and then leaves things up to the negotiation where (C) simply states a presumption. It does not state it in the form of a should.

And then finally (D) is the version in which everything is negotiated. "Sponsors should negotiate with health authorities in the host country whether any products provided during the research will continue to be made available to participating subjects who still need them after the trial is concluded and, if so, the costs and duration of those products."

All four versions are addressing the question of people who were participants, who needed

a treatment during or something during the trial, got either the effective treatment or perhaps -- I mean, the experimental treatment that was successful or perhaps in the control arm an established effective treatment, and they still need it after the trial.

DR. SHAPIRO: Alta, are you with us?

PROFESSOR CHARO: Yes, I am.

DR. SHAPIRO: Thank you very much. Good morning.

PROFESSOR CHARO: Good morning.

DR. SHAPIRO: Alex, is this a clarifying question?

PROFESSOR CAPRON: Yes.

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: I want to make sure that I understand the revision has another change which I think I like and you say the research project -- product or other effective treatment. That is to be responsive to the situation in which it was found that the experimental intervention was not useful but the established was. Is that correct?

DR. MACKLIN: Yes. And, in fact -- well, either. It could be either. In other words, it could be --

PROFESSOR CAPRON: Yes, okay.

DR. MACKLIN: -- it could be that the established effective treatment turned out not to be

effective or too harmful but there was a control arm that had an established effective treatment or it could be that the product -- the experimental product is successful but afterwards for whatever reason that may not be available but some effective treatment would be available. That is the change, you are right.

PROFESSOR CAPRON: And just also to -- that change could be made in version A, I suppose, as well, or was that intended only to be made in the others?

DR. MACKLIN: The intention was just to have one that stands as the current version.

PROFESSOR CAPRON: I see. Okay.

DR. MACKLIN: It could be made. I mean, that could be an amendment to A, you know, but this was just to say what it currently says because that is what we debated yesterday and then these alternatives.

PROFESSOR CAPRON: Could I ask one other question? In light of Larry's concern about the relationship between Recommendation 2 and Recommendation 4, would we have a chance to discuss the possibility that even in the strong version B, the phrase would be "as long as they need it until it becomes -- until such time as it becomes a licensed product that is available for treatment" or some

such. I mean, there is a difference between forever and, as Larry said, there was some discussion in 4, Recommendation 4, about what happens to the rest of the people in the country. Or is that a -- is that incompatible with --

DR. MACKLIN: Well, I mean that essentially weakens B because this says if they would not otherwise have access to it. Now it could be a licensed product but they may not have access to it because although it is a licensed product they just simply cannot afford it. So it is a different -- it would make a different point.

DR. SHAPIRO: Let me suggest something here. Just a way of proceeding in our discussion.

PROFESSOR CAPRON: I also wanted to say thank you. I think it was very helpful to have these alternatives.

DR. SHAPIRO: I want to focus, if it is all right with the commissioners, on item B here. Although we are trying to avoid strong and weak, good and bad, and those kinds of phrases, it is very hard to do so. But B obviously is -- I mean, to me, is the clearest and strongest obligation if you want to put it that way. It is a strong obligation.

And in some ways, to me, it is the clearest and most satisfactory because as, I think, maybe Eric pointed out yesterday, if -- you do not have a

stopping rule with B. Whereas otherwise you need a stopping rule and it is hard to figure out what that rule would be. If it is not the end of the trial is not a good stopping rule then everything -- anything else is pretty arbitrary as well.

And so I really want to see if -- if the commission is uncomfortable with B or some appropriate version of B then, of course, we have to move to A, C or D and have that discussion. But it seems to me that either saying we like or feel uncomfortable with B, that is too much in some way, would be helpful to get -- either accept that or put it aside and go on with the next recommendation.

Larry?

MI: As I said before, I think we have an obligation. There should be an obligation to the trial participants but I am not for -- and I am totally uncommitted for ever commitment.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, I feel the same way. I mean, on what basis should they have such an obligation? That they were able to do a trial and there is no end to it and it does not matter what it costs. I just do not think that can happen. It just cannot happen. And I do not think we ought to have recommendations that really are not do-able.

DR. SHAPIRO: Bette?

MS. KRAMER: I had a clarifying question. Would this include if it were a placebo arm in a study, would this include the people in the placebo arm?

DR. MACKLIN: Yes.

MS. KRAMER: Okay. Thank you.

DR. SHAPIRO: Other comments or questions with respect to B? I do not understand why it is not do-able. It may not be advisable but why is it not do-able?

DR. CASSELL: Well, I mean, I suppose it is a very expensive drug. Do-able in the sense of anything can be done, right? Enough might and enough concern and enough real care, and you can do anything.

DR. SHAPIRO: Okay. That is fine. I understand.

Rhetaugh?

DR. DUMAS: I would argue that it is do-able and it says to provide it either free or at an affordable cost. So it need not necessarily be something that is free forever. I like B and I would support that one.

DR. SHAPIRO: Steve, and then Larry, and then Arturo.

MR. HOLTZMAN: There are many products which one might wish to test which in their nature do not

take the form of a pill. They take the form of, for example, an infusion product, which assumes an infrastructure of a certain kind and type. For example, refrigeration, electricity, clinics, et cetera, et cetera.

The issue of a provision to a subject population who are participants from the perspective of a sponsor, say a pharmaceutical company, is not the cost. If you are dealing with a few thousand people, all right, being able to provide it in terms of the cost of the drug for free or whatnot is not your issue.

I am more concerned about the do-ability of this for all cases and the pragmatics of it. So suppose the participant moves, for example. Is there an obligation to continue to follow them?

So I am inclined more to the presumption and it being a strong presumption, all right, that dealing with the individual case by case to see what makes it possible.

DR. SHAPIRO: Thank you.

Larry?

DR. MIIKE: I had the same -- I was just going to make the same comment as Steve. It is -- especially if -- just look at the consequences of it. You have an NIH and a CDC project going on in these countries. How are you going to actually implement

this in any way? I just do not see it. Especially now you have a tempering phrase here, "at affordable cost." I suppose that means affordable cost to the host country and the participants. I just do not see any way in which you can do this.

DR. SHAPIRO: Arturo?

DR. BRITO: I have a little bit of a discomfort with this because of several reasons. One is something we have talked about before, is about the therapeutic misconception or the idea of undue inducements to get people to participate or what have you, and it is really more undue inducement, the therapeutic misconception here. The other is I fear that this may deter people from doing some research in foreign countries.

I think that the obligation here is really -- and I have kind of swung back this way. The obligation here to the participants just to be honest from the get go of what will and will not be available. And I think as long as the participants are not made worse off, okay, through a research study, then the obligation is not necessarily to continue to provide the treatment.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: It raises a question in my mind, though, of what the benefit is then to the host country and to the people who are involved. It seems

to me that if it is not feasible to carry forward whatever it is that is being tested in the research then it is not feasible to do it in that country.

MR. HOLTZMAN: Not necessarily. Right. I can think of the situation, for example, with an infusion product which could be broadly available in the urban centers of a country where there is electricity but not in the rural areas and some of the participants in the trial may have come from rural communities.

DR. DUMAS: So in a sense you would exploit the rural dwellers in the interest of the more urban ones.

MR. HOLTZMAN: That is -- I am imagining a situation in which there is a broad base in the trial and I can imagine people also who become mobile and move.

DR. DUMAS: Okay. I think that this does not say that if there are exigencies, I cannot say that word too good, that cannot be overcome that they could not be negotiated. I think a setting for the principle and then if there are reasons they find that make it impossible then it is impossible but I do not think we should eliminate the principle.

DR. SHAPIRO: Jim?

PROFESSOR CHILDRESS: I think we seem to have a lot of agreement actually just despite the

unclarity about which recommendation to emphasize. And I am torn because I think that whether we use the language of ideal or strong obligation or prima facia obligation or presumption that there seems to be a consensus that we really want to state something here that this is a direction that ought to be pursued vigorously.

And yet the pragmatics that have been emphasized, the questions of feasibility and so forth, are certainly very strong and point in the direction of some kind of negotiation. And I guess that pushes me more sort of along the lines of Steve towards something like C as long as that presumption is understood in a very strong way.

DR. SHAPIRO: Other comments?

Now one could -- if pragmatic concerns, that is logistical concerns of one kind or another are the reasons to not stick with B, that is one set of issues. That can be accommodated by some kind of language. However, there are other reasons to be against B which have been raised here, such as the incentive structure is wrong and so on. There are different kinds of reasons to be against B. Some of which are pragmatic but others are much more -- are -- cannot be overcome in some sense. The incentive issue cannot be overcome as long as you have that. And those of you concerned that this -- as Arturo, I

think, may have said that this accentuates the therapeutic misconception and so on, that cannot be overcome either if you are promising health benefits of this kind. It is just a sort of built in principle.

So for whatever set of reasons you might have, different commissioners, how many of you would favor moving from B to something -- I do not want to say less indifferent than -- how many of you would favor moving from that and using something like C or A as a basis for trying to form a recommendation? I want to have a show of hands.

All those in favor of moving in that direction?

(A show of hands.)

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I am sorry, Harold.

DR. SHAPIRO: Yes.

PROFESSOR CHARO: I am sorry. I am a little bit confused. I thought that A was the current version. So when you talk about moving from B, I am a little confused.

DR. SHAPIRO: B is the -- what, I guess, I call the stronger version, that is it has an indefinite time period associated with it.

PROFESSOR CHARO: Right.

DR. SHAPIRO: That is the difference -- a

key difference between B and A where that issue is up -- time is one of the issues to negotiate under A, the current version. Whereas in B time is not a negotiable thing.

PROFESSOR CHARO: Right. No, I guess -- I am sorry. I apologize. Every once in a while without the hand motions it is a little hard to follow the discussion.

DR. SHAPIRO: I understand.

PROFESSOR CHARO: Are you now asking people to raise their hands in favor of A/C?

DR. SHAPIRO: Right.

PROFESSOR CHARO: As opposed to B?

DR. SHAPIRO: Correct.

PROFESSOR CHARO: Okay.

DR. SHAPIRO: Thank you very much.

Let me see a show of hands again. I am sorry.

(A show of hands.)

PROFESSOR CHARO: I will put a hand up for C.

DR. SHAPIRO: Okay. It is clear that a majority of the commission really prefers moving to something like A or C.

PROFESSOR CAPRON: Was her hand --

DR. SHAPIRO: Her hand was up.

PROFESSOR CAPRON: Oh, her hand was up.

DR. SHAPIRO: Hand was up. A/C. Okay.

And now let's just put B aside for a moment and see if there are any suggestions regarding A and C or I guess people want to be close to a strong presumption. I guess that is how Jim phrased it.

Is that the general feeling here, Alex?

PROFESSOR CAPRON: The problem that I have been having in the discussion is trying to figure out how we would state the criteria for judging that the presumption has been rebutted because we have done that vis-a-vis other recommendations and explained criteria. And that is actually -- I mean, to me -- I have been sitting here trying to come up with a list.

On the one hand there are reasons for limiting vis-a-vis any particular participant of the type Steve has raised where it becomes logistically difficult because of choice made by the participant.

Would the notion that NIH cannot without multi-year budgets commit itself indefinitely into the future, is that a reason? Is the fact that the company is a small biotech company developing a vaccine and its financial underwriters are unwilling to place its existence at risk? Is the notion that it would simply be too -- so burdensome that the rate of innovation would decline that the company says, well, you know, we could be testing ten or 15 different promising things but with this kind of

obligation we are only going to test one because the financial obligation even for a large company -- I mean, I do not know what the list -- and these are -- in other words, these are policy considerations why it may not make sense to have the policy rather than individual factors which an IRB or -- I mean, this is not even for an IRB.

The other times we have an IRB we have a process where that involves a group of people who are applying a set of criteria. Here it seems to me we are setting up something where if it does not happen people from the outside will say either, "Well, that was anticipated and the way they went about deciding not to do that met the criteria that were set and it is a legitimate choice. It is not an unethical research project for that reason."

I do not know what that process would be or what criteria people would be expecting to apply. I have that difficulty.

DR. MIIKE: May I respond to that?

DR. SHAPIRO: Yes, Larry?

DR. MIIKE: I want to respond in two ways. One is that I do not -- I do not see why we are putting a presumption exists in front of this one. We should just make a bold statement that this should be done. Second of all -- that makes it a little stronger.

Second of all, whatever we do, it is not a legal mandate or something that is going to be absolutely -- they have to do. It is sort of like it is our ethical -- we are making an ethical statement about it here. So what would then happen in cases of NIH, et cetera, is that this is our recommendation.

Our recommendation is not, oh, you guys can -- you know, maybe if you want to negotiate on continue providing the effective treatment, that is fine. Because all we are doing is sort of raising the standard about what they should be doing. So whatever we suggest, if people choose to ignore it, they are going to ignore it.

But I think that -- what the importance is that we do not say it is a presumption that there should be -- there is an obligation to provide these benefits but there should be flexibility enough in terms of the time and how it actually is going to be priced, et cetera.

PROFESSOR CAPRON: Larry, I agree.

MI: I think that is all we are saying.

PROFESSOR CAPRON: I agree with you and I was already starting to try to write out -- if we had the first sentence -- in other words, if we had B and then we had another sentence which says this presumption may be overcome -- and I was trying then to say what it was that would overcome it because I

agree with you it is a matter of looking at something.

I mean, suppose this did not -- suppose NIH launches a big trial of something and does not do this. And suppose we were still in existence and someone came to us and said, "Did they do the right thing?" I guess I would want to know, well, how hard did they try to do this? I mean, what -- did they cost it out? Did they figure out what was involved? Did they take the considerations of the types Steve raised and so forth? Did they go through all that?

But I would like to let them know in advance the criteria I would use in saying, yes, this was reasonable after all. They operated under what was really a presumption and they overcame the presumption. Or is it just ad hoc'ing on our part?

DR. SHAPIRO: Okay. A number of people want to talk.

Eric?

DR. CASSELL: Well, I find what Alex has said persuasive and I am trying to figure out a way where we can make it clear. What we feel is that a sponsor has an obligation to subjects in a trial after the trial is concluded. That is our presumption that that obligation exists.

The minute we begin to specify it, we get into the kinds of troubles that Alex was just talking

about. I really believe that our statement -- the ethical -- the statement of ethics is an obligation continues after a trial is over to the participants of the trial. The nature, duration and extent of that obligation should be negotiated before the trial starts.

DR. SHAPIRO: Okay.

Steve?

MR. HOLTZMAN: What I do not like about C is the fact that the word "presumption" feels awfully thin. Okay. I think we are all kind of responding to that. And yet at the same time I actually disagree with you, Larry, that the should is just a hortatory, whatever the word is, word there.

I mean, I think the way we think about ourselves or ought to think about ourselves is if we write a "should" it means that we would be happy if it was codified that no trial would be undertaken unless it met the condition.

So my view is that we want something that says there is a rebuttable presumption. Okay.

I would then go along with Eric that I think that what is less important. It is not so much the length of time and the cost, it is also the nature.

And the kind of case I have in mind is where someone like the CDC gets together with the representatives of a Health Ministry of a country and

says, "The fastest way we can prove this is by doing clinical trials in 15 or 18 or 30 sites broadly distributed around the country. Now if successful, what is the infrastructure we will need to be able to provide for all?"

And it is possible you will not be able to provide for all but there is a generalized benefit and working out, as best they can, and it is not the best of -- it is just the best of all possible worlds. It is not the best world.

So I think that that is the role of the negotiation with the local representatives and giving them the autonomy they deserve to make judgments about what is in their best interest.

DR. SHAPIRO: Bernie?

DR. LO: On the one hand I am sympathetic with Alex's concern that it would be nice to have some guidelines for investigators and IRBs to follow. On the other hand, I think if we look at the big picture it would be a very big step to say that your obligation as a sponsor, as a researcher, does not end when the clinical trial ends, that you have an ongoing obligation.

I do not think we can sit here and predict what all the contingencies are going to be. There is a lot of research. We are not familiar with the types of research going on. I would rather, you

know, sort of like a supreme court, do what we have to do, establish a broad principle, say that there may be exceptions, we may give one or two examples, but I would just as soon let that be worked out. That is -- other people are going to have to interpret the notion that we believe very strongly that you should continue to do as much as feasible after the trial ends but not to try and specify so much that we will say things that are so theoretical that they are not going to be very helpful.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: As I am listening to the discussion I am finding myself wondering if option B slightly reworded captures what people are saying. If B were to read "After the trial is concluded sponsors should try to continue to provide the research product..." da, da, da. It seems to indicate that they are expected to make the effort, that we understand sometimes it may not be possible, and that a case by case look is going to be necessary.

And in response to Alex, I think what you would be looking at is whether or not it seemed like a sincere effort to find a way to fulfill this requirement.

DR. SHAPIRO: Larry?

DR. MIIKE: This is in partial response to Steve. I mean, no matter what -- how we phrase this, our recommendations do not have the force of law. That is what I meant. I mean, we are an advisory body.

DR. SHAPIRO: That is right.

DR. MIIKE: And, therefore, I would like to make as strong a statement as possible without being specific about the actual operational side because I agree with Bernie that what we really want to do is establish the principle that there is an obligation to continue providing care to the participants in a trial.

I do not think we can go beyond that. It is for others to work out whether they are going to take us seriously or whether they are going to say that is a default position and we will try to do it unless circumstances say we cannot and how, et cetera.

And I think by doing this it gives the host country representatives a reason for bargaining on issues that they thought they might not have been able to bargain with before, and it is up to them to decide whether they are going to bargain so hard that they may not have research done in their country, and it is up to them to decide what the flexibility is in the give and take between them and the drug sponsors.

DR. SHAPIRO: Well, let me indicate where I

think we are here and I am not going to worry right now about the exact language because we are not going to be able to draft it sitting here today but I think we are agreed, as Jim said a few moments ago, that we believe there is an important obligation, post trial obligation, to the participants in the trial.

The number and complexity and variety of research projects, interventions and risks and so on associated with this is too large for us to think that we are going to devise a rule that will be appropriate in all circumstances, the number of sponsors, there are different kinds, different varieties of sponsors, different kinds of trials, risky trials, trials that are virtually without risk and so on that we are not going to be able to specify in any finite sized recommendation just how to deal with these situations but we should try to draft language that we believe that a strong obligation exists.

It can be met in a variety of ways. We might, in fact, give some examples as Bernie suggests and -- but our chief message is that people out there ought to be talking about it and coming to some agreement about it in individual cases.

That is what I understand us to be agreed on and we will try to develop language that reflects that. I think, you know, we cannot go farther than

that this morning. We do not have time to get all those words down but I think it is a pretty clear notion of what we are agreed on.

DR. CASSELL: Yes. Just briefly because the obligation exists even if the trial is not successful.

DR. SHAPIRO: Yes.

DR. CASSELL: And so we are not -- there are no products. The trial failed and yet the obligation continues to the subjects of the trial.

DR. SHAPIRO: We will draft language here and we will take a look at it. I think I have a sense of where we are on this.

Let's go on then to the Recommendation 7 or Recommendation 7 and 8 on Chapter 2. Let me turn to Ruth to -- because I think Ruth has provided an interesting new framework for considering these and I would like her to describe that to you.

DR. MACKLIN: It would probably be useful if you turn to Chapter 2 where that recommendation exists and someone tell me what page that is on, please. 7 and 8. The original 7 and 8.

DR. SHAPIRO: 14 and 15.

DR. MACKLIN: 14 and 15. And you may still have Alta's version, which I think if you put it side by side that was in the memorandum, in Eric's memorandum, because we are going to be referring to

both.

Now we start out -- just a brief reminder of what the discussion was yesterday. After a lengthy discussion about whether or not these recommendations should apply to research on conditions that affect only women or whether it should apply to conditions that affect women and men both in what Alice and I came to believe was a rather hasty decision. The commissioners urged the deletion of the word "only" thereby making the recommendation as it stood with 7 and 8, either in this version or Alta's version, changing the recommendation so that it did not refer to conditions that affect only women.

So our comments begin with that -- against that backdrop so I will just read what we wrote here.

To delete the word "only" thereby making this recommendation apply research on conditions that affect both women and men makes no sense. It makes no sense because it is simply not true that the research could not otherwise be conducted -- okay. We are looking at the language in the recommendation -- since it would be conducted using exclusively male subjects.

However, the recommendation could still make sense if we were to include or to add an all together different recommendation. To wit: This would be an additional recommendation and it would take this

form: "Researchers should recruit women as subjects in all studies on conditions that affect both women and men." That would have to be an additional recommendation and as we discussed very briefly, as I mentioned yesterday, we would then need to have some other paragraphs that say something about the stratification, the analysis of the data separate for men and women, et cetera, in order for that additional recommendation to make any sense.

So this paragraph concludes by saying, "This additional recommendation would be necessary if Recommendation 7 were to be broadened to refer to research that affects both men and women."

Now that is the first observation. Now we go to Alta's proposed revision, which upon studying it carefully Alice and I found to be problematic because Alta's version differs significantly from the current recommendation or the wording in the current recommendation.

Her wording refers to local custom as requiring that a husband or other family member must be approached to gain permission before approaching an adult woman for recruitment. This is distinct from the requirement of a husband's signature or oral permission for his wife to be actually enrolled in the research.

The existing Recommendation 7 and 8 or 7

rather on 14 and 15 does not refer to approaching a husband for permission to approach the woman but refers instead to the requirement that the husband provide consent or, as we prefer, permission for the woman's participation.

So that is an observation on Alta's.

And now here is our suggestion: Going back to the original Recommendation 7. We suggest that all this would be clearer if Recommendation 7 consisted of the first paragraph only with one change in wording of the first sentence. The bolded material on line 17 is the change in the first sentence and the rest of the paragraph is the existing Recommendation 7 or the first paragraph of Recommendation 7.

The newly formulated sentence says, "Researchers should use the same procedures in the informed consent process for women and men to serve as research participants." The change there is from referring to the recruitment procedures, which we have abandoned, and instead talk about the informed consent process.

Now if we retain that as Recommendation 7 and that is the only wording that will be in the actual recommendation, it would then be preceded by the following paragraph, which is new material:

"Much research is directed at conditions

that affect both women and men. Yet it is important to consider research that affects only women. A prominent example is research related to contraceptives and their use. Typically recruitment for such studies takes place in a clinic or health center where women come for family planning or other medical services. In these settings, the contact that researchers have with potential research participants precedes any contact researchers have with the spouse. In this initial encounter, a discussion of involvement of the spouse in the subsequent informed consent process should take place without involving the husband in the consent procedures. Otherwise, it would be impossible to conduct some research on common serious health problems that affect only women. The likely consequence of the inability to do such research would be the denial of subsequent benefits of contraceptive and other research to all women in that country. Health authorities may not be willing to approve the introduction of contraceptive products that have not been tested in that country. The prospect of denying such a substantial benefit to all women in a particular culture or country calls for a narrow exception to the rule that researchers should use the same procedures in the consent process for women and men. In order to justify such an

exception, researchers must provide evidence that (1) it would be impossible to conduct the research without obtaining permission of women's husbands in addition to their own consent; (2) failure to conduct this research would probably deny its potential benefits to women in the country; and (3) measures to respect the woman's autonomy to consent to research are undertaken to the extent possible."

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Alta, I will let you comment first and then Alex and Steve.

PROFESSOR CHARO: Ruth, I find it interesting that I apparently did not understand the recommendation the last time it was presented because in the rewrite I was trying not to change the meaning. And I am finding the same confusion apparently here.

The way I am reading what you propose, which mostly does not bother me, it appears that it would create an exception for our general rule that nobody consent for anybody else. I do not know if that is the intent. Are you suggesting that there will be times that men should be able to enroll their wives?

DR. MACKLIN: No. Let's -- let me read the relevant sentence there again. "In order to justify such an exception, researchers must provide evidence that (1) it would be --" no, I am sorry.

PROFESSOR CHARO: So are you saying --

DR. MACKLIN: If they want --

PROFESSOR CHARO: -- there will be exceptions --

DR. MACKLIN: I am sorry.

PROFESSOR CHARO: -- to our rule that men --

DR. MACKLIN: No. It says --

DR. SHAPIRO: Are you reading in the right place?

DR. MACKLIN: Yes. "It would be impossible to conduct the research without obtaining permission of women's husbands in addition to their own consent."

Now let me just say that recommendation -- we still have the phrase "in no case." In Recommendation 8 -- I suppose that has to be put into Recommendation 7. We still want the phrase, "In no case may a family member's permission replace the requirement of individual informed consent." Is that --

DR. MIIKE: Excuse me, Ruth.

DR. MACKLIN: Is that -- that is in 7 you see. So --

DR. MIIKE: Ruth, it is in 7.

DR. MACKLIN: It is in 7.

DR. MIIKE: It is in your 7.

DR. MACKLIN: Okay. It is in 7. So in

other words, we say first "in no case may it substitute." So this is the husband's permission in addition to the woman's individual informed consent. I mean, that is what the intent is and if it says, "In no case may it substitute," that should make it clear and then there is this additional phrase that --

PROFESSOR CHARO: But I would only ask that that is pulled out and highlighted because I find -- it may be because it is only -- you know, 8:00 o'clock here but I find that it gets lost in the shuffle when the exceptions follow the recommendation paragraph and you have all these exceptions. I just would like it to be pulled out a little bit more clearly.

DR. MIIKE: Ruth, when you read your revised Recommendation 7 you only read the first sentence. You added a sentence. You still have -- in the rest of it, it explicitly states that.

PROFESSOR CHARO: I read the whole thing, Larry. I promise you.

DR. SHAPIRO: Okay. Let's -- there is a lot of people who want to speak here. I have Alex, Steve, Diane and Jim.

Alex?

PROFESSOR CAPRON: I wanted just to have some feedback from people with experience. There is

an empirical statement that is stated in terms of a typically where these things happen and then a description that says in these settings, and then this seems to be a universal statement: "The contact researchers have with potential research participants precedes any contact they will have with the spouse."

And what I worry about, Ruth, is we are later talking about a process of community involvement and if you think of situations where there is such community involvement, wouldn't the fact of the research already have been discussed in the community? And if it were research that involved the potential for something where women would be asked to do something and their husbands in the local custom are always involved first before a woman is recruited or actually is even given medical care that people would know about this?

I mean, the notion that you, in effect, can get to the women without the men knowing that you are doing that, which is what this seems to turn on -- I am just asking is that a realistic description of the situation.

DR. MACKLIN: Well, the typically -- and here I guess I am drawing on my own knowledge and experience in the area of reproductive health internationally. The "typically" refers to what is the case and what normally does take place. And, in

fact, earlier in the chapter there is a discussion or a description of some research that was conducted at a women's health facility. Some research in Chile and the research was actually -- it was a description of the procedures and also the study. So, I mean, that is just an illustration but that is typically what is the case.

Now what you are referring to is the proposal that there be community involvement or community consultation in some sense and that is something that has not yet occurred. It is -- even if it were to occur, that is it is something that we propose and endorse, there are two questions. I mean, this could be elaborated, I suppose. There are two issues here.

One is the relevant community need not be only the geographic community. It could be the community of women at risk, that is we do not anywhere define community and what is the relevant community.

Secondly, even if it were the community that included the husbands, it still does not follow that researchers would then have contact with the individual husbands of women who might then be the perspective of --

PROFESSOR CAPRON: I was not suggesting that they would have such contact in that process but that

the husbands and members of the community -- I mean, obviously if we are talking about an urban reproductive health clinic where women go -- the role of the husband as the permission giver may be irrelevant. But if we are talking about going into a more community based rural area to do HIV maternal transmission -- I mean is it only fertility? Is that what we are talking about? I mean, only -- maternal transmission to offspring only affects women and it might well be research to do that. And our assumption is that you do not just march into the village and do it.

DR. MACKLIN: Yes. But then we have the leader. I mean, then it is another recommendation that deals with that. That is a --

PROFESSOR CAPRON: Then the men in the village -- the people are aware that there is going to be someone asking their wife to enroll. And the notion -- I mean this proceeds on the notion that you get to the women before the men know anything is happening and you say to them, "Do you want to involve your husband in this choice? It is your choice."

Even though if you are a physician in that community you would know that the woman does not come in for treatment without her husband coming along or otherwise saying to you, you may intervene in this

fashion with my wife, and you would not do that. And here you are saying the researcher would sort of short circuit that cultural expectation.

I thought we were dealing with situations in which the question is the researcher does not want to short circuit because he feels that it will damage the research. He does not feel that he can get permission to do it that way from the local people and wants to go to the IRB and say, "The only way I can do this research is the husbands have to know that I am doing it and they have to say yes their wives can enroll. May I have that as an exception?"

And we are not addressing that in this recommendation it seems to me. We are presuming that that does not happen and that is what worries me -- or in this discussion. I know it is not a recommendation.

DR. SHAPIRO: I have got a lot of people here who wish to speak. Let me just get the list down. Okay. First Steve.

MR. HOLTZMAN: I think there is a way of addressing your concern, Alex, to make it not conflicting with what Ruth has written here but sort of different kinds of cases and capturing them, and that is maybe to move up a couple of thousand feet to say what is it that we all agree to. All right.

I think what we clearly all agree to is that

ideally we want women to be treated the same as men in the recruitment process. All right. And then we are going to address the question of when it is morally okay to involve the men in the process of approval in a differential manner. All right.

There are different ways that could play itself out and the question before it, it seems to me, with the way Ruth phrased it, is when is -- does it require the case by case approval of the woman? That was what was written here. You are pointing to a different case where you go to the leaders first. So we have to answer the question does it require the case by case approval of the woman herself.

And the second -- I think where we do agree is that if the failure to depart from the ideal of equal treatment will result in a trial not taking place that in turn would result in a medical benefit being not available to the women, we think that is the justification for departing from the norm and some of us would submit that the paradigm case of that would be a woman's only disease or contraception or whatnot.

But there are cases where the failure to include women in a trial for a disease that afflicts both men and women can result in women not getting the drug.

So the point we were making yesterday, we

did not think was nonsensical as suggested and what was written today because it did put in there in Alta's language that failure to conduct this research with women in the trial would probably deny its potential benefits to the women.

And so I would ask Ruth that if there is a case -- if you can imagine a case in which the failure to include women in the trial for a disease that afflicts both men and women would result in the women being denied the benefit, is your position that that trial should not -- we should not use differential procedures to involve the women? Because the strong statement as you put it -- I do not think you would say that.

DR. MACKLIN: Well, I guess the question -- I mean, we addressed this yesterday and this is -- we are speculating about whether clinicians would give a drug to a woman who had a disease -- let's say it is malaria. That is malaria was tested, no women were in the trial, you now have the drug. Women get malaria. Only men were in the trial and the question is whether physicians in that community would not give the women the malaria drug because they were not in the trial. Your presumption or assumption seems to be --

MR. HOLTZMAN: My presumption is that there is a range of cases and I do not know the answer in

every case.

DR. MACKLIN: Well, but it is no different from what it historically has been in this country when women were not involved in trials or were involved in very small numbers and no clinician would deny -- except for pregnant women, no clinician would deny women the benefits of a drug simply because it was tested only or primarily in men.

We are speculating now on the probability or the likelihood that if there were only men in the trial and if people knew there were only men in a trial, the average doctor in the rural health clinic, who probably has not a clue about who was actually in the trial, then decides -- the women come to him and he says, "Sorry, we are not going to treat you because the people who were in the original trial were only men." That is just not a plausible scenario for the kinds of cases that you are considering, namely a disease that affects both women and men but the trial included only men.

So what was nonsensical -- what we claimed was nonsensical was the claim that the trial could not otherwise be conducted because it could otherwise be conducted. It could be conducted only on men.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I am still troubled by these recommendations and I have tried to list my

objections to this whole discussion and there are five that I have come up with so far. First, I have tried to step back and ask why we need a statement on women's rights in our report and I looked back at how we framed our report in Chapter 1.

And on page 3 of Chapter 1 the first extended example of unethical research in a report on International Report is the example of Puerto Rican women and oral contraceptives, which is actually a study of U.S. citizens and not an international study. And this example that has become now extended is also on women and contraceptives.

And I compared our current version to the version that Alex circulated and I have only had time to skim it but I much prefer the way Alex is setting up our report where he refers to studies that are done in countries that include people of color, impoverished people, and this is a much broader frame of inequities that concern us in our report.

I think we are narrowing our focus to women's issues and those have not been the issues that have come before us that prompted this report.

My second concern is that I cannot imagine how this would play out productively in an actual research study in a developing country. The recommendation assumes control by researchers. It assumes that researchers are going to be authorities

on marital relations and local customers. I cannot imagine how a researcher would talk to a potential female participant and advise her on the risk of talking to her spouse. I just cannot imagine how that could happen in a productive way.

My third concern is that the recommendation assumes negative marital relations in developing countries and it does not allow for the positive exchange between a husband and wife as exemplified in the discussion that we heard yesterday from one of our research participants who talked about how her husband helped her, how he sought information for her. I think we are assuming a negative marital relationship in developing countries.

My fourth concern is that in the very next Recommendation 9 we are much more favorable to the influence of a community leader who could be male and who could make negative decisions about all the women in his village. I would prefer a much more general statement about individual autonomy not limited to marital relations because there is a possibility for a loss of autonomy in other situations than a women in her marital relation.

And then my final concern -- and I say this very gently -- is that this smacks of hypocrisy. We, ourselves, do not have a strong record on gender equity and certainly not on social equity more

generally.

Yesterday I noted in -- when I was thinking about this recommendation that all the researchers who spoke before us and advised us so well were male. They were all Caucasian males. And all the research participants who spoke to us were female. So I think we are just being a little bit hypocritical in the way we are pressing this recommendation.

I would prefer that we back away from it and talk more generally about individual autonomy and not allow anyone to speak for anyone else rather than limiting this to a woman in a marital relation.

DR. SHAPIRO: Thank you.

Jim?

PROFESSOR CHILDRESS: I am tempted to pass given that eloquent statement. Thank you very much, Diane.

I will only -- I will roll out the one planned comment to try to deal with the issue, the important issues you are raising. I actually -- I think the proposed Recommendation 7 that Ruth and Alice have presented, perhaps, could be treated the following way -- I want to make basically two sets of comments.

I think we might just take on their page 2, "Researchers should use the same procedures and informed consent process for men and women who serve

as research participants. In no case may a spouse's permission replace the requirement of individual informed consent."

I think those two sentences ought to be the recommendation and this would, in part, address your concern by getting the discussion part, if we are going to include it in some kind of more nuanced statement, in factual material rather than recommendation. And that states what really is critical for us as a kind of obligation or principle at work in these matters.

So I would propose that we do that and then consider much of the rest of the material as textua. It is obviously going to require a lot of work.

The second set of comments would relate to the proposed exception that again would be in the text rather than the recommendation. And this would be on the last page of Ruth's and Alice's handout today.

I think when I heard it and first read it, the -- what brought me up short was the narrow exception to the rule and I think it would be a lot clearer if in the -- in the -- if we -- if just before "in order to justify such an exception," we actually said something else. We said -- and again it is a little repetitious but I think that we want to avoid misunderstanding and misinterpretation here.

To add after "consent process for women and men," "this exceptions involves obtaining the permission of the husband's in addition to the woman's own consent. In order to justify such an exception, researchers must provide evidence." So we are very, very clear about what that exception, is and that we are retaining the emphasis on the woman's own consent.

I think with those sorts of changes, I would be comfortable with the recommendation and again with the -- trying to develop the text in a way that would fit with the recommendations.

DR. SHAPIRO: Thank you.

Larry?

DR. MIIKE: First, an editorial comment. Whatever the changes are in the discussion around the exceptions, exceptions usually follow the rules so it should not be preceding the discussion. It should be a succeeding discussion. It does not make sense to talk about the exception before you begin to state what the rule is.

Second of all is that I think -- I guess the way we deal with the concerns that Diane especially has raised, is a clearer distinction between the recruitment process, which involves community leaders as the filters to the potential subjects, which I do not think anybody has problems with because it is a practicality of that and it happens in our country,

too. You just saw the community video. Versus the actual consent process, which I think Ruth now has tried to distinguish better in this round.

So if we start with the recruitment process and talk about the community filter first, and then get down to the consent process, and that -- it is a fact that in some of these countries it is -- it is a male dominated society and the husband may be the one to make a decision. We can address it that way, and maybe that can reach Diane's concerns. So we go from a cascade of the community filter to the individual.

DR. SHAPIRO: Bette, and then Bernie.

MS. KRAMER: (Not at microphone.)

DR. SHAPIRO: Bernie?

DR. LO: Yes. I wanted to follow on Diane's very forceful remarks. I like very much Jim's suggestion of making the recommendation the first two sentences in Ruth's revised 7, which I think really does bring home the main point. I think that, in this report, we are really asking people to take a big step away from current practice. We are holding out an ethical ideal and we should really just be very clear that we state that and not get hung up in the exceptions and the details and the funny cases.

So I think if we separate that out we may be more forceful.

I also want to just make an empirical

comment to support what Diane said. One of my former colleagues, Susan Allen, did a study of HIV testing and counseling in Rwanda and when she first started the project -- this was almost a decade ago -- she was told that, in that society, it would be culturally inappropriate to ask women for individual informed consent and she was told that they did not understand, the cultural mores were that you got the husband's consent first, and she did not do that.

She went and tried to figure out a way of going to the woman first and leaving it up to the woman to decide whether to advise -- whether to bring her husband or partner into the process. And she did not go in there saying, you know, we are going to give you the pros and cons. We raise it as an issue for you to decide.

She is now at the University of Alabama in Birmingham and I think she is an example of how it is possible -- I mean, many times in this report we are saying, even in a culture where something like informed consent in a Western model does not make sense, if you are imaginative, if you are persistent, if you rely on the good sense of your participants, you can actually do a lot more than you might think. Cultural norms are changing throughout the world and we should not assume that -- so I would like to accent the positive.

Rather than saying, you know, that we may be stuck in some situations where the research is so important you could not do it otherwise unless you are going to get permission from the husband as well as the woman.

But I think, rather than spending time on that exception, we should spend more time on the flip side giving a positive example of how you can really make autonomy work in a culture where some may say that it is not the historical case or the practical norm.

I think just to go back, you know, to the first two sentences of Ruth's analysis in the new Recommendation 7 gives the right message that that is what we want to say and let's really make that stand out.

DR. SHAPIRO: Okay. I think -- again let me try to summarize where we are here because I do want to move on to comments on Chapter 5. It is clear that we are all on complete agreement with the -- as Jim said -- the first two sentences of what is Recommendation 7 altered. There is some new wording in here but the sentiment, I think, is really quite clear and we will certainly have to make that clear. Perhaps it is useful to adopt Jim's suggestions the way he did that.

I mean, for example, the way it is currently

written we talk about the -- just to respond a little bit to Diane's important points. We talk about the risks of talking this over or having -- working with a husband but there are benefits. This is what you were pointing out. And so, at the very least, it has to be balanced in some appropriate way.

But I think some of Jim's suggestions were very useful and I also like Larry's suggestion very much of getting the community issue up front and dealing with that and then dealing with the individual, which is the way this usually happens. I think that is a very useful suggestion and so we will produce new language on both of these.

The issue about whether or not we ought to take up in one way or another the issue of -- which Diane referred to as women's rights but there are women's health issues which are important and need addressing in all countries and internationally as well.

And the question I really want to ask the commission, which I am not clear about, is whether your sentiment is that we should say something about that in this context or not? That is what I am a little unclear about.

Alex?

PROFESSOR CAPRON: I think it is worthwhile to recognize this and I -- as I understand the

suggestion that the language, which is on the third page of Ruth's document, is commentary now. It is not a recommendation. It is a commentary and a discussion. And I think we can recognize that there have been problems with women not having access to health care, and that particularly around reproductive health issues, these problems are especially acute for women.

And then we can say that -- as Bernie suggests, if we can cite -- if his colleague has written up a description of what she did and so forth, we can give it as an example and say where attempts to deal directly with women are not possible, IRBs and researchers may approve research in which husbands are approached first, provided that -- and then the kinds of considerations here.

I think we have to think, Mr. Chairman, of how this relates to Recommendation 8, however, which we have not talked about and the more I have listened to this discussion and to Diane's points, I find myself looking at Recommendation 8 and trying to figure out what we are doing there.

Recommendation 8 seems to suggest in its first sentence -- and I think this is relevant because I think that maybe we have sort of a gemisch of the whole thing here -- that where culture or custom traditionally involves family members, I

thought that, as we had discussed this yesterday and we were imagining the circumstances with the husband and with other people, that we said we do not want a situation in which -- it was Larry's example about the Samoans, I guess. No, it was somebody else's example.

DR. SHAPIRO: A speaker's.

PROFESSOR CAPRON: Okay. That we not assume that everybody follows any particular tradition. So it is really the last sentence of that recommendation which says, which if we revise it, instead of saying "if", "When a potential subject wishes to involve family members in the consent discussions, the research should take appropriate steps to accommodate this wish," and then we have the statement which is now -- and this is why I think this is connected to 7, something -- you know, "However, in no case may a family member's permission replace the requirement of individual informed consent," and then I wonder if we say that, do we want simply to emphasize, to follow that, researchers -- in particular, researchers should use the same procedures in the informed consent process for men and women to serve as subjects.

And all that other stuff -- I mean, I find this language that Diane objected to and that Jim suggested, moves out of the recommendation, because

it does not belong in this recommendation. This language about you should warn people about the difficulties or the risks of involving their family members.

We can talk in commentary if we have an example of where people can be told, in effect, it is possible that all of that is a custom. If you are not comfortable, if you would feel better talking about this without them there, we will, in effect, protect you and allow that discussion to take place without them.

But (it seems to me) it is paternalistic the way it reads as a recommendation.

DR. SHAPIRO: Okay. I have Steve and Rhetaugh.

PROFESSOR CHARO: And a hand up.

DR. SHAPIRO: Trish, Larry and Alta.

MR. HOLTZMAN: I would like to thank Diane for her remarks. I do believe this should be a report about international research and not about women's rights. I nevertheless think that there is something that we need to address here and so let me use a real live experience.

In 1995, we launched a trial looking at genetic predisposing factors to cardiovascular disease in a developing country, and, in specific, in a tribe, okay, which was male dominated. And as we

sat down with the IRB and as we talked about what we were going to need to do to get the consent, it was our IRB, where our IRB plus the local IRB, you ran smack into the U.S. regs and these kinds of questions about how do we go about this, what is a culturally sensitive way to do this, and there was -- there is no guidance there as it currently stands.

Effectively, we found ourselves having to ask questions about -- can we depart from what seems to be the requirements of the current federal regulation and it specifically came up in terms of involvement of leadership, but the leadership were men, and those men were the husbands of the wives who we wanted to include in the study.

And so I do think we need to provide guidance and we can state certain kinds of ideals which -- to which we all aspire but that we then have to be able to be clear about doing it in a way which acknowledges that different cultures are different and as long as you are not contributing to exploitation. And I think to sort of test it, it is a benefits test, is there going to be a benefit that would otherwise not be available that is significant that outweighs the diminution and the rights of the exploited population or the lesser of the population that is held at a lesser standard that we can articulate something like that.

Unfortunately, most of the time that population is women.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: I think what we have done -- I went back to page 6 and looked at our initial recommendations and in Recommendation 1, it speaks to informed consent and it says that the standard cannot -- may not deviate from the standard but that the approach can vary. And now we are trying to tell people how to vary the approach.

I think that we are getting too much into details of advice. We have made that statement and we have said that people, in essence, have to figure out a way to meet this standard and they can vary their approach.

I like the idea that Steve mentioned of maybe having some guidance, but I think we are getting too specific in making recommendations about how this informed consent should be obtained so I would like to argue for fewer definitive recommendations on the details.

DR. SHAPIRO: Trish?

PROFESSOR BACKLAR: (Not at microphone.)

DR. SHAPIRO: Larry?

DR. MIIKE: Looking back at the discussion and particularly Alex's comment about what do we do about Recommendation 8. Actually if we modify what

Jim's recommendation was, it was that, you know, this is the informed consent process, nobody can replace that, recommendations 7, 8, 9 and 10 all address those issues. And I would think that 8, 9 and 10 should be commentary following 7 that teases out these various other types. We talk about communities. We talk about family members. We talk about spouses in all of those recommendations and there should be a discussion about -- here we have a very simply stated Recommendation 7 and the discussions continue on about the exception with the spouse or possibly exception of the spouse, and the involvement of community members and family members. These recommendations can easily be turned into a discussion that follows it.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I would like to respond to a couple of things Diane said because she laid out quite a number of concerns here.

I appreciate the suggestion that the report is not about women's rights but I think I disagree about the degree to which the topics of international research and women's rights actually have a strong overlap.

I think Ruth has worked in the reproductive health field internationally and probably can give you better empirical data but my impression from

working in reproductive health is that, in large portions of the world, lack of access to proper family planning methods or to legal abortion, is the single leading cause for morbidity and mortality for women in their prime years.

Look at hospital admissions in -- I think it was -- Peru and you will find that the overwhelming number have to do with the sequelae of inadequate reproductive health measures. As a result, although we are talking about a whole variety of diseases and conditions that affect people around the world, it is, I think, surprising to many people to realize how profoundly reproductive health problems are in the essence of many women's health problems.

It is also a topic on which there is a unique nexus between women's health and women's political status within the family and within the country.

I think it is probably naive to imagine that the situation for women is the same in all countries, regardless of what gender relations are in the United States, because people said yesterday we have health inequities here but it is not the same thing as health inequities in Uganda. There are degrees of severity.

I also think that without having any -- without disparaging marital relations in general in

any particular country, it is possible to say that it is our position in the United States that investigators should treat women as individuals in the same way that we treat men and that, therefore, their husbands, their fathers and their family members are not in a position to make decisions for them nor to be necessarily involved in the decisions that these women make for themselves with some extreme exceptions.

And that we going to tackle this problem by looking for every possible way to treat these women as individuals and that includes allowing those women to decide when, and if, they want to involve other family members in the whole process of discussing the research and deciding whether or not to enroll.

I do not think that is really a disparagement of marital relations. I think it is a recognition that women can decide for themselves whether or not their particular marital relations would be better off with a discussion with their husbands.

Finally on the topic of community leaders, I find myself concerned that we are slipping into a discussion in which we are assuming that community leaders should be able to make decisions that would affect only one portion of the population and not the entire population. And on this I actually would

dissent, and I understand the need for involvement of community leaders and I said yesterday why I thought that they, politically speaking, have a different position in the world than the spouses or family members of individual women in terms of speaking for a whole community of people.

But I would be very unhappy if we wound up with a report that suggests it is appropriate for the municipal leader of a town that is being approached for some research to decide that, you know, women will be treated differently than men or that married women will be treated differently than unmarried women.

I understand the role of political leaders in making decisions for all their citizens, but not in having investigators use the community consultation with leaders to reinforce the kinds of inequities that we see at the personal and family level.

DR. SHAPIRO: Thank you very much.

Diane?

DR. SCOTT-JONES: I want to respond just a little bit to Alta because she prefaced her remarks by saying it was a response to me. I really want to extricate myself from any back and forth about women's rights because I am not naive, Alta.

I do recognize that there are many problems

that women face around the world and profound problems they face right here in the United States of America, and I think there are ways to bring in issues related to women in the way, for example, that Alex has set up this new first chapter.

He talks about AIDS and research on AIDS. In African countries women are more than half the victims of AIDS, unlike in other parts of the world.

There are many ways to bring in issues related to women but I think I stand firm in my view of this presentation of women in these recommendations. I also like Bernie's statement earlier that, cultures change over time and I think that we should keep that in mind when we talk about cultural differences, especially when we are placing ourselves in a superior cultural position to other countries because cultures not only vary over time but they are not monolithic in any one point in time so you could go to Kenya or Uganda, the countries where there are just enormous problems with AIDS. But you could find many educated women who might see these issues in exactly the same way we do and you would find some people in that country who are not educated who would be very much like uneducated people in this country in their views.

So I just hope we will be cautious when we talk about cultural difference because people use

that sometimes in sort of a superficial way. We should keep in mind that cultures change over time. They are constantly changing and they are not -- there is not cultural uniformity within any given country at any one point in time.

DR. SHAPIRO: I think the report already contains a considerable amount of information that leads to Bernie's conclusion. Bernie's suggestion that, in fact, things are not as different in many cases as one could imagine and, therefore, making up these caricatures are not always very useful and helpful and are counterfactual, and we ought to be very, very careful about that.

And while we ought to say nothing about the superiority of what we do compared to what other people do, we still have to decide what we feel obligated to do. We cannot decide what other people feel obligated to do but we can decide what we feel obligated to do and that is our responsibility here.

Just two more comments here and then we are going to have to try to summarize where we are and see where we go next.

Carol and then Bernie.

Carol, did you have -- I am sorry. I thought you had a hand up. I apologize.

Bernie?

DR. LO: I want to go back to Recommendation

8. I want to support Jim's suggestion that -- I think it was Jim who said that the operative thing is, if the potential subject wishes to involve family members in the consent discussion, researchers should take appropriate steps. And I think that is what we want to say.

In line 16 I would suggest we change "adhere to" to something else. Either "sensitive to or respectful of." I think the point is we need -- the researcher should be cognizant of the cultural issues and not assume that things will work in another country the way one might assume they work here, but not necessarily to adhere to those local customs but to help the participant ascertain whether the participant herself or himself, I guess, adheres to those customs and then to help that participant find a way of working out a consent process that seems personally appropriate.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: Could I respond on that? Actually, Bernie, it was my suggestion -- and as I thought about it, unlike the notion that I have no personal autonomy because I am a patient and expect someone else to make the decisions for me, the notion of involving one's family in this process, I do not think is very culturally specific. I mean it seems to me that, what we have heard about is that it

occurs so commonly, that I would prefer if we not link that to culture or custom and simply say when a potential subject wishes to involve family members in the consent process the research should take appropriate steps to accommodate this wish. And should just recognize it as --

DR. SHAPIRO: I agree with that. I think Bernie does, too.

PROFESSOR CAPRON: Yes.

DR. SHAPIRO: I mean, I agree with that and we ought to be sensitive to that. I think Bernie probably agrees also.

DR. LO: Yes, that is fine.

PROFESSOR CAPRON: Drop all that culture/custom language entirely and just go to that operative thing at the end of that.

DR. SHAPIRO: Okay. We are going to have to end our discussion on this here for this morning since we have guests who are here that need to address us on other topics.

I think it is -- I mean, I think from the discussion we can draft recommendations here which would, I think, be acceptable to the commission. I am a little unclear on one issue and that is whether we should -- and I am going to take that under advisement for the moment. And if any of you feel strongly about it, please let me know.

And that is whether we should deal with the issue specifically with respect to diseases or issues that affect women only. And I do not want to take any more discussion on this right now but that is something which I would like to hear from you about either later today or by e-mail or something as we go through and redraft this chapter.

I am going to suggest that we take a ten minute break right now and then we will move on to ethical and policy issues in the oversight of human subjects research.

We have obviously some unfinished business with respect to the International Report. We will have to think carefully about just how to proceed on those aspects. We have Chapter 5 and also some of the material that Alex -- yes, Larry?

DR. MIIKE: And we have not discussed Chapter 4, which was my main concern in my e-mail topics.

DR. SHAPIRO: Yes. All right. Let's take a ten minute break.

(Whereupon, at 9:47 a.m., a break was taken.)

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