42nd MEETING

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I N D E X

P R O C E E D I N G S

OPENING REMARKS

ERIC MESLIN, EXECUTIVE DIRECTOR

DR. MESLIN: Dr. Shapiro is on his way and he has asked me to open the meeting now. We are still waiting for a couple of commissioners to arrive so what I would like to do is inform the commission and the public who are here what our agenda is for the day and how we are going to proceed.

This is the 42nd meeting of the National Bioethics Advisory Commission and we have a very busy agenda ahead of us. We are going to spend the first part of the day, the morning, going over a draft of the International Report.

For the public who are here, I want to make it clear to them that if you have picked up these materials, as we hope you have, it is our intention that the International Report will be going out for public comment on or about the 18th of July. The documents that you are reading are not the public comment draft. This will be revised following today's meeting and it will be widely circulated within about ten days time and I say that just to avoid any confusion by the public or the media who are here reviewing the materials that you have in our hand.

Let me briefly then go over just a couple of

other housekeeping items and then we are going to turn directly to the agenda.

You have in your table folders a number of additional items, including my Executive Director's Report. You are welcome to review that, commissioners and the public. It is essentially a noncontroversial report reminding you of what our public comment process is, identifying a number of letters that we have received and correspondence from previous reports, informing the commission and others that the draft agenda for the Third Global Bioethics Summit has been prepared and will be available to people.

If there are any commissioners who have questions about these items, I am happy to go into some detail about them.

I would also like to inform commissioners that as a requirement to the Federal Advisory Committee Act we have distributed some materials to you from the Deputy Ethics Counselor of the Department of Health and Human Services, Hal Thompson, through the Ethics Office, and a Mr. Ed Swindell, providing you with materials for your review and understanding about ethics rules as members of federal advisory committees.

I am encouraged to inform you that you should and must read these and be aware of them. If

you have any questions about those ethics rules, please feel free to direct them to me.

Are there any questions or comments either about the Executive Director's Report and the materials attached, or about the agenda or any other parts?

I should inform the public that although we are not in full quorum at this point I do want to check and see whether Professor Charo is on the phone.

Alta, can you hear us?

PROFESSOR CHARO: Very clearly. Thanks.

DR. MESLIN: Right. Alta was unfortunately delayed in Wisconsin due to the thunder storms that were out there. We are glad you could join us by phone, Alta.

PROFESSOR CHARO: It is a pleasure to be there.

DR. MESLIN: Right.

I circulated to commissioners, just a couple of days ago, some materials that Ruth Macklin and Alice Page and I, with Harold Shapiro's input, prepared for you to facilitate this morning's discussion about the International Report. For ease of discussion, we thought we would identify those items in the report that based on discussion that the commission has had by e-mail and other ways would be

crucial to focus on.

This meeting is designed to allow you, the commission, to agree that the report itself is acceptable for dissemination for public comment. Agreement does not entail or require that you agree to every single line and word and comma. It does mean that you are comfortable enough with the recommendation and with the text that you are prepared to have the public comment on those.

For the public's benefit, our process at the commission using a public comment mechanism is we will be providing a revised draft of this report on the 18th of July. Public comments will be received up until September the 1st, post-marked September the 1st, or by e-mail.

There will be a Federal Register notice informing the public of this but for those who are here, you can call our office, 301-402-4242. You can go to our website, www.bioethics.gov. Or you can fax a request to us at 301-480-6900. Any of the staff can give you those particulars if you did not take them down.

Once the public comments have been received and analyzed by staff, and shared with commissioners, it is likely that modifications to the report will be made, and our timetable has the commission discussing the full report again at its October meeting, the

24th and the 25th, in Salt Lake City, Utah.

With that preliminary introduction, and I notice that Eric Cassell is here so now we are in -- I think we are in quorum if I am not mistaken. I do want to begin. Bernie Lo will be stepping out in a little bit and many of you know that Bernie has given comments already.

What I would like to do is begin with the notes that I sent around to you and just confirm that you have all received this note from me from July the 7th so that you know about which we are speaking.

And then, Bernie, I am actually going to allow you to make some early comments, taking our chapters slightly out of order, knowing that you have to leave.

Bernie Lo?

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

DISCUSSION OF DRAFT REPORT

DR. LO: Thanks, Eric. My apologies. I am going to have to run, going to come back and then run out again, and then come back. So I am testing the Metro system here today.

I want to thank Ruth and Alice for their work and also thank Eric for the six-page memo he sent out, which I think really helped me clarify what some of the issues are. I think some of the things I raised seemed to have struck a chord with others and

I am not going to sort of belabor those points, but there are two issues where I may just be out in left field, in which case that is fine, but I just wanted to make sure I tried to be clear on what I was trying to say.

One is an issue of, sort of, how we characterize the problems going on in clinical trials conducted in some sectors of the U.S., and another is really an issue of clarification of one of our recommendations in Chapter 5.

On the first point, it seems to me there are problems with some clinical trials conducted in the U.S. in that the subjects of research are selected to be drawn disproportionately from groups that do not have good access to health insurance and, therefore, do not -- cannot be reasonably expected to be able to have access to drugs if proven effective in a clinical trial.

There are a number of studies where recruitment is made from people who are homeless, people who attend clinics and public hospitals, and the level of access to health care outside the trial for those people is getting worse, I think, rather than better.

In San Francisco, we are actually closing the pharmacy for San Francisco general hospital, which means people will not get medicines for high

blood pressure, diabetes, standard things because of budgetary cuts. That is the hospital of last resort for a sizeable part of the population.

They are recruited into clinical trials and sometimes targeted because there is a higher prevalence of the condition, and I think I am troubled by what sometimes, I think -- I may be reading into this -- is the sense that things may happen here, but by and large, people do have access.

My sense is that there are trials here that are designed to target people who do not have access, and I would just like us to say we think it is wrong if it happens in a Third World country and we think it is wrong if it happens here. It is ethically problematic either way, and I guess I do not see what we lose by saying we have problems in our own back yard and we should deal with it.

You know, again another example: Earlier on there is the example of contraceptive clinical trials in Puerto Rico a number of years ago. You know, that is really in our back yard and so I think we need to sort of be willing to say we blew it here, we still have problems, we think it is wrong, we object to people being entered in clinical trials where the likelihood of their having access to a drug if proven effective is not very good.

So I just want to sort of leave that out as

a plea, and I do not think that it weakens our argument, but I think it makes us more consistent in where we direct our criticism.

Let me just raise one other point which is all the way at the end. I understand that Chapter 5 is the chapter that has, you know, sort of been not as -- we have not had the opportunity to discuss it as much.

Chapter 5, Recommendation 5 has the recommendation for oversight where -- let me just flip to it for a minute. "Researchers should include in the research protocol a description of the mechanisms of oversight at the institutions where the research is to be conducted. U.S. IRBs should assess the adequacy of these mechanisms and the review and approval process."

Two things: One I think we need some clarification language, and it can be in the discussion in the recommendations, what we mean by "oversight" because it can mean lots of different things. One is that it could mean are we supposed to oversee what IRBs are doing in the host country.

Another thing is we are going to oversee the informed consent process particularly in a situation where we are saying that signatures and thumb prints, which are the usual means of documentation, may not be appropriate. How then are we going to assure

ourselves that people were not coerced and understood and really comprehended what they were getting into? It seems to me that is a big issue.

The third issue is, is the protocol carried out in practice the way it was written when it was submitted? In Nancy Kass' study there was -- there were a number of respondents who said, "You know, we really do not know what actually goes on out there once we approve the protocol?" It is somewhat true in the U.S. as well, but it seems to me we have less assurance that we are going to find out, or we may have less assurance we are going to find out, if there are problems with implementation abroad.

Finally, I think it is the adverse event reporting in a clinical trial which sometimes falls under the mechanism of oversight and I would just like to say I would like to, sort of, sort that out because it seems to me on some of those, I think, we can really hold the researchers accountable. They ought to be accountable for -- if I am a PI doing a study in a developing country, I ought to know what the consent process is and be able to satisfy myself through site visits, through checks, through whatever kind of direct independent observation process that the consent process is, in fact, a valid one.

I think I ought to be responsible for assuring that the protocol in the field is actually

carried out the way it is written. It seems to me there is some quality control things that ought to be written in that are standard in a lot of U.S. clinical trials and we ought to expect to say that.

I think particularly now with the increasing emphasis on monitoring adverse events, I ought to have some system in place for monitoring adverse events in developing countries.

So I think I ought to be really responsible for that and it seems to me the IRB ought to be able to have some judgment into that, although again there is a caveat that Nancy Kass' study alluded to that U.S. IRBs may be not very expert at judging what goes on in developing countries according to some of the researchers.

I do not -- I mean, I am a little more concerned if by "oversight" we mean someone here is going to check up on what an IRB is doing abroad. I mean, there is a number of nice quotes elsewhere in the study that say we do not have a clue what goes on there. You know, some of it, I think, is alarming. You know, we do not speak the language, it is far away, the phone system does not always work, whatever. But I think I am a little concerned about a U.S. IRB passing judgment or a researcher in the U.S passing judgment on the deliberations of an IRB without some greater assurance that there is real

knowledge of what goes on.

I know that sometimes with a lot of good communication you can have a good sense, but what bothers me about this recommendation is that it is to me something I would like to see. It seems to me it is very far off from what goes on now and we need to take into account in the accompanying language the sense we want to get there, but that we are very far from that now and some things are going to be harder to provide oversight over than others.

So I am going to stop there and see if that strikes a chord with anyone?

DR. MESLIN: Bernie, I am going to ask you in a minute if you can make some specific proposals for how you want to deal with some of those but I know Trish wants to make a comment.

PROFESSOR BACKLAR: Yes, after --

DR. MESLIN: Oh, I should make the note that when you are speaking you should push a button so even though you are not going to speak, the next time you do push a button.

Reactions to Bernie's suggestion because we do want to put it into some context?

Jim Childress?

PROFESSOR CHILDRESS: Well, particularly regarding the first one. It seems to me that since our audience is not only researchers and sponsors in

the U.S. but, in fact, a worldwide audience, that we would look rather silly if we do not recognize the problems in the U.S. And it is pretty hard to make our report credible if we fail to see, for example, why in the World Health Organization in a ranking of health care systems our's is 37th given the great quality we have. Obviously that is largely due to unequal access, and I think failing to build that into the report in an adequate way -- and I think we actually do at some points later on say more than we say up front. It might be a matter in part of shifting some paragraphs around.

DR. MESLIN: Other thoughts? Bette?

MS. KRAMER: My recollection is that we discussed this issue in San Francisco and that we had decided to incorporate in Chapter 1 some language that was very, very much up front and that addressed the situation in the United States.

DR. MESLIN: Alta, I know you will let us know when you want to speak but this might be a good chance to check in with you.

PROFESSOR CHARO: Thank you. I would just say that I actually did take a try at a paragraph, which you reproduced in your memo, on the top of page 3 of your memo, that I say exactly that.

DR. MESLIN: So just so commissioners are following along, even though Bernie was making

comments about Chapter 5, Bette was referring to earlier explanatory language that now Alta has already circulated to us.

I want to make sure that we are on your point, though, Bernie. You started with oversight and I want to make sure that we are not getting away from your oversight concern.

DR. LO: Alta's, the way I printed it out, it is the next to the last comment about Chapter 1. Is that right, Alta, where it says, "While most Americans do have access to the fruits of health research."

PROFESSOR CHARO: Yes. And although it is now in that memo listed as something for Chapter 1, I really did not have any -- I did not have any attitude about where it would go. I just was trying to capture the point that was made in San Francisco.

DR. LO: Yes. I guess I would be a little more blunt. I think it is more than controversial. It is problematic or troubling or just plain wrong.

PROFESSOR CHARO: That is fine by me.

DR. MESLIN: Larry?

DR. MIIKE: While we are on that specific suggested quote by Alta, I do not agree with the last sentence of that section, which states boldly that our concerns overseas are because of our concerns of unequal access in the United States. It is a

parallel concern. I do not think it is one that one -- the international area follows because of our domestic.

DR. MESLIN: Alex?

PROFESSOR CAPRON: Sticking with the point that Bernie was making, do I understand that on page 25 your concern is principally with the placement of the requirement for assessing the adequacy of host country review on the IRB's shoulders, Bernie?

DR. LO: I guess I -- that is partly it. I guess I would start by saying I would want us to clarify in the accompanying language what we mean by oversight and sort of break it out a little, and to try and say some of this oversight investigators ought to be used to be doing as part of their preparation of protocols and IRBs in the U.S. are used to reviewing at least in the domestic context. That would be the consent monitoring, carrying out the protocols, quality assurance and monitoring of adverse events.

Now it is not always done well, obviously, given the recent criticisms that we have had over gene therapy, but at least it is on the board. There are examples of how to do it well.

I am more concerned -- you are right -- that when it comes to overseeing or judging the acceptability of ethical review by the host country

IRB, I think it -- we ought to know about it and as an investigator I ought to have some sense that it is done right, but I think that is a very, very new task and I am not sure there are parameters on, sort of, how to go about doing it or how to set it up.

PROFESSOR CAPRON: Well, my sense was that a few of the people, perhaps Dr. Pape from whom we heard, who themselves move between two institutions, have facilitated the American institution in being familiar with what goes on in the developing country institution, but I think I agree with you that in a way it is odd to put this as a responsibility on the IRB.

We have a discussion in here about the movement away from SPAs to MPAs and certainly the suggestion is that -- whichever U.S. agency it is, if it is the Office for Human Research Protections or whatever -- that negotiates the assurance is the body that has that responsibility. And in the ordinary course it would not be true, to the best of my knowledge, that in the United States were an American investigator collaborating with colleagues at another U.S. institution that his or her home IRB would be passing judgment on the adequacy of the processes of the other IRB. They would pass on the research protocol. They might ask for changes in a research protocol which had been approved by another IRB but

they would not be generalizing that to saying that the other IRB does or does not have adequate processes or mechanisms or anything else.

I mean, it does seem to me that, that is a responsibility. It would be difficult for an IRB to engage in even if there are examples of some that are seen through years of interaction with a particular investigator who, in fact, has two home institutions to have developed that level of knowledge, and as we were told, I believe, even exchanges between the two IRBs. And I think that is obviously something that can have great benefit, but I do not suppose that we would require that.

And I am not sure whether Bernie's comments strikes Ruth and Alice as pointing out something which they agree would be a problem or if they did, indeed, have in mind that we had indicated that we wanted the IRB to play that role, because I am conscious of the fact that sometimes we have had discussions of a point and seemed to have come to a conclusion and this is their attempt to convey that conclusion.

So if we have substantively said that we thought the IRB rather than OHRP or some other body would be doing this, I would be interested to be reminded about it if there are countervailing points. Otherwise I would agree with Bernie's point and I

think that the appropriate place to correct the discussion is around pages 24 and 25 in the chapter.

DR. MESLIN: Ruth?

DR. MACKLIN: Yes. I think we can handle this by clarifying. I mean, notice the specific words here and, in fact, it is the case that IRBs in this country would do an analogous thing with respect to a multi-center trial.

The wording says, "Researchers should include in the research protocol a description of the mechanisms of oversight at the institution where the research is to be conducted and the IRB should assess the adequacy of these mechanisms." Now suppose there were no IRB review in the host country. That would be something -- but there was someone else who rubber stamped it.

In this country if there are collaborating institutions or if people are transferring human biological materials from one place to another, you look to see that there has been IRB approval in another institution.

So, I mean, spelling this out as Bernie requests, I think, will handle it. It surely does not imply that the U.S. IRBs are scrutinizing the actual work of the other IRB but if it is material -- if it is information that should be in the research protocol then the research protocol should describe

things like there will be progress reports, there will be -- I mean, any of the quality assurance. So that all the U.S. IRB is looking to see is that the protocol that is submitted by a U.S. researcher to this country and to another IRB includes the -- some description of what is going to be done there and that is in the protocol.

It does not follow that the IRB here is going to determine what the IRB in another country is going to actually do. So, I mean, with the kinds of points that Bernie makes that investigators are capable of doing and not capable of doing, maybe if we spell those out it will be a little clearer.

DR. LO: No. I think this may be a situation where just some clarification would be useful and I think Alex's, you know, way of framing it, I thought, was useful, as was Ruth's.

PROFESSOR CAPRON: If I may, Ruth, I am glad that we are all intending to say the same thing. I think the phrase "a description of the mechanisms of oversight," I agree with you, is unexceptionable. The kinds of examples you gave were not mechanisms of oversight as I understood them. I mean, progress reports have to come back to the U.S. IRB because a U.S. investigator is conducting the research. That is the U.S. IRB's own obligations and so forth.

It is the adequacy of the mechanisms. It

does not seem to me a progress report is a mechanism of oversight at the institution. The mechanism of oversight is the IRB. And assessing its adequacy seems to me would be knowing that it has an assurance with an appropriate federal agency is the way that you determine its adequacy.

Now I think we can in commentary perhaps say more about the value of collaborative relationships. We talk elsewhere right from the beginning in Chapter 1 about the building up of capacity in the ethical review process and this would certainly be something that could be cited in an exemplary fashion as -- if that occurs without the suggestion that it is the obligation of the IRB as opposed to the obligation of an OHRP to assess the adequacy of that mechanism.

It would certainly be true that that is an important task knowing that the mechanism is not merely a proforma, that the IRB is appropriately constituted, that it has some way of getting the results that are expected of it.

DR. MESLIN: Eric Cassell, you had your hand up before.

DR. CASSELL: No.

DR. MESLIN: I want to just take everyone's temperature and see whether, Bernie, the comment that you started with because you are going to leave shortly and then come back later, hopefully, has that

been addressed well enough by the commission so that you can leave knowing that you have got an answer to your question at least?

DR. LO: Yes.

DR. MESLIN: Good. Ruth?

DR. MACKLIN: Just one more point. Following what Alex just said, is the phrase "mechanisms of oversight" the wrong phrase here? In other words, do we have to -- there are two options. One is to keep the recommendation and clarify in the text. The other is to change the wording of the recommendation so it does not mislead or have the implications that Alex, suggested so I want to know which is better.

PROFESSOR CAPRON: Well, I was taking your first point to be correct that the IRB locally -- a U.S. IRB would want to know that there is a process and a description of it would be that there is an IRB there that is appropriately constituted and that operates under either an SPA or an MPA at the institution.

It is the second sentence that they have to assess the adequacy of that mechanism in the review and approval process that would concern me, and I would continue to be dubious that U.S. IRBs take that as their function vis-a-vis collaborating institutions. Certainly in multi-center trials they

look at the protocol.

And, as I say, they sometimes -- I mean, people who conduct such trials sometimes pull out their hair because one IRB will look at something that has been approved elsewhere and say, "Sorry, at our institution that consent form or that description of how the project is going to be conducted will not fly." But they are not there by saying ergo the University of X IRB must be inadequate. They are simply saying we cannot have our investigator participate under those terms even if he is going to the University of X to do it where they think it is okay.

DR. MESLIN: Bette, and then Bernie. Bette?

MS. KRAMER: Bernie, do you want to answer that?

DR. LO: Well, yes. To pick up on Alex's point about oversight. I mean, it seems to me that we are saying that researchers have to provide in the protocol and IRBs have to review is a process by which the researcher is going to ensure that ethical issues are addressed adequately after the protocol is approved by the IRB and the protocol actually goes out in the field and is implemented.

It seems to me I am thinking of things like consent, actual implementation of the protocol, and adverse event reporting, which to me is different

than oversight at the institution, which really has a ring of sort of compliance with regulations and sort of how the institution works.

It is really that the trial itself as it moves forward adequately addresses human subjects protection as it is being implemented.

DR. MESLIN: Bette?

MS. KRAMER: Before Bernie leaves I would like to go back to the first point and that is the attention we are going to pay to domestic research and I wonder -- are the other commissioners satisfied with the language that Alta has suggested? Is that extensive enough?

I am afraid -- as I think about the report and all of the allusions to the -- the allusions to the fact that most Americans have adequate access to health care, I am concerned that this one paragraph of just a few sentences is sufficient to state our position, that that is not the case.

DR. MESLIN: Alta, was the breath an opportunity to say something?

PROFESSOR CHARO: It is possible that if we went through the entire report line by line we would find every reference to the U.S. situation. I think the point has been made several places that we have a lot of people who do have access and a very substantial minority that do not. And if we

continually make both those points, I think, we will be fine.

DR. MESLIN: Bernie?

Thanks, Alta.

Bernie?

DR. LO: Yes. I think that, you know, when we see subsequent revisions of -- you know, we will have to just sort of go through and make sure there are not other places where we say something that is not quite what we mean to say. I noted some of those and I think we will just have to look and see as the draft evolves to make sure we have handled those okay.

DR. MESLIN: Jim?

PROFESSOR CHILDRESS: Bernie, it might be useful if you could give some documentation of the kinds of examples we are talking about where we are actually targeting that population. We are all familiar with them anecdotally but it still might be useful in this kind of report to have documentation.

DR. LO: I had tried to give a cite, which I do not have, to an article run in the Wall Street Journal a number of years ago about Indianapolis. I do not know if that has been tracked down because that was a news story that got a fair amount of play. I just do not have the exact reference. I think Alice has got it.

PROFESSOR CHARO: Eric?

DR. MESLIN: Yes, Alta?

PROFESSOR CHARO: I also want to just remind all of us about the reason why we are discussing this. It is not entirely about a characterization of the U.S. health care system. It is about understanding the justifications that have been used for putting people into research situations at all. As I recall the analysis, it was that one of the reasons we are comfortable with the notion of making people research subjects is that there is a broad-based benefit that will come back to them eventually.

And keeping that in mind I think it is fair to say that the majority of people in the States, most research benefits are likely to rebound to them at some point in the future. So although it is absolutely true, as Bernie was noting, that there are substantial swaths of society for whom that is not yet true.

And keeping that in mind, I think the pressure has lessened a little bit to try and do a kind of complete description of the inadequacy of the U.S. health care system, because the point simply is we have a reason why we justify research on human beings in the United States and where that justification does not exist in the U.S., as in the recruitment of homeless men, we find that it is, in

fact, quite alarming to us and that is why I wrote that we find -- it should not be surprising that same kind of alarm or distaste is triggered when you look abroad. I mean, it is about the lack of a justification.

DR. MESLIN: Eric Cassell?

DR. CASSELL: I want to underscore Bernie's first comment about this subject of health care. It is not just homeless men. It is large populations of poor people.

In general, the report reflects a disease fallacy that when people sicken and die, it is the disease that is the whole issue, when in point of fact it is not the disease, although the disease may be the thing that kills them ultimately. All the things that go with poverty, the increased death rate from every disease among the poor more than among the comfortable. And certainly in the countries which we are targeting where malnutrition and other factors play a much larger part probably than the absence of medical care.

I think that we just have to make it clear that it is this situation that we are trying to bring good ethical research into, not simply something having to do with a bad thing called a disease and so forth and so on.

DR. MESLIN: Alex?

PROFESSOR CAPRON: I have shared the concerns that Alta and Bernie have expressed on this subject and they led me to look back at the first chapter, and right from the beginning to think that it would be good to tie what we are doing in here more firmly with the whole history of human subjects research and, in particular, with some of the discussion that the National Commission had 25 years ago that led to language in the Belmont Report.

I have prepared and asked the support staff here to produce a few pages at the beginning, a revision of the way into the report, and I gather we have time this morning for the discussion. And rather than read it out to you, it may be easier just if you will expect that there will be this opportunity for people to look at it and we can discuss it.

I think Alta's suggested language in the memo does belong in here but I think that the sense that we are somehow looking at problems which only occur abroad and that are new to the field because of research which occurs when a rich nation does research in a poor nation can be combatted.

And I think the report already has right at the beginning the very firm statement about the premise that research will be relevant to the population and that that emphasis, what was needed,

and what I tried to bring in was the notion that by looking abroad we then have a perspective to look back at what happens in this country and to be reminded that it is equally a concern here and it may reflect on either the adequacy of the federal regulations or of their implementation.

And what I have is simply a draft and I am sure that others will have a lot of improvements in it but it is a suggestion I have for changing the way we begin the discussion, and rather than just make it as a comment, I sat down and tried to write it out to give us something, and I am sorry that I do not have a printer with me so I am dependent upon it being printed out in a few minutes.

DR. MESLIN: Thank you.

Ruth?

DR. MACKLIN: Maybe once we see Alex's pages it will set this whole discussion to rest.

Alice Page and I looked through the entire report after getting these comments, especially Bernie's comments and the discussion that ensued, to see what we actually say about the U.S. health care -- people's access to treatment in a percentage. Without a lot more empirical information and statistics, we cannot say anything more specific than using words like "some, many or most." And, in fact, those are the words that are in here. "Some,

many or most."

Otherwise, you have to be very specific and have some kind of statistical backing. Surely, it would look ludicrous if we mentioned only homeless men in studies. It is a very small percentage of the population.

Eric Cassell says, "Well, it is not only homeless men. It is other people, too."

But we really have to have something more precise and Jim mentioned earlier that if the report is to be credible we need to acknowledge why it is the United States is 37th in this ranking.

Also, in order to be credible, we cannot portray the United States as looking like Uganda. We would -- this report would be a laughing stock if, in fact, some of the countries in Africa read this report or people in those countries, and then looked at this and said, "They are trying to say that things are just as bad in the United States as they are here?"

The reason that things are as bad in this country as they are is that there has been no political will to provide universal health care and we are not going to go down that path in this report but, in fact, no matter what the political will is in Uganda they cannot afford to provide even drugs for tuberculosis and malaria. In this country you can

spend $60 billion dollars on some missile to shoot another missile out of the air but they cannot afford or have decided that they are not going to allocate this money for health care.

So I think we would have to say a lot more if we want to go down this road of saying, "Gee, things are really bad here, too, and we have the same problems here as you have in Uganda."

DR. MESLIN: Diane, and I apologize. I had you on the list and I did not recognize you before. I am sorry.

DR. SCOTT-JONES: I just wanted to add a couple of comments to this discussion and I think that in the report we can strike a balance without saying that the United States is as bad as Uganda, uniformly. I think the real issue that is causing concern is the differential access to health care and there are pockets in the U.S. where conditions are as bad as in developing countries. And it is not just access to health care. It involves some of the other issues.

For example, on page 3 there is a reference to individuals being incapable of informed consent because they are illiterate, unfamiliar with the concepts of medicine held by the investigators, are living in communities in which the procedures typical of informed consent discussions are unfamiliar. That

also characterizes communities within the U.S., as well, and I think it is important for us to make a strong statement in this first chapter about these conditions in the United States that in certain communities are very much like those in developing countries.

DR. MESLIN: Eric, were you going to comment?

DR. CASSELL: Well, I do not think that -- I mean, we can get into an extended discussion of it, but the issue is not simply making us look good or as bad as Uganda. That is not what the issue is. The fact remains that there are people in the United States below the poverty level. There are numbers below the poverty level who do not have access to adequate medical care or medication and so forth.

It is not that we are terrible. That is not the point. The point is to make the contrast between a developing nation and us because our people have where their people do not have, is the fallacious contrast. We have this problem -- these problems also. That does not change the issues in Uganda. That does not change anything in Uganda or what are problems we have to address there.

It really tries to take away using us as a contrasting good against that particular bad. The bad there in terms of consent and all of those things

remains. It does not matter what you say about the United States. So we are not trying to say that this place is terrible. We are trying to point out that there are realistic problems here and the contrast is the mistake.

DR. MESLIN: Trish Backlar?

PROFESSOR BACKLAR: I just wanted to make the point that when this report goes out for public comment, it is going out at a time when there is a great deal of public discussion about access to medications and drugs. And I personally know how difficult that may be if you do not have the right kind of insurance and certainly there are many people in populations that I am very familiar with, vulnerable populations, who have terrible difficulties in accessing medications because of the type of insurance or lack of insurance that they have.

This is a real problem for many people and we might even have numbers on that. I do not know that those are not available to us, but I do want to point out it will be very embarrassing for a report to go out that indicates that we do not have these kinds of problems precisely at the time when we are having a public discussion about this.

DR. MESLIN: Larry?

DR. MIIKE: Yes. I think we are just

falling into our usual mode about talking about what I consider background and peripheral issues without getting on with the rest of the report. I mean, everybody has expressed their concern. If you have some serious problems, do what Alex has done, which is put some suggested language in. Well, let's move on.

DR. MESLIN: Thank you.

PROFESSOR BACKLAR: Thank you.

DR. MESLIN: Are there any other comments? We are essentially letting Harold get his notes together. Now that Bernie has left, we are going to return to the memo, which is really where we are now with Chapter 1.

Chapter 1 comments?

Yes, I am -- so for those -- let's really focus on suggestions for new language, if necessary.

Alta has indicated a couple of large blocks of proposed text in a memo that I circulated. I think it would be useful to get a sense from the commissioners as to whether these blocks of text -- realizing that Alex also has some blocks of text to suggest -- are going in the direction that you want them to. You simply need to agree more or less with those blocks of text and we can do edits to make them more appropriate but in order for us to get through the morning in the most useful way possible, we need

to get your general consensus on these proposals.

Alta, I do not want to turn back to you because you have already -- and spend more time, but is there anything you want to say in the event that I have put your paragraphs in the wrong spot in the memo? Do you want to say anything more about these two large blocks?

PROFESSOR CHARO: No.

DR. MESLIN: Okay. Are there any comments from commissioners about whether these -- this text should or should not be incorporated into Chapter 1?

Diane?

DR. SCOTT-JONES: It would be helpful if Ruth and Alice or Alta have suggestions for where to place these particular blocks of text because we have read the chapters as given us and it would be helpful to know what they would substitute for, where they would go.

DR. MESLIN: We might want to ask Alta as well but I do not know whether -- Ruth or Alice, do you have thoughts about where they might go?

DR. MACKLIN: Actually our strategy was to see whether or not the commissioners -- they are not going to substitute for anything. They would be in addition.

DR. MESLIN: Be insertions.

DR. MACKLIN: They would be insertions and

our strategy was -- rather than redraft any chapters or make those decisions, we wanted to see what the commissioners thought of those paragraphs. So all we can say now is they would go in a suitable place to support or further elucidate what is there in chapter 1, but they would not replace any existing text.

DR. MESLIN: Rhetaugh and then Trish.

DR. DUMAS: Yes. I would just like to say that I think that the material that has been proposed by Alta is acceptable to me and it is clarifying, and I think it addresses -- although maybe not to the extent that some people would like it -- the issue that we have just heard raised about comparisons between other countries and this country.

So I am happy with the statement and I think that the one on page 3 of your report having to do with conditions in the United States is adequate for purposes of this report, as I see it. I think we would make a mistake to get into a lot of detail having to do with comparisons of hardships and bad problems.

I think we need to keep the emphasis on ethics of research involving human subjects, no matter where they are, and when they are in resource poor countries, what kind of provisions, exceptions, or what have you, are warranted.

DR. MESLIN: Trish?

PROFESSOR BACKLAR: I just -- I thought possibly that Alta's suggested language should go in somewhere in the section on justification for writing this report, and that starts on page 10.

DR. MESLIN: Larry, and then Eric.

DR. MIIKE: I actually have a constructive suggestion instead of just all lashing out. On Alta's first quite long excerpt, I have some qualms about it but it is okay with me, and if it is going to be somewhere, it should be in sort of a point counterpoint discussion in Chapter 4 around Recommendation 4, which is the one I suggest we split rather than combining, access to country, because that would be where that discussion should go.

Alta's second quote on the situation in the U.S., as I said, I do not agree with the last sentence of that short answer and I would delete that part. The rest of it I do not have a problem with.

DR. MESLIN: Eric?

DR. CASSELL: On paragraph 3 of Alta's proposed insert for Chapter 1, I am not -- it is not clear to me what that means and I wonder if Alta could make that clearer. Just make it manifest what you are saying, Alta.

PROFESSOR CHARO: Sure. I can try to rewrite it and make it more straight forward. Basically if a sponsor is, in fact, the cause of the

unaffordability of a drug, it would seem that the sponsor's claim that it is now time to test cheaper alternatives is a claim that is weakened because the sponsor is responsible for creating the situation that now leads us to need to look at cheaper alternatives.

The rest of the material tries to explain that in most situations the sponsor is not the sole cause of this problem but that there will be some times where it is.

DR. CASSELL: And then how does that impact on the issue of designing the trial so that it is ethically acceptable?

PROFESSOR CHARO: In those situations where the real problem is solely the unaffordability of a particular kind of drug and not the variety of conditions that are identified elsewhere, it seems to me that it is harder to conclude that it is ethical to test cheaper and less effective alternatives because the drug is not affordable, since that is a correctable problem.

And it is especially problematic when it is the same company that is making the expensive drug that is now saying, well, now we have got to test the cheaper alternative.

Do you understand what I am saying?

DR. CASSELL: I understand it. I am not

sure of its applicability here.

PROFESSOR CHARO: I am sorry. I could not hear you.

DR. CASSELL: I say, I understand what you are saying but I am not sure of its applicability in a report about ethical issues for overseas research that are supposed to impact on the kind of research that is done, and who does it, and how subjects are chosen, and so forth.

PROFESSOR CHARO: Well, let me put it this way. If drug company, you know, Molly, you know, if Molly makes the right drug and they sell it at a price that is completely unaffordable in both private and public sectors in another country, and then they want to hire a researcher from my institution to run trials on another drug that they are going to propose that is the cheaper and less effective alternative, and I am sitting on the IRB, I think that it should be something I consider.

Should we, in fact, get involved in testing a less effective drug than a standard therapy when the sponsor could, in fact, make the right drug available at a price that is affordable. I think that is a relevant part of my analysis as to whether or not I should approve this protocol as an IRB member.

DR. CASSELL: Well, I actually do not, but I

mean the commissioners will have to express themselves, but I, myself, find that paragraph not useful.

DR. MESLIN: Any other comments on that language?

DR. SHAPIRO: On that particular paragraph?

DR. MESLIN: Yes.

DR. SHAPIRO: I have a comment on the -- I have a whole series of comments but only one I want to raise now on this first proposed change. It occurs in the second paragraph here, the one that begins "All these problems." I will eliminate any editorial comments.

I think in a good deal of the discussion we have had, in my judgment, there is a confusion over the ethics of doing research and just what is appropriate or inappropriate in a system governed by various kinds of market organizations, intellectual property rights, patents, et cetera, et cetera. And I think those are two different things. Therefore, I would suggest -- and I think confusing them does not help us straighten out where the ethical responsibilities lie.

If, for example, the high price of pharmaceuticals is a problem there are many solutions to that. Only one deals with just how pharmaceutical companies ought to behave. I mean, it is easy enough

just to suggest another one that resource rich governments buy these medicines and give them away. I mean, that is just another solution. I am not suggesting it, but it is another solution and it is just as ethical as anything dealing with property rights and changing the system under which these drugs are developed.

That leads me to change the second paragraph here by taking the sentence that begins "One area" and simply crossing out the next seven lines down to the sentence that begins "One recent response." And the way I could tie it in to the issue, which is a genuine issue, that is the cost of pharmaceuticals certainly is an issue, I would just write, "One recent response to the cost of pharmaceuticals, for example, has been an agreement to lower..." and so on and so forth because that is a plausible enough response, and it is a serious problem.

I do not find dealing with issues of protections of licensee's legal rights, fiduciary views of stockholders, profits, and so on, something which we really have thought carefully about or know whether or not this is the source of the problem. It may be the source of the solution.

I do not want to argue that point, but it seems to me it is just unnecessary and the points that Alta makes very effectively here can easily be

made without taking on that, which is a much bigger subject, which we really have not dealt with in any way.

Yes?

PROFESSOR CAPRON: What I am unclear about is whether this is something which is part of the issue in Chapter 1 or in Chapter 3 about the design of studies. It seems to me that it might fit better there and I turn to the authors to ask if they have a sense. I mean even with the chair's modifications, which strike me as honing us in on what is most relevant to our report as opposed to additional problems.

Do you think it should be in Chapter 1 if it is anyway?

DR. MACKLIN: Well, it should be Chapter 1 because Chapter 1 sets up the whole problem to which we return. At various points in Chapter 1 we say, "See Chapter 3," and maybe that is all that is needed is that note. Chapter 3 is much more specific on laying out the various research designs and then saying which ones are acceptable or unacceptable and for what reasons.

This is a much more general point so I think it should remain or if it goes anywhere with these modifications it should go in Chapter 1 with a reference to Chapter 3 where there is a much more

specific discussion.

DR. SHAPIRO: Larry?

DR. MIIKE: I had mentioned earlier that I thought it belonged in Chapter 4 and the reason is that --

DR. SHAPIRO: Alta, what a paragraph?

DR. MIIKE: No, no. I mean the whole quotation because it depends on how you -- what you take away from this discussion. If we are talking about research design, that is one thing. But I read this paragraph to sort of say that pharmaceutical companies owe a duty to these countries to make prices -- make things affordable, et cetera.

And if that is the case then it does not belong in Chapter 1 and it does not belong in Chapter 3. It belongs in the discussion about what is the appropriate response in our recommendations about obligations to test subjects versus obligations to country inhabitants.

DR. SHAPIRO: I, myself, did not read that conclusion into here. I understand how one could read it that way but I have got to agree with Ruth. It ought to fit somewhere in Chapter 1. It is useful and we will refer back to it as we go into 3 and 4 as appropriate.

Let's go on to the second comment. Just to make sure if there is any question regarding the

second comment that Alta made, and there is a comment with respect to this chapter that is attributed to Larry also, but any comment on what is really on the top of page 3 in the memo that was distributed to us?

If not, then let's -- I have some -- excuse me. I am sorry, Arturo. I apologize.

DR. BRITO: I have kind of a general comment about it and I was thinking how to phrase it because I -- I think one of the issues here is just right at the onset of this. We are talking about the paragraph that starts "While most Americans..." right?

DR. SHAPIRO: Yes, indeed.

DR. BRITO: The fact that it goes on to say, "...do not have access to fruits of medical research, many have only limited access and some have near no access at all," we are not really talking about access to medical research, are we? I thought the issue here is that because individuals -- or the fruits of the medical research, right?

DR. SHAPIRO: Fruits of medical research, right.

DR. BRITO: The confusing thing here is that somehow this deviates. I guess it depends on where it is going to go but it seems to deviate from -- the issue at hand is that because a substantial number of Americans do not have insurance at one point in time

or another, not because it is a complex system necessarily, just because the system does not have universal health care -- there is not universal health care. I think the issue here is that people are -- when they lack health insurance are more likely to become vulnerable and, therefore, enroll themselves into research or be subjects of research. Is that not -- maybe I am missing the point of this paragraph here and where it goes but the --

DR. SHAPIRO: I will turn to Alta in a minute. My understanding of this is that we would not feel good about using that population as human subjects since they do not stand to benefit from any of the possible successful results. It is just trying to show that even if this took place in this country we would not feel good about it.

DR. BRITO: Okay. That is -- what I do not --

DR. SHAPIRO: That is all it is trying to do.

DR. BRITO: What I do not feel good about is having somebody not so much because they are not going to bear the fruits of that research but because at the point that they are in the research they are very vulnerable and being taken advantage of, and could suffer consequences during the research.

DR. SHAPIRO: That is an additional point.

I agree.

DR. BRITO: So that is -- So I guess it depends on where this is going to go but --

DR. SHAPIRO: Our authors will work on this after we adjourn this morning.

Let's turn now to -- any other comment on this paragraph?

Let's turn now to the comment attributed to Larry.

Larry, do you want to say anything further about this?

DR. MIIKE: It was just -- it was more an incidental comment about what -- you know, what we were talking about and were not talking about -- problems relevant to a country's population. So the initial impetus for my making this statement is really a little concern to me, but I do have two other things.

One is that I think that when we get -- once we get past that simple statement, then we get into issues like the one I originally raised, which is so what. If it is a problem that -- are we saying that if it is a problem we can deal with in the U.S., in the population in the U.S., we should do it in these other countries. And my answer would be, no as long as you meet the ethical imperatives.

But there are two other things. Out of this

arises -- once we talk about the health needs of the country, then we have two opposing forces. One is on the side that says those who argue -- that says, "Okay, we have to make it affordable in that country," and then all of the issues around lower prices, you know, prediscussions before the trials continue on, et cetera. Issues around my -- discussions around Recommendation 4 in Chapter 4.

The other side is this issue about most effective treatment, and that side impinges on the trial itself where one -- if you are going to take an either/or position, one could argue that those who say that the -- we must have exactly the same ethical standards in the U.S. as in these other countries, and that even though the host country is willing to conduct trials, we are not going to let them do it that way. The whole issue about the AZT and pregnant women trials. Those are the kinds of issues that come up once you get beyond just the simple statement about health issues relevant to the country.

And I have not looked at the report to see whether that kind of tome is in there, but clearly those are two issues that arise once you get past that initial statement.

DR. SHAPIRO: I agree. Those issues are going to be right before us very shortly. My prediction is that it will not be a simple black

line, yes or no. There is going to be areas which are going to require decisions as each case goes along. That is my own judgment. We will have to see how the commission feels.

Steve?

MR. HOLTZMAN: Thank you.

I think it is important to take Larry's dissention, and let's put aside the second for the moment, which goes to the trial design, and tackle squarely when is it morally acceptable to conduct a trial in another country.

There is a sense that I get in reading this -- and I do not think it is intended -- or let me make that a question. Assume for the -- that a gating condition is the health problem being studied (a) has to be relevant to the country in which you are studying it and (b) that there has to be a prayer of a chance at least -- let's just make that gating for the moment -- that the resulting benefit will become available -- will be reasonably available.

And what we need to get clear on at a level, which I do not think we have exactly, is what -- are we saying that if you could as easily study it in the U.S., you ought study it in the U.S., because I think that is where there is not a complete clarity.

So, for example, on page 7 where we make the case, we seem to be saying that all things being

equal, just because it is cheaper over there you should not be able to, or are we saying it is okay if all things are equal. And I find that we are not entirely clear on what we are saying on this issue. Now maybe others feel we are but I do not feel we are.

DR. SHAPIRO: I will speak for myself on the cheaper issue, which I think is another issue that tends to bedevil us unnecessarily. It is my own view that if other ethical requirements we laid out are satisfied, substantive ethical requirements are satisfied, that the fact that it is cheaper is sort of an irrelevant issue for us to consider. That is just my own view. That is for someone else to consider. Our concern should be whether the substantive ethical procedures are, in fact, fulfilled.

MR. HOLTZMAN: You see --

DR. SHAPIRO: That is my view.

MR. HOLTZMAN: And even the language of cheaper, I think, maybe is the wrong language to put here for the following reason, Harold: Because the real live situation is that for many of these conditions, which exist both here and in the developing countries, your rate of accrual of patients will be faster.

DR. SHAPIRO: I understand.

MR. HOLTZMAN: A consequence of that is that development and hence availability will be accelerated --

DR. SHAPIRO: I accept that.

MR. HOLTZMAN: Right. But not necessarily other than in very large terms for the developed nation. I think that is the hard question we should deal with as opposed to creating, you know, a make believe case that I go to a Third World country because it is cheaper per subject. No, the issue is I can get the approval faster. What moral responsibility accrues to us by virtue of taking advantage of that fact, if any? That is the question, I think, we should be tackling.

DR. SHAPIRO: I think that is -- I do not want to take us off that. I think we do have to get directly to those kind of questions. I think that is absolutely right as we formulate our recommendations. I mean, I have my own view on the answer to that. I do not know whether this is -- I will share it at some appropriate time. We ought to get to it.

In general, Larry, I found myself responding positive to the suggestion you made here, and we need to incorporate it in an appropriate way in the report.

Okay. Any other comments?

Let's go on then to just taking these. We

can circle back to these areas as we go through this but I want to make sure that we get through at least the comments that have been noted in this memo and then we can deal with other issues as they come up.

Bernie had some recommendations regarding the repositioning of the recommendations with their justification to bring them closer together. Apparently the staff recommended moving recommendations 1, 2 and 3 to be inserted later in the document.

I, myself, feel not strongly but just exactly the opposite way. Namely the justification should be brought forward to where the recommendations are, but that is -- I think we will let the people who are going to actually write this decide that in the end but, I think bringing them together is a good idea.

But are there other comments on that particular issue?

Okay. We will bring those together and leave it, Ruth, for your judgment as to whether to bring them forward or bring the recommendation backward or whatever the right way to describe that is.

There is also a proposal. I think Alta may have been the author of this or at least of this particular language, which essentially takes

Recommendation 7 in Chapter 2 -- can someone tell me which page that is on?

DR. _____: 14.

DR. SHAPIRO: Thank you. Which is on page 14-15. And tries to articulate it in what I believe Alta believes is a more effective and less ambiguous way.

But, Alta, let me turn to you to see what you would like to say about this.

Is Alta there?

PROFESSOR CHARO: Oh, yes. I am sorry. It is every once in a while people have been hard to hear. I think it speaks for itself and there was some e-mail traffic between me and Eric on this point.

DR. SHAPIRO: Larry, and then Eric?

DR. MIIKE: In the combination I think there is some confusion being introduced, which may be in the original two recommendations, and that is the line that begins sort of in the middle of the paragraph, "Where local custom requires..." It seems to me that what this thing says the way it is written is that I think it confuses the issue of seeking permission to talk to the woman with not -- with seeking permission from someone else in place of the woman's permission.

I think that if you read this where the

sentence says, "Where local custom requires a husband or the family be approached for permission before approaching an adult woman," then all these other things follow. I think what was meant originally was that -- this to me is that -- I think we agree that that can go on regardless of what it is as long as the woman's permission is obtained.

Anyway, there is some confusion in there. It is not really clear to me what is being said.

Second of all, it goes back to the original recommendation which has been incorporated here by Alta. I do not really like condition one of the three. I can live with two and three about the substantial problem, et cetera, but I do not know how one would ever decide when it would be impossible to conduct research under these conditions, and I think that is sort of a condition that I would rather see deleted.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: My goal here was not to change the substance of Recommendations 7 and 8 but just clarify. If it did not work, it did not work.

Larry, the idea here was to very clearly separate the concerns about recruitment processes from the concerns about enrollment, which is why there is not a sub-A on recruitment and a second one on enrollment.

As far as the three conditions that are listed -- and you may recall from the San Francisco meeting that after that exchange about whether we should abide by local customs that have been documented in which one cannot recruit women directly but must go through their husbands or other family members, that compromise was developed. Bernie Lo actually produced some language that was presented to the commission, and as I recall a majority of the people thought that it was acceptable, which was say that U.S. researchers should, in fact, approach women the same way they approach men. That is approach them directly. There will be many settings, as I recall being mentioned, in which that is not going to be a problem. For example, reproductive health clinics.

Where there is a local custom that says you are not supposed to do that, they should not follow that local custom unless there is a compelling reason to do so, and the conditions that Bernie had listed in this language tried to capture for him and for others what they thought that compelling circumstance would be.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, my problem is with the serious conditions having to do only with women. Tuberculosis, malaria, hepatitis C are serious

conditions having to do with women and to do research only on men in those conditions, we would find nowadays, after all we have made a similar criticism in the United States, we would find inadequate particularly since many women are pregnant and so this would affect research on women who are pregnant who have these serious deceases.

I think the basic issue is we do not like the idea that women somehow are second class citizens and that their consent cannot be obtained like you would obtain the consent of anybody else and that is -- if that is what you are trying to address, the seriousness of the health condition, it is not the crucial issue. It is how you want to approach those women.

I also believe that they should be approached directly where that is possible, and where it is not possible, the justification should be given in the design of the protocol. And if the justification is inadequate then the protocol does not get approved.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I would like to follow on Eric's comment to try to see where we are, and it seems to me there are certain things it is very clear we agree on. Such that one wants people to be approached in the same way regardless of gender, and

as soon as one departs from that you start asking what are acceptable and unacceptable departures.

In no event may someone -- there be substitute consent, so that is very clear.

And that what is articulated by Alta, effectively, is a position which says that if the autonomy right of the woman is to be abrogated in the form of seeking an additional consent from the husband, that that is only morally allowable if the condition to be treated or to be studied is one which women benefit from. And then it says only women benefit from, only affects women. So effectively the notion is that the woman's autonomy, in some sense, is not being overridden because the benefit is accruing to women, and women specifically.

And what Eric is asking is the question, is that the only condition? If one considers a serious health condition or health condition which affects men and women, why is it the case that that would not equally be a case of not eroding the woman's autonomy? I think that is the question we have to decide.

DR. SHAPIRO: Any other comments? I want to focus on exactly that issue.

Alex?

PROFESSOR CAPRON: Pardon me if I have missed a crucial part of the discussion just now but

it -- I thought Alta's revision was preferable. I did not see it substantively as that different, and perhaps I have missed something. It just seemed to me it sorted out the issues much more clearly.

The present version of Recommendation 7 and 8 seems to me to jump from one thing to another and so that if we are looking for the substance of what is expressed, I find Alta's way of expressing it -- whether we call it Recommendation 7A or B or Recommendation 7 and 8 is irrelevant but preferable.

On the issue of whether the requirement that the problem be one which only affects women, I think Eric raises an appropriate concern that that, of course, would put this research in the same category as a lot of research on common conditions that affect men and women in the United States where for years we had no data on the women.

It seems to me that the further condition here, however, that failure to conduct the research would deny the benefits to women in the country may be an adequate safeguard because as I understand that, Eric, it would mean that if you are conducting research on a treatment in X country and the researcher wants to use women whose access into the trial is totally dependent upon their husbands giving permission for them to be in the trial, and the IRB in effect says, "Gee, that is not a condition that we

can live with," the only circumstance where it would be justifiable to say you should live with that, we should do this, is that not only does the research have to be done in that country because the drug approval process in the country requires local subjects and so forth, but that there will be no other circumstances in which there will be data, which would allow the medical practitioners, as opposed to the drug approval process in the country, feeling comfortable that the results that were gathered in that country on men are applicable to women as well.

So that if you can do the research, get the drug approval process by doing it on men in country X, but the doctors in country X will use the treatment on women based upon the fact that it was tested on women through a better consent process in country Y then there -- you should not have women recruited into the process in X and it should not go on there in country X it seems to me.

Now I do not know if that is what the intent here is but that is what it seems to say to me and I am not bothered by that.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: To me, Alex, it is clear there is two different ways one can recommend here. The first -- if you -- let's use Alta's language

because it is clear. If you go down to the line that starts with the word "health problem that affects only women," whether or not you want the word "only" in there, and that limits everything else that goes on so it is unaffected. Or whether you delete "only" and then in point number two, further down, you say "failure to conduct this research with women in the trial would probably deny its potential benefits to women in the country."

It seems to me those are your two alternatives of how to think about it, right? You would go for the first one with the "only women" if you believe the fact that it has to be a woman's condition which could be the sole thing that could override the autonomy right of the woman. The second one says that that is not necessary. What is sufficient is that there is a benefit to women.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Hands up. Okay. Hands up. You can speak now.

PROFESSOR CHARO: Let me just remind you that the language about only women is taken verbatim from what was discussed at the San Francisco meeting. If the consensus now is that there ought to be a change and delete the word "only," personally I would not object and leave the rest of it exactly as it stands, and deleting the word "only" I think still

conveys most of what is currently there and still provides a pretty strong statement about how we want our researchers to go about this in their work.

DR. SHAPIRO: Thank you.

Jim?

PROFESSOR CHILDRESS: I would just recommend deleting "only" and going in the direction that Steve suggested. In addition, I think we get a better sense of both paragraphs if we take the second sentence, "if a potential subject," and put that down at the beginning of B for enrollment because it really is an enrollment question, that is, it is a consent procedures question rather than a recruitment question.

And then it seems to me the whole paragraph flows and then the subsequent change that has just been made for me makes it a really strong and helpful paragraph.

DR. SHAPIRO: I think my -- I am sorry. Ruth, I am sorry.

DR. MACKLIN: I just want people to realize the consequences of what this -- of changing it will be. If the husband's signature is required -- I mean, if we go with the strong statement for only women -- conditions that affect only women, if a woman's husband says, "No, you may not be in this trial," then that would preclude the possibility of

women being in the trial.

Granted we all agree that the husband should not have the authority to enroll the woman, but this gives the husband the authority to deny the woman the possibility of being in the trial. The reason the word "only" is in there is -- as I think Alex correctly described it, but without an example, let me just give the example.

In countries where women may want to use contraceptives, their husbands may not want them to use contraceptives. There is no available tested contraceptive. Someone comes in and proposes testing a contraceptive that could be beneficial to women. The Health Ministry would never introduce this contraceptive unless women in that country were the research subjects. If all the husbands who wanted their wives to have 50 babies said, "No, you may not be in this research," or "we do not think this is right for you to be in this research," you would never have the research being conducted, which goes to Larry's point about it being impossible to conduct the research otherwise.

Now the problem here is that this would be a condition that would affect only women, and I believe Alex is right when he says if you are doing research on TB and you do not have women in there, the practitioners are still going to use that drug for

women and furthermore -- well, let me just leave that point.

So there is a particular purpose of saying only women because there are conditions that affect women, which if they are not -- if the research is not done then you would never have any of those benefits to any of the women in that country.

So this is specifically targeted to recognize that autonomy -- the autonomy of the woman or her authority to say I want to be in the research is more important overall than making sure that you have research that has both men and women in it.

If you broaden this to conditions that affect women and you take out the word "only" then you have got a general situation in research and you do not deal with that specific problem.

DR. SHAPIRO: Arturo, and then Eric, and then Alex.

DR. BRITO: Ruth, one of the problems -- and I wrote an e-mail to this effect earlier, and I think Alta responded with some of the changes, and I think it is an improvement. One of the problems I have with this recommendation is that I think it actually takes away from the substantive ethical principle we are trying to convey here that is mentioned in the first paragraph about the requirement for individual informed consent.

I do not know if we need -- I frankly do not know if we need this entire paragraph in this -- the second paragraph of research, however, in the recommendation itself. I think it actually does more harm than good.

I think it takes away from the individual informed consent principle because we are talking about things that are more public health issues and I have mentioned this before in other parts of the paper about how sometimes I think the tone is -- we do not stick to individual rights. That it is not just an Americanism or American ideal but it is also something that is mentioned in all the international documents.

I do not know how what you just said is not taken care of by what is mentioned in the first paragraph. In no case may a spouse's permission replace the requirement of individual informed consent, period.

PROFESSOR CHARO: Hands up.

DR. SHAPIRO: Eric?

DR. CASSELL: Just take the example that you gave. Contraception in this set of villages. The husbands all say, "No, there will be no research on contraception. You can do all you want to get it, you cannot have research on contraception." On the other hand, if -- and consequently in that example

the no is still a no.

If you take away the word "only" it does not deny it for any serious condition applying only to women.

If you take away the word "only" we will not have the situation where practitioners are using treatments that were designed on men, dosages set up for men, and then treating women with them. Of course, practitioners do it. I have been a practitioner. I have done wrong things my whole life thinking it was the right thing to do.

That is not the issue, whether practitioners will do it. The issue is what is the best research strategy that best supports the respect for persons, not just autonomy, respect for persons, and at the same time accomplishes the goal. Our goal is to promote research that is beneficial for -- among other things -- the population of the host country.

DR. SHAPIRO: Steve?

Excuse me. Alex is next. I apologize. Alex is next.

Steve, you are after Alta as a matter of fact.

PROFESSOR CAPRON: I agree with the concern that Ruth expresses, but it does not seem to me, Ruth, that this recommendation goes to that concern. There is a difference between a researcher saying, "I

want to override local custom, I want to find a way with adequate protection from the women against later retribution by their husbands to do the necessary research." And the local IRB is willing to approve it and the local -- the host country process is willing to allow something which goes against local custom.

As I understood it, the question is what happens when the local IRB tells the researcher, "In our country you cannot do that study without getting the husband's agreement to allow the wife to enroll." The usual response, I think, without this discussion would be no, no, you cannot, therefore, do the research.

So I think we are talking about something different here. We are talking about a situation in which the researcher says, "I am willing to find husbands who are willing to allow their wives to enroll. I am willing to abide by that custom. May I conduct the research with this additional qualification on the recruitment process or is that an illegitimate qualification?"

And this recommendation, as I see it, was designed to carve out a way if a project meets certain requirements. I guess in the end I agree with Eric that taking the word "only" out has the advantage of saying if it is possible to set it up in

a way in which you are looking at a disease that affects both men and women and you can get women in that country enrolled through this process. It would be better to have the data on the women but I mean -- so I do not think it is contradicting the situations in which you are dealing with a woman specific, i.e. reproductive condition.

But I do not see this recommendation as responsive to the example you give as such. Do you -- and I guess at some point, Harold, I would like some dialogue on this because I am in agreement with Ruth as to the problem but this recommendation seems to me the flip side when the investigator says, "I want to go ahead. I think I have found some men who will agree to allow their wives in. I want to get these data. This is the only way I can get these data in X country and have them approve this drug. Can I do it?"

DR. SHAPIRO: Alta?

PROFESSOR CHARO: First to Arturo's point, if there is a concern that by discussing first recruitment and then enrollment are reducing attention to the very strong statement being made about enrollment, an easy solution is to simply break it into two recommendation. Recommendation 7 on recruitment practices and Recommendation 8 on enrollment practices.

With regard to the question of whether or not to continue to use the word "only," in an ideal world I would prefer to keep it in. It is not an ideal world and I would be happy to see any progress on this point because it is my impression that currently when investigators from the U.S. go into countries where women are not approached directly but where husbands and other family members are approached to see if it would be permissible then to speak to their wives or daughters or sisters, we are in a situation where we are in a widespread way buying into a practice that is not needed and is insulting. And this would make progress towards reducing the frequency of that practice and would carve out an exception even without the word "only" in which we are no longer going to insult women this way but we are also not going to penalize them in a concrete fashion when insulting them is the only way to get something that is valuable to them.

I think that the second condition that Bernie had drafted, which has to do with failure to conduct research would probably deny potential benefit to women in a country, as Alex mentioned, is an important way for IRBs to try and distinguish when they ought to let their investigators buy into these practices and when they ought to tell the investigator no. If you have to go through the

husband then do not do it there, do it some other place.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: My understanding of this recommendation is the same as Alex's and so I really would like to understand what Ruth was saying if she has a different understanding. I think if there is another issue there, it is how do we feel about people undertaking trials for the benefit of a population of women in a manner which would violate local customs if that is what is necessary in order to get the health benefit, which seemed to me was what Ruth was addressing.

DR. SHAPIRO: Diane wants to speak but, Ruth, do you want to answer? Make any comments at this time or do you want to wait?

DR. MACKLIN: Let's hear from Diane first because there are a lot of points already.

DR. SHAPIRO: Okay. Diane?

DR. SCOTT-JONES: This may be taking the discussion in a different direction but as I am struggling to fit all of this in. I am reading Recommendation 9, which is somewhat parallel to the previous Recommendation 7 and 8, and in this recommendation we agree that it is fine to approach a community leader and ask that person for permission to go ahead and approach individuals.

And at the very least we should make these recommendations consistent with one another. Why should it be possible to go to a community leader and say, "May I approach the women in your village about enrolling in this study?" How is that different from the issues that would arise in Recommendation 7, which was formerly 7 and 8? We are here saying we would abide by the local requirements.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Diane, I think there is actually a response to your concern. I do believe there is a difference between community leaders and family members when it comes to saying which person -- which kind of person should be a filter. I think of community leaders as akin to political leaders and political leaders actually exercise a kind of function all the time. As I mentioned in the e-mail that I sent, the Attorney General of New York State is well positioned to say to certain companies, "You may not approach the citizens of this state with offers for certain kinds of lotteries or sweepstakes or any number of kinds of consumer offers because we think of them as being either exploitative or misleading, et cetera." And that is a role that is exercised on behalf of all citizens, not on behalf solely of women or men or the elderly.

So to the extent the intent -- I think it is now actually Recommendation 8 -- I am looking at my text. Maybe I have got it wrong but the intent of the recommendation on community leaders in my mind would be that it is about community leaders speaking on behalf of the entire community and not just segments.

If what we are trying to do there is endorse the idea that community leaders can say, "Well, you cannot approach the women but you can approach the men," then I would agree with you that that is just ridiculous.

But if it is about community leaders saying, "You cannot approach our community," then I think of it as being an appropriate political function as opposed to husbands saying, "You cannot approach my wife," which is simply buying into the rank kind of sex discrimination.

DR. SHAPIRO: I think the issue you raise, Diane, that is there is sort of a lack of symmetry between 7 and 8 and the current 9, the way it is, is an interesting point we ought to address when we get to 9. I think we ought to just put it -- if you do not mind, we will just put it on hold for a moment and we will get back to it shortly.

Ruth?

DR. MACKLIN: I do not want to belabor all

this. I mean, the commission has to decide what they want. Let me say one more thing about only women. If the recommendation is going to be changed, namely changed so that it does not say "only women" and it is conditions for both, then I think we need some additional paragraphs that would require any such research -- where the U.S. IRB would have to look at any such research and see whether or not the results of the research are going to be interpreted, whether there is going to be a stratification, whether the women are going to be broken out from the men, and whether those research results are going to be interpreted so that you can apply them.

When the IOM, the Institute of Medicine, had its committee on women in health research, one of the big issues that arose and that was raised by the methodologists is, okay, fine, you want women in all studies, then you have to have a methodology that enables you to apply the results of having women in the studies. You have got to stratify the groups. You have to look at the differences. You have to analyze those differences. You have to have a large enough population of women and men, et cetera, et cetera.

If we just make the point that this research should involve women and men without also saying something about the interpretation and analysis of

the results so that if they are different for men and women, they could be applied differently, then I think we are glossing over an important point about the research and its applications.

So if that is the direction the commissioners want to go, then I think we need those paragraphs in order to say that. We also have to think about the likelihood that that is going to happen in some of this research, but that is a separate point.

DR. SHAPIRO: Well, my judgment is here -- and if I am incorrect then the commission should tell me, but we do -- that we do want to rewrite this paragraph. There are two key suggestions. One is the question of "only," which I think -- at least I am persuaded -- is not the right focus here. And the other is a suggestion made by Jim that we should move some language back down to (b) which I think is also a good recommendation.

As I understand the recommendations being made here, and it may need some additional text, that is quite possible, it is -- in fact, getting rid of the "only" broadens the issue in what I think is an appropriate way. And so I -- unless people object to that, I propose we go that way, and we do have to ration our time here this morning.

Steve, Larry and Alex?

MR. HOLTZMAN: Clearly I agree with that, but I think to Ruth's point about adding the additional paragraphs, whatever, I would like that signalled in the rec where in the line that starts with "failure to conduct this research," I would insert "with women in the trial would probably then deny its benefits," and that would tie into Ruth's clarifitory (sic) paragraphs.

DR. SHAPIRO: That is helpful and we are going to have to work on the language here.

Larry?

DR. MIIKE: I think, though, that what the result will be is that first -- well, first of all, I am assuming that any research that -- research that is being done would be addressing serious health problems in these countries so that if one gets rid of "only" you have essentially made the exception to the general rule because if there are going to be serious problems to be addressed then this recommendation without the "only" would open basically any kind of research of a serious disease is through this exception so it becomes the rule and not the exception.

DR. SHAPIRO: This does not bother me actually because the recommendation requires someone to, you know, present --

DR. MIIKE: Yes, I understand that.

DR. SHAPIRO: -- reasons.

DR. MIIKE: But then I -- the way it is written it sounds like it is an exception. Where we should say there --

DR. SHAPIRO: Yes, I understand that.

DR. MIIKE: -- are certain qualifications that need to be met before you continue on with the research.

DR. SHAPIRO: Yes, that is reasonable. Alex?

PROFESSOR CAPRON: Three comments. First, I think that the point under condition one at the end of the paragraph -- and this is -- I am looking at Alta's recommendation but it is the same language -- is unclear if we -- if we move the language that Jim wants to move and so if we do that we have to revise it.

Second, I want to make sure in agreeing to this, and I think Steve's modification to point two is now necessary if we take the word "only" out, that what we are talking about here is denying the potential benefits of the research results to women in the country because it is not the potential benefit of being a research subject that otherwise we have just opened up, and if that is agreeable I would say that we change the word "its" before "potential" and say "the potential benefits of the research

results."

The third concern -- question is on Jim's suggestion that we move that sentence. And, Jim, when you first stated it, I thought that made a lot of sense but if we do that we have to be very careful because look at what will happen. If we say, "If a potential subject wishes to involve a spouse or other family member in the consent process researchers should discuss the consequences of such involvement with a potential subject and then abide by the subject's wishes. In no case may a spouse or family member's permission substitute for individual consent by a competent adult." We would be saying that in those circumstances where by tradition an individual regards health decisions as ones which he or she delegates to others, and that is the tradition, and it is an explicit delegation. In other words, it is not allowing husbands to decide for wives. It is husbands or wives, or whoever, when faced with health choices saying, "These are not my choices. I am the sick person ergo they are the choices of someone else." We would be saying that is unacceptable.

Now if that is what we mean, fine, but there are large segments of the world population which take a very different view and, of course, I would agree that we should not allow that to simply be an assumption that someone else wants the decision to be

made but where it is explicitly decided I want you to involve this person and I want you to listen to them in choices, we by this recommendation as put together with these two sentences would be saying that is unacceptable.

Now if that is what we mean that it is always unacceptable and that research is different than health care in this regard, even research on health care where the subject is also a patient, fine, I guess. I mean, I can see an argument for keeping it separately but I am a little worried about a view towards autonomy meaning I decide for myself, which is not the worldwide cultural norm, and I am not sure I want to say that it is wrong in those countries where the researcher has found explicitly that that is the choice of the subject.

MR. HOLTZMAN: See, I have no problem with that but it has nothing to do with the placement of the second sentence because the problem still is in (b) whether you put it there or not.

PROFESSOR CAPRON: I understand.

MR. HOLTZMAN: So I think we have to address the substantive question but as it now stands the second sentence in (a) just breaks the flow completely and really refers to consent procedures which we are addressing under enrollment rather -- it is really the recruitment question.

PROFESSOR CAPRON: I agreed with your movement but the movement simply highlighted --

MR. HOLTZMAN: Right, the need to make that --

PROFESSOR CAPRON: -- the need to make a substantive decision --

MR. HOLTZMAN: Right. I agree with your --

PROFESSOR CAPRON: -- are we saying that --

MR. HOLTZMAN: -- exception point, sure.

PROFESSOR CAPRON: -- the research rules are different. I mean -- and if in Korean society or whatever, when health care decisions are made the patient expects that the eldest child will make those decisions for him or her, and we are saying, "Well, if you get into research you have to follow the American view that you make your own choices."

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Yes, hands up.

PROFESSOR CHARO: I think that in some way, Alex, that this is a problem that we are creating by reading too much into the language here. It is common practice in the United States, for example, to say that individuals have to give consent for their medical treatment but routinely they will delegate decision making authority to somebody else or to a physician and that delegation is what is considered to be their consent. And I think that we can

understand the word "consent" here the same way.

Somebody in Peru says, "Well, you know, you have my permission to let my husband, father, sister, you know, cousin make these decisions for me." That would be our understanding of having given consent by virtue of a delegation but it is a delegation of the individual who is going to be the subject. And I think that this can probably be handled in the text without having to worry about rewriting the recommendation.

DR. SHAPIRO: Well, let's just make sure that we, first of all, understand what we want to say. I think my own -- I agree myself with what Alta says as long as it is the individual that decides how their situation is going to be handled and we get permission from that individual to handle it in that way. That satisfies me but I do not know how others feel about that.

It is just that they cannot be volunteered is what we are trying to say here.

DR. DUMAS: Right. That is right. I agree with that.

DR. CASSELL: That is the essential issue.

DR. DUMAS: Yes.

DR. CASSELL: And I accept this entirely. I have taken care of populations where whole decisions are a woman's decision, ultra orthodox Jews the women

make health decisions but they do not volunteer their husbands any more than their husbands volunteer them.

DR. SHAPIRO: Okay. I do want to proceed on.

Eric has handed me a note which I have not yet read from Bernie which also focuses on Chapter 2 and let me just read it. I have not -- I am reading it for the first time myself now.

Do people have copies of this?

DR. MESLIN: Yes, they have been distributed. Yes.

DR. SHAPIRO: All right. Well, for the purposes of the -- I do not know if it has been distributed otherwise for the purpose of those who are attending today. He said, "I would suggest two additional recommendations: (A) researchers should indicate in the protocol how they will minimize the likelihood that potential subjects mistakenly believe that the purpose of the research is to administer treatment; and (B) IRBs may approve protocols where documentation of informed consent through a signature or thumbprint is waived provided the investigators have provided adequate justification for the waiver.

The first -- I do not know where Bernie wants to -- I just got this as a statement.

DR. MESLIN: Here is an extra one.

DR. SHAPIRO: I am not sure -- let me make a

suggestion. I am not sure where Bernie wants these and how he wants them inputted.

Ruth, excuse me. I apologize.

DR. MACKLIN: That is okay. No, it is -- there was some discussion about this. Where they would go -- for example, the therapeutic misconception, there is a discussion of the therapeutic misconception. The statements -- and I think it was Trish who originally made the suggestion that this should rise to the level of a recommendation, there is a discussion in the text that says something very much like this. It is right in the text.

The question is whether to take what is in the text as explanatory or supportive material and make it rise to the level of a recommendation.

Similarly, the waiver of signature is in a lengthy discussion of the problems of signing and how people do not sign things in other countries, et cetera, et cetera, and we make the point that the IRB should accept different procedures but not different substance for informed consent.

Here again the recommendation -- the suggestion is to make a specific recommendation for waiver of signature rather than leaving that as a discussion in the text.

So that is basically moving what is already

there in the discussion and raising it to the level of a recommendation.

PROFESSOR CAPRON: How does this relate to Recommendation 2 on page 6?

DR. MACKLIN: It actually is a more explicit specification of what that means. I mean, I think it relates to it by further elucidating it. I am not sure it adds anything.

PROFESSOR CAPRON: Well, I mean my point was shouldn't we meld these two together? I mean, I thought when I looked at his (b) here that we had already agreed to that. It was Recommendation 2. And so --

DR. SHAPIRO: I think that is right.

PROFESSOR CAPRON: And so to the extent that he says these are additional recommendations, I do not see them as additional. That one. That was my only point in raising that.

DR. SHAPIRO: Let me -- I think you are right on that. Let me -- I am sorry. Bette?

MS. KRAMER: However, it is handled, I thought that both of those subjects were handled very well, the therapeutic misconception beginning on 24 and then following with a documentation of informed consent. And I, myself, felt that something was missing as I completed the language in those -- each of those sections that there was not a final

conclusion, which rose to the level of recommendation.

DR. SHAPIRO: Yes, I think --

MS. KRAMER: Certainly the supporting language is there.

DR. SHAPIRO: So you would support making a recommendation on the --

MS. KRAMER: Yes, I would.

DR. SHAPIRO: Yes. Trish?

PROFESSOR BACKLAR: I think that Bernie and I both were thinking of the --

DR. CASSELL: I cannot hear you.

PROFESSOR BACKLAR: I think Bernie and I were both considering that (a) the therapeutic misconception recommendation should go at line 28 on page 26 after the discussion about the therapeutic misconception simply because that is a very thoughtful and well put together discussion, and it seems as though something is lacking as Bette says when you get to the end and there is nothing that attracts your attention to it in a significant fashion.

DR. SHAPIRO: Alex?

PROFESSOR CAPRON: I agree. And it seemed to me that vis-a-vis the recommendations on page 6, Bernie had already recommended that those be moved back and I guess I wonder from -- again from Ruth's

and Alice's point of view if there is a problem if there is a problem with either moving the text up or moving the recommendations back, whichever.

DR. SHAPIRO: We discussed that precisely. Ruth and Alice are going to look at that and see whether they want to move one forward or the other backward, however you think about it, but to bring them together.

I want to say a word about this therapeutic misconception. I think in view of the things that we are considering and saying in Chapters 3 and 4, I think it is quite important to say something explicit about therapeutic misconceptions. A lot of things we are doing are going to make this matter worse and so we better straighten it out early on and this is one way to at least highlight it. So I certainly agree with that.

Steve and then Trish.

MR. HOLTZMAN: With respect to -- this ties to the documentation issue. I think we are making it very clear that signed consent is not necessary and you should just effectively -- what you care about is the substantive requirements of consent as opposed to the specific procedures.

I would just ask Ruth and Alice to think about if you look at, for example, Recommendation 1 -- so page 6, line 13, where you say "consent

documents should include all the basic elements of disclosure," I think we use documents to mean things like the consent form and also we use to mean the documentation presented, for example, to an IRB that consent took place. All right. And I think that -- so at least when I read this it has made it sound like you need a consent document, e.g. that someone signed and then, oh, by the way, that has to be a signed consent document. So you just might look at how we use our language. Okay.

With respect to the therapeutic misconception over on page 26, we cite the confusion potentially arising there between the fact that someone may be getting extrinsic health care in the context of a clinical trial and that can engender therapeutic misconception but what we do not tackle is the case where someone is going into the trial in order -- because they are suffering from something for which there is no good cure and the experimental medicine is the best opportunity.

Now is that a therapeutic misconception? I am not sure how people who know this literature -- is that considered a therapeutic misconception when I am dying of cancer, nothing will treat me and I read that there is a hot new medicine potentially available in a Phase III?

DR. MACKLIN: Yes. I guess the cancer

example is not the best to demonstrate the therapeutic misconception because it is Phase III and there is lots of other meds out there and they have been there for a long time.

The more telling example is something that is being tested that is of uncertain efficacy and we certainly have enough -- it is a clinical trial. It is of uncertain efficacy and there is enough evidence for the number of clinical trials on various drugs that never actually get approved because they are not sufficiently efficacious or they are too harmful.

So the therapeutic misconception specifically is that the aim of research is to provide treatment. The intention of research. And that is the key because somebody is going to go into the trial and get randomized and if they get randomized -- of course, if it is cancer they are going to be randomized against a standard treatment which will give them treatment but if it is in the placebo case -- I mean, in the case of anything with a placebo they are not.

So, I mean, as we describe and define the therapeutic misconception it is the belief that the purpose of research is to confer benefit to the individual.

Now as a matter of fact, it will be the case that entry into research will for some people confer

benefit. Okay. That is not the misconception. The misconception is about the purpose and the intention of research to confer therapeutic benefit directly to individuals rather than to learn something that will contribute to knowledge.

DR. SHAPIRO: Other comments? Okay.

What time did we get started this morning?

DR. MESLIN: 8:30 right on the dot.

DR. SHAPIRO: 8:30. Okay. I was not here then.

I want to -- I am going to suggest then we take a brief break because I am going to want to skip over now other issues in Chapter 2 and come back to address directly the issues that come up in 3 and again in 4 with respect to placebo controls and establish effective treatment to supply that. What we really mean -- this is everywhere in that chapter and unless we straighten out where we feel -- what we feel on that issue it is just hard to make the other -- the rest of the chapter fit together.

So let's take a ten minute break. If we can, let's try to reassemble at 20 to.

(Whereupon, at 10:33 a.m., a break was taken.)

DR. SHAPIRO: Colleagues, as I indicated just before our break, I wanted to go on to an issue that comes up in Chapter 3 recognizing there are

other issues in Chapter 2 and as you have before you some suggestions from Alex with respect to dealing with the initial material in Chapter 1, which I hope you will get a chance to review some time today or this evening so that we can deal with it. I think we have an hour tomorrow morning. It is unrealistic to go through this right now.

And you may have some reactions to that and Ruth and Alice may have reactions to it as well but I do not want to deal with that right at the moment since many of us have not read that material yet but I want to thank Alex for putting it -- taking the trouble to put it together.

I also want to encourage commissioners if they have done so, if they have heavily marked up copies of the report, as I do, really to pass it on to Eric so as we begin rewriting, which will begin this afternoon, we can take advantage of some of the observations that you may have.

So if you do have a marked up report that you are willing to share, please hand it to Eric at our lunch break and that may be helpful to us as we go ahead.

I want to now focus our attention on one particular issue, which as I said before, comes up in Chapter 3 and that is concerns placebo control trials. It is really quite important that we be

clear as we can even though we might disagree amongst us as to exactly what we want the report to say in this respect.

I think we all agree that where there is no established effective treatment and there are proposed treatments of placebo controlled trials that are entirely appropriate, I do not believe that is a controversial issue. The issue comes up rather where there is an established effective treatment and the question then is are there any circumstances where a placebo control trial is nevertheless still ethically appropriate.

Where I -- my own view on this matter, which certainly could be changed by persuasive arguments, is that where there is an established effective treatment that is presumptively the way a trial should be carried out but there may be good and sufficient reasons in particular areas and particular circumstances to have a placebo control arm, although the researcher would have to justify that in some way. That is just where I currently sit on that issue but I really would like to get the commissioners' view on that.

So, for example, if you look at page 15 -- and I do not mean to pick out this particular sentence as the -- except that it happens to be one of the ones that caught my attention as I read

through Chapter 3, on lines 22 to 24 where it says, "It is generally accepted that a placebo control trial would not be ethical if an established effective treatment that is known to prevent serious harm such as death or irreversible injury is available for the condition being studied," although I am not quite sure what available means and if it means available everywhere or what. I was not quite sure about that.

But if this was meant -- and I may be misinterpreting here -- to be -- to say that placebo controls are never ethically justified in the case where an established effective treatment exists and that -- I may be reading more than was intended here but I am just saying that to highlight the issue and try to see where commissioners are on this issue because I think my own view is that it is central to everything we say -- not everything but many of the things we say in Chapter 3.

So let me open the floor for discussion and comments, indications of where you think we should be on this particular issue.

Arturo?

DR. BRITO: Once again the only time it is justifiable to do placebo control trials in my mind, unless there is a specific example somebody has, is when you are concerned about a public health of, for

instance, large populations and large communities. But this is not what this -- what the tone of this whole report is about. We are talking about individuals.

So when it comes to individuals, placebo control trials, I do not think, are justifiable in any situation so I agree with Harold there. So I -- that is just my --

DR. SHAPIRO: Well, in that case I did not express my -- I did not express myself well enough. I apologize. In addition to not having good ideas, I do not speak very well.

DR. BRITO: No, you speak very well.

DR. SHAPIRO: But the -- my view is a little different than that. That established effective treatment is the presumptive control but it can be overridden in certain circumstances. So in certain circumstances placebos might be appropriate but that has to be justified. That is just my view.

DR. BRITO: Okay. I would like to hear the examples of when they can be overridden when an established effective treatment is available and maybe that would help.

DR. SHAPIRO: My own view is that if a placebo control trial would answer an important health related problem in that country and the established effective treatment would not, that that

is perfectly appropriate to think about it. It has to be --

DR. BRITO: Once again then when you are answering that -- you are talking about something for a population. Therefore --

DR. SHAPIRO: I am talking about information that would be generated out of the trial that would impact the health of the population --

DR. BRITO: Of the population at --

DR. SHAPIRO: Relevant population, population of sufferers, right.

DR. BRITO: Right. But at the cost of the individual.

DR. SHAPIRO: In that country that is correct. Yes. Alex and then Eric?

PROFESSOR CAPRON: I guess I would like to have some explanation as to the rationale here. In the cases which are cited in the text on page 15, line 24 and following, I understand that the argument is that where you are going to a group of people who, if you were not conducting the research, would receive an established effective treatment, it would be wrong to deprive some of them of that treatment.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: And I guess it would require a truly exceptional justification.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: I mean, I would like to have you give a justification in that case.

The cases which have caused difficulty in the international arena are not those.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: And the argument, therefore, is not one of wrongful deprivation. As I understand it, the principle concerns are two. One, that research will be exported to places where there is no established effective treatment as a way of either making the research easier to conduct or making it cheaper to conduct because you are not obliged to give the established effective treatment. And a rule against it in that circumstance would be a prohibition designed to prevent that act which would be seen as an ill motivated act.

So the justification in that case would be that is not why we are going there. We are going there because there are other reasons to do the research in that country.

Then you get to the second concern, which is if you are coming from a country in which you would supply the research -- excuse me. Supply the established effective treatment, is it wrong to treat the subjects that you are dealing with differently than you would treat subjects in your own country who would by the previous discussion be entitled to

something which they would otherwise have access to?

And here the argument is not that your motivation is wrong. We have already established you have good reasons independently for wanting to do it there but that it is -- it is somehow unfair to people who you are -- on whom you are placing some demand of being research subjects or placing some potential burden not to treat them as well as you possibly could. Is that correct? Is that -- or have I got it wrong?

DR. SHAPIRO: I guess that is -- I mean, I was not concerned --

PROFESSOR CAPRON: I want to get to the underlying rationale for how we apply it not as a general principle in the U.S. and otherwise, which I agree with your conclusion but what is the rationale for saying that the established effective treatment, which is not now present in the country, ought to be applied? Is it the notion of some kind of reciprocal obligation? Is that in the end where the argument lies?

DR. SHAPIRO: Let me just try to respond.

PROFESSOR CAPRON: Say reciprocal to the gift that they are giving by being --

DR. SHAPIRO: I -- first of all, to go to the first part of your comment. I certainly agree that where the established effective treatment is

what they would have received, it would be inappropriate to deprive them of it. So if they are in a country where the established effective treatment is available and they would have benefitted from it, like the U.S. or anywhere like that, then it would be inappropriate to use placebo controls. I agree completely with that.

The question is in my mind -- comes up where the established effective treatment is an irrelevant control for that country because it simply cannot meet the needs of -- the health needs in that country in any foreseeable time period.

And in those cases other kinds of experiments can be considered. I do not say they ought to be initiated but can be considered. I do not think they should be required under all circumstances to import the established effective treatment.

Now the people in that particular country cannot be made worse off because of the trial by depriving them of treatment they otherwise would have received. I completely agree with that. So that is -- it is that case that I am thinking about.

PROFESSOR CAPRON: I, like you, do not express myself well and I wanted to know whether what the argument is, is that -- not that they -- that such research could be conducted but that if you were

applying only the first rationale for the not using a placebo, that is to say you would be depriving something of someone, that clearly does not arise here. Is there a second obligation -- an affirmative obligation to bring it in and, if so, does it rest on this notion of treating the subject as well as you possibly can?

Now if that means that the established effective treatment in another country, in the United States, requires medical infrastructure that is totally unavailable, or clean water, which is totally unavailable in the country, and the argument is, well, we cannot do that because we cannot do it, then that is an argument as to why it is an impossibility.

But if it is possible but it was simply more expensive and because you are using an active control you require more subjects in total and more expense and more time, do you still have that obligation to do it is what I want to know and, if so, does it rest on this argument that because the subjects are being -- are making their contribution, you should treat them as well as you possibly can?

DR. SHAPIRO: I do not think so.

PROFESSOR CHARO: Hands up.

DR. SHAPIRO: That is just my opinion because I think a competing ethical requirement is to do something of use to the people in that country and

I balance -- I put that on the scales to think about and do not have just a standard flat rule.

PROFESSOR CHARO: But this is -- that is where you lose me. If you are testing an intervention which could be beneficial to them in that country if it proves useful, the question is what do the controls get? Do they get the best that you could do under the circumstances?

DR. SHAPIRO: No, because it may not answer the question of interest. To find out that the control does not work as well as the established effective treatment may be an irrelevant finding for the health needs of that country.

PROFESSOR CAPRON: But that is not the only finding you will have. You will have a finding about how well the tested intervention works, won't you?

DR. SHAPIRO: Not unless you have a control somewhere you won't.

Eric, and then Carol.

DR. CASSELL: Well, I think it is wonderful of the commission to give both of you the opportunity to polish your skills of articulation. Otherwise lacking, I have noticed, yes.

(Laughter.)

PROFESSOR CAPRON: Well, you do not have that problem.

DR. CASSELL: Thank you. I agree with you,

Harold, and I think if we took the famous trial that starts this off in lots of minds, the use of a full four drug regimen for AZT in a population and then that regimen would stop at the end of the same period would -- might briefly benefit somebody's CD4 count but not very long, and it might do a lot of damage. Nobody knows what that does in a malnourished population for one thing.

And that, it seems to me, is an example of something in which a placebo control is irrelevant to the population in which it is being studied, number one. And, number two, it may be dangerous in that population when it is not dangerous in a better nourished population with better medical care and for that population and for that period of time they should not be getting that standard regimen.

However, there are not a lot of trials like that and I think that is the point you are making and that is what all the other -- I mean, the fact that the Helsinki and then this one and then that one, and everybody says the same thing does not make it any stronger in cases like that but it does say as a general principle you should not deprive a population of care they might otherwise get.

DR. SHAPIRO: Carol?

DR. GREIDER: Yes. I just wanted to again agree with what you had said, Harold, and to point

out that a study can only establish what it sets out to establish and the controls are part of the experiment. So if you find in a study that your regimen that what you are testing against the established effective treatment is less effective, that does not tell you how effective it would be against placebo if your control -- and so how you design the experiment can only give you a certain answer. And so in some situations it might be a meaningless result and I think that was a point that you were making.

DR. SHAPIRO: Bill?

MR. OLDAKER: I also agree but I think that what we are talking about is trying to set up the ethical parameters which we already know in developed countries that established effective treatment must always be given. But in countries where it is not available it seems we would be saying that we are carving out an exception to be looked at. Not -- it would not be for all cases but it would be certainly acceptable under the proper circumstances where it is not reasonably available to conduct these types of trials.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I think the genesis of this principle has to do with actually two features. One is the -- not to deprive of what would otherwise be

normally available but also is the extent to which there is potential harm because examples -- and we have articulated this in this -- for example, there is nothing wrong with doing a placebo control of a new version of Ibuprofen, for example, because the minimalist harm that will result is the person is in pain for an extra two hours. So I think just -- as usual, flat out statements usually do not work as you start to get into the real cases.

I want to come back to Alex's point, though, as when we move to the case of a country where an effective therapy is not available, though it is available in the world, while it is true that a study will only prove what a study is designed to prove, there -- you can have cases where there are two alternative studies.

So, for example, in the case at hand we have heard arguments that a noninferiority study would suffice to justify making the therapy available. You would have shown it was effective by showing it was not inferior. So I think the ethical question is the one that Alex is focusing on, is if it is the case, right, that you have an alternative study which involves the effective control, first off do you have an obligation to use that. And then the second is if you have -- if that study would not prove what you sought to prove such that you had to do the placebo

control, is it ethically allowable to do so?

And I think if we could just tackle those two cases.

DR. SHAPIRO: Well, my own view, Steve, is that the established effective treatment is the presumptive control. Okay. You always try to control that way and if there are ways to answer the appropriate question that way that is what you do. And you need to build a case for anything else. I am just trying to say that I think there probably are cases where that would be allowable and you just have to make the case. It is not an easy case in all ways and it is not obvious.

MR. HOLTZMAN: But I think that -- I am not going to disagree with you. I want to work with you on this one. All right.

DR. SHAPIRO: Yes.

MR. HOLTZMAN: Let's assume you are true. Then I think we need an answer to the critic who says that that effective control is irrelevant in the situation. What is special about the research context that puts a moral obligation on you to provide it as the control since it -- what is the nature of the deprivation? Is it the fact that you could have it available to you that creates a situation of otherwise you would be depriving? I think if we could articulate that it would be the

basis of your argument.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Yes, hands up.

PROFESSOR CHARO: I would like to say that I think Alex has articulated that justification and I would assert that when people are volunteering for research that we do owe them something as a result.

That it would be entirely sensible to say that even if the established treatment is not ordinarily effective in country, that it should be provided if possible unless that is not going to allow you to answer the scientific question that has to be answered to make the research useful.

The language that I proposed --

DR. SHAPIRO: Well, I agree with that.

PROFESSOR CHARO: I am sorry. The language that I proposed on page 5 of Eric's memo attempts to capture these situations and to say that placebos are appropriate when reasonable alternatives have been exhausted and that those reasonable alternatives, which include these other kinds of controls have to be examined to make sure that they do not create a net increase in risk because of some of the design inferiority that can come along with them.

DR. SHAPIRO: Thank you. I think I agree with you. I certainly agree with your statement on page 5 which I read.

Steve?

MR. HOLTZMAN: You see, I think this is going to take us directly back into Chapter 4 when we start talking about justification for, for example, provision of ongoing care and what is the moral basis of that. Is it the justice as reciprocity basis? Is it health as a primary care? I think what we are going to have to get into is exploring what is the nature of the relationship between the researcher and the subjects which creates certain moral obligations. That is my sense.

DR. SHAPIRO: Ruth, yes?

DR. MACKLIN: Harold, if you think there is an inconsistency between the statement on page 15 that you read --

DR. SHAPIRO: Right.

DR. MACKLIN: -- and the recommendation, which seems to me to incorporate everything that people here seem to be agreeing on, namely Recommendation 2 on page 40, which sets up the presumption of an effective established effective treatment.

It says this should be done whether or not it is currently available but goes on to say in cases where the study design does not provide that then the protocol should include a justification and all of the text before that explains all these factors.

Now the problem with the statement on page 15, I guess, is that it says it is generally agreed. Now in a discussion that Eric and Alice Page and I had about your comments, we thought we would change those words. Instead of saying "it is generally agreed," to "leading experts agree," because we have Bob Temple, we have Bob Levine, we have the written literature in which even the people who are debating the appropriateness of placebos in some context, all seem to agree on that point. Namely that if you are going to have death or permanent disability then it is inappropriate to use the placebo.

So I think if we focus on the recommendation and we just -- this is meant to be a descriptive statement about the agreement.

DR. SHAPIRO: I did not have any problem with the recommendation at least as I recall it right now and maybe I read more in the statement than was intended.

I am trying to at least articulate a position that says there are an awful lot of complex problems out there and a lot of complex diseases and just what the most relevant experiment is to help to address the health needs of a particular area or particular population may not always in various circumstances require the established effective treatment as a control.

I do not know. I am just trying to leave room for that to happen. That is all. And I think the recommendation does that so I agree with the recommendation.

Eric?

DR. CASSELL: Related to the recommendation, I would like to hear an example that would pass the no effective treatment test. Tell me one that you would find acceptable, Ruth.

DR. MACKLIN: Say that a little more clearly.

DR. CASSELL: Well, the recommendation says you should have concurrent treatment except under certain circumstances. I would like to hear what you think those circumstances are.

DR. SHAPIRO: Jim?

PROFESSOR CHILDRESS: Let me just build on that, I guess if you are looking at the recommendation on 40, another way to say it would be do we give enough indication in the text to give the kind of richness that would be required for the justification and I am not sure that we do. The other part would be do we need to say more in this recommendation itself since many people have looked at the recommendations and do not read the text that carefully. Do we need to build in more of the -- or at least kind of an example of the justification that

would be acceptable? Is that the direction you are going in?

DR. CASSELL: Yes. I think the exemplification is important in this particular thing but more perhaps than in some others because it has been so widely argued.

We are generally agreeing that we think you should not have a placebo control trial except under certain circumstances and then we do not say and these are some circumstances that came into our -- that we thought were acceptable.

Now IRBs may disagree and so forth and so on but these are examples.

DR. MACKLIN: The problem with examples is that then you get bogged down in the examples. The text that immediately precedes the recommendation sets out criteria. It does not provide -- mention an example but it sets out criteria.

Once you start with the example, if people disagree about the example you do not make any headway. So what starts on line 25 on page 39 and goes to line 7 on page 40 sets out several specific criteria that must be met and otherwise you have got -- you can rebut the presumption.

I do not think we can go -- do any better than that without getting into examples that might turn out to be controversial. This is supposed to

provide the framework for determining in any particular case whether or not you have met the criteria.

DR. SHAPIRO: Alex and Steve, then Arturo.

PROFESSOR CAPRON: Ruth has said basically what I would say. I did have a question about the fourth point on lines 5 through 7 on page 40. I did not understand what was being advanced there, Ruth, as one of the criteria that could be examined. The language is a clear case that controls are intended to stimulate the current state of care --

DR. MACKLIN: Simulate.

PROFESSOR CAPRON: Simulate. Oh, I am sorry. I just misread it. Boy, is that a misread. Simulate the current --

DR. CASSELL: (Not at microphone.)

PROFESSOR CAPRON: Thank you.

(Laughter.)

PROFESSOR CAPRON: Sometimes you are just too damn articulate diagnostically.

That goes to a -- that goes then to a point that I want -- I think we need to make clear earlier on and that is there is a difference between a placebo being justified as a placebo and a placebo being justified because there is no good care being given in the country as it is. I mean, if the argument is that the placebo simulates the current

state of care because the current state of care is merely hand holding or whatever, and it does not amount to any known therapeutic valuable intervention, then we are back -- we are in a different realm it seems to me, Harold, because before when it was being discussed the assumption was that is all there was.

There may be situations in which some form of treatment is now being given and it is not the world standard but the argument there, it seems to me, is different than the placebo argument.

DR. SHAPIRO: I agree.

PROFESSOR CAPRON: And yet in our earlier discussions to the extent that they influence the way the final draft of this is, those two were being equated.

DR. SHAPIRO: Yes, I agree with that.

PROFESSOR CAPRON: Yes.

DR. SHAPIRO: I agree with that.

Let's see. Steve?

MR. HOLTZMAN: I thought that the work that was done on page 39, lines 25 through page 40, line 7, was really wonderful. I mean it did lay out the criteria so I think there is a presentation question that given that we know that the world tends to only read our recommendations, whether this recommendation, we should pull some of that text up

into the recommendation. But I think in terms of the criteria being laid out, which again -- the background against which judgments will have to be made, I thought this nailed it.

And I could then imagine a range of cases -- Alex's point about it is different than a placebo. But if I -- if I am a big drug company and I can provide an effective treatment and I want to use placebo, I have one set of justifications as opposed to someone else who could not have access to the effective treatment and, therefore -- so I think you cannot nail them. You have to just lay out the criteria like Ruth and Alice have and look to people to make judgments.

DR. SHAPIRO: Larry? Let me -- Larry had made a comment about this particular recommendation. Do you want to --

DR. MIIKE: Yes. I was just looking for simplification. I mean, contrary to what Steve said. I like recommendations that are short and to the point because when they get too long it kind of gets a little too confusing and the justification should be in the text that follows. I think that the current version that we have is changed from the one that I originally talked about but even this one I think is redundant.

We do not have to say that the experimentals

have to design it so they justify. We do not have to say that the IRB has to review it for the justification. So I am just -- just state it in a more simple way but I have no problems. As long as the message is conveyed and, as I say, I would like something short and simple with the explanation in the text rather than trying to cover everything in the recommendation.

DR. SHAPIRO: Okay. Arturo?

DR. BRITO: I think I am going to prefer to make some of my -- I will rank my papers and present them that way because I am a bit troubled by some of the conversation that occurred earlier and I understand, you know, a good study design and the need -- and when you are comparing a nonplacebo trial that you need larger numbers but I am a bit troubled by how that can be interpreted.

When I read the recommendation -- except maybe some of the redundancy that it refers to but I am happy with it for the justification.

The only comment I make now is I do not know if we need to think about do we need to include in the recommendation a comment that Steve made about when you are talking about things that are not really more than minimal risk. You know, does justification need to be provided for placebo control trials for things that are not life threatening or, you know,

can cause severe medical problems down the road? But for the other comments I will reframe and then write them.

DR. SHAPIRO: Okay. Alex?

PROFESSOR CAPRON: Do we assert here by quoting Bob Temple and so forth that what we are saying here applies in the United States fully under current interpretation? I mean, when we began our process 18 years ago or whenever it was, we heard from Temple and other people in the FDA as to why placebo control designs are used and a very strong scientific presentation of them.

We are now taking the position that at least as to any serious condition where death or irreversible injury would be involved, placebo control designs are ethically unacceptable unless there are all these kinds of justifications.

The justifications do not seem to go to the placebo design. They seem to go to the withholding of a known effective treatment, which could mean not the world standard treatment but some other known effective although not very effective treatment in the country in question.

We are, therefore, saying in the United States that all the companies that do placebo control designs are wrong or is Temple -- is what we say here from Temple and Bob Levine, who is not cited at this

point, but Ruth says is in support of the same point, that today, in fact, researchers in the U.S. as to serious illnesses do not use placebo controls? Is that the current -- is that a currently correct statement?

DR. SHAPIRO: Steve, did you want to say anything?

MR. HOLTZMAN: I mean, if you think back to what Temple was pointing out, he was specifically dealing with the example of psychotropic drugs. Right? He was dealing with psychotropic drugs and his point was that because of the variability of response, a noninferiority trial will not do what you need it to do because there -- you will not know whether your control had been effective. Hence that it is as effective as your control is irrelevant in terms of is it effective at all.

I mean, under current standards, and I think Ruth is right in what she states about the cardiovascular so to use a real live example, my company is conducting or we submitted a BLA with respect to an anticancer drug where the FDA agreed that in some ideal world it would be great to do a placebo control but there is no way you can ethically do a placebo control and it drives the statisticians crazy that we are using historical controls but it would be unethical to do otherwise.

So I do not think it is necessarily inconsistent. I think Temple was saying with respect to certain kinds of studies you cannot get the proof unless you use a placebo control. Now ask the question is it ethical to do so? And the argument in the case of the serotonin reuptake inhibitors were that it was not such a dire consequence. It was on the, so to speak, spectrum with the Ibuprofen example that could justify it.

PROFESSOR CAPRON: It would have to fit within that?

MR. HOLTZMAN: It would have to fit within that. If it is the case that you would be withholding life saving therapeutic intervention by giving a placebo you are not allowed to do that and we do not do that.

PROFESSOR CAPRON: And that is consistent with what we said in the report on --

MR. HOLTZMAN: It should be.

PROFESSOR CAPRON: -- persons with diminished capacity.

MR. HOLTZMAN: Right.

DR. SHAPIRO: Hold on a second. Jim, then Trish, Arturo.

PROFESSOR CHILDRESS: But along those lines I just want us to be cautious on 17 and in quoting Temple. When we had his testimony and we were trying

to develop the other report, I am really concerned that we not think that discomfort does not count as a harm on the top of page 17. It depends on the discomfort, the context and so on and so forth, and I just do not want us to slip in that trap here.

Okay. It may well be a harm.

DR. SHAPIRO: Trish?

PROFESSOR BACKLAR: (Not at microphone.)

DR. SHAPIRO: Arturo?

DR. BRITO: I have a request that when we speak about placebo control trials, placebo control trials in essence are not unethical. What I find the difficulty with is placebo control trials when an established effective treatment is available and in the conversations going back and forth it is very hard to keep up and then when Dr. Temple spoke back then and he -- I am not -- I am confused about when he was speaking about when established effective treatments were available and when they are not available.

So if we can just make that clear when we are talking about this and the same thing within the text.

DR. SHAPIRO: I think one of the phrases that might be useful, I really ask Steve and Ruth and others to think about it, is Steve used the phrase just a moment ago when the noninferiority trial

simply does not answer the question, okay, that is a pressing or compelling interest.

Then you have to start making -- consider other things and I think maybe that is a useful -- I mean, I find that a useful phrase. I am not -- you know, I am not a physician. I cannot give out all the examples.

PROFESSOR CAPRON: But even there that will then push us back to the issue, "Is the question ethically acceptable?"

DR. SHAPIRO: Correct.

PROFESSOR CAPRON: Because from the drug company's point of view, the advantage even when there is an accepted effective treatment, is a noninferiority trial does not answer the question that they want to ask, which they might want to ask, which is does this drug have a greater effect than a placebo, i.e. is it approvable as an effective efficacious intervention even though doctors would like to know is something else that is already around better so that they would not be using it.

But I mean a lot of stuff has been developed on kind of a me too basis without proof that it is better than the existing things. I mean, as I understand it there is a -- that is not an unusual practice.

Steve, are you going to tell me it is

unusual?

MR. HOLTZMAN: Yes, it sure is. I mean, particularly in a world of pharmacoeconomics considerations and formularies being able to show that it works as opposed to "its at least as good if not better" is absolutely useless these days so I think -- I do not think that is a correct portrayal. So then, in fact, the drug company actually has an interest in showing the superiority or noninferiority. Okay.

PROFESSOR CAPRON: It may well but doesn't a drug company -- correct me if I am wrong. Until recently, at least with the economic pressures, a lot of things have been approved and the objective of the drug company was to get the drug approved using a placebo control. It could then do further studies if it believed it could show that its drug was superior to or comparable than but cheaper than or whatever argument for superiority it wanted to put forward from an established treatment but it was not required by the FDA to show that and, indeed, the FDA could not refuse to approve something simply because there was another established treatment that was more effective.

MR. HOLTZMAN: The real world has changed over the last decade.

PROFESSOR CAPRON: Right, but it has not

changed because of ethical pressures is my point and so if we say that it is not a -- it is not effective because -- excuse me. That the design would not answer the question, the relevant question, I just go back to say relevant to whom.

DR. SHAPIRO: I agree completely.

PROFESSOR CAPRON: And you might say that the drug company -- well, if all you are developing is a me too drug and there is no reason that it would be more effective than the existing treatment you should do it and they say but the question for us is do we have an efficacious treatment.

MR. HOLTZMAN: Okay. So --

PROFESSOR CAPRON: And then we will deal with marketing later, thank you very much, aren't we entitled to do that.

MR. HOLTZMAN: Yes. Well, with all affection, it is a very abstract argument you are making, is that getting a drug registered is useless if you cannot market it. Whether or not you can market it is a function of what is in your label and your label will either say have the comparison to the standards or it will not, and you cannot market outside of the label. And so when one looks at the trial one does not say how do I get this thing registered. One just says what do I need to show in order to make this thing marketable and that has

always been the case. That is the real world, Alex.

DR. SHAPIRO: I think the issue of whether the research question itself suffers from ethical -- is a very important one and is everywhere in all trials, and that really needs to be considered. That comes up, I believe, in -- I think it is in Chapter 4 but Ruth can correct me where you give some examples saying if the central question is this then this is the ethically appropriate trial, if the central question is that something else is the appropriate trial, that does not overcome the question of whether the central question itself has -- is ethically acceptable and needs to be addressed.

I mean, I agree with that point that nothing should be said here gets around that basic issue as to whether the whole question being addressed has any ethical basis or not.

Okay. Any other comments? You wanted to read --

PROFESSOR CAPRON: Could I ask one question?

DR. SHAPIRO: Yes.

PROFESSOR CAPRON: As part of the discussion leading up to the point where we were talking on page 39 -- and I think I have wide agreement, Ruth, that the language on 39 and 40 is very helpful, there are two -- at the top of that page at line 2 the statement on page 39, to examine the various

alternatives we need to contrast proposition B with two other candidates. Is that simply something left over from an earlier edition because then we go on and say (c) and there is no (d). I just want to make sure that I was not missing something. It is a question. Is this merely an editorial problem or is there a substantive --

PROFESSOR CHILDRESS: And further there is after (c) the and as though --

DR. SHAPIRO: Right.

PROFESSOR CAPRON: Yes, exactly.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: Exactly. Did something get left out intentionally or otherwise?

DR. MACKLIN: Yes. I think we made a revision. I think we made a revision and did not -- we had more propositions in there initially. We had (a), (b), (c) and (d). We took out one. We changed them and this needs to be fixed.

Pardon?

PROFESSOR CAPRON: We no longer need (d), whatever it was.

DR. MACKLIN: No, we no longer need (d).

PROFESSOR CAPRON: Okay. Thank you.

DR. SHAPIRO: Trish, and then Jim.

PROFESSOR BACKLAR: Yes. Can I make a simple request and that is that -- are we going to

have another look at this before it goes out for public comment and, if so, it would be extraordinarily helpful if there would be some difference in the changes that you make like bolding. Some way that when we go back to read this just as readers --

DR. SHAPIRO: Well, I think --

PROFESSOR BACKLAR: No, not possible?

DR. SHAPIRO: Well --

PROFESSOR BACKLAR: All right.

DR. SHAPIRO: No, do not feel that it is not possible but I think you will get a -- I do not know that we will have a chance to sit down in a meeting to go over it. We can certainly send out a new draft and have some short period for comment before we send it out.

PROFESSOR BACKLAR: Okay. And then just -- this is two things in one.

DR. SHAPIRO: Right.

PROFESSOR BACKLAR: And that is that the recommendation number --

DR. SHAPIRO: Which one?

PROFESSOR BACKLAR: Number 2 that has that paragraph before which lists on page 39 --

DR. SHAPIRO: Right.

PROFESSOR BACKLAR: -- and you list the criteria for the assessment. In some of the other

reports we would -- with the recommendation you would still have a little discussion following it and maybe if you do not want to lengthen the recommendation it would be wise to put that paragraph following the recommendation imbedded in there.

DR. SHAPIRO: Eric?

DR. CASSELL: I just want to go back to the set of four -- the four recommendations on the -- not recommendations, the four criteria on the top of page 40. There are three. Three that have -- one if you cannot do the study at all. The other is if you are not advancing the care of the people in the host country. And then there are two about exploitation and then we go back to controls are intended to simulate the current state of care in the host locale.

I think if we are going to take exploitation as being one of those things, which is actually how this -- one of the reasons that this all gets fired up, we ought to separate it out. It is not -- I do not think it is under beneficence. For one thing it is a matter of injustice and exploitation as a matter of injustice. But I mean you can make the case but I think it is injustice.

And it is a separate issue and it is a clearly important issue that when research is done that exploits people, and that is why there is no

placebo control because it is cheaper and quicker and slicker and all that stuff. We ought to make that clear that that is a separate set of criteria. That would only require actually moving those things to a different position.

DR. SHAPIRO: All right. Let's -- before we -- Jim, I have been -- I always have trouble if someone sits right on my right. I apologize, Jim. Please?

PROFESSOR CHILDRESS: Let me agree with Eric.

PROFESSOR CHILDRESS: Another inarticulate person on your right.

PROFESSOR CHILDRESS: That is right.

(Laughter.)

PROFESSOR CHILDRESS: Let me agree with Eric and suggest also that in looking back over this, the exploitation plays such a central role we ought to make sure that we really do define it well and work it out that is in the report as a whole. And I did not go through it as carefully as I could have with attention to that but I have -- before we leave this discussion I would like to go back to pages 15 and 16, and we have spent a lot of time discussing the first -- it is generally accepted that a placebo control trial would not be ethical in lines 22 and following.

But I would also like to just call attention on line 30 at the bottom of 15 and the top of the next page where it is generally accepted that if a clinical trial is testing an experimental intervention for a disease for which there is no available treatment it is ethically justifiable to give research participants a placebo because in such trials there is nothing with which to compare the experimental intervention.

But I would just remind us that we had a lot of controversy about the initial AZT trial as to whether we should have simply used historical controls given the fact that there was nothing available then in the antiretroviral area to treat HIV infection or the Ara-A trial in the context of herpes simplex encephalitis. Again a condition that had about a 70 to 80 percent mortality rate.

So what I just want to emphasize is that it may be okay to go ahead in both of these and lay out it is generally accepted as long as we recognize that there will be some difficult questions to arise and we have already dealt with some of those in regard to the first generally accepted.

The second observation I would make is -- and this just picks up some of the earlier discussion -- is that a lot depends on how much we build in to what is generally accepted and there is a kind of

specification that has gone on in the first one that has to do with prevention -- established effective treatment that is known to prevent serious harm such as death and so forth, and yet a lot of our discussion focused on the more general level. I think it is important for us to be clear that it may set out a general principle or standard and whether we can take it as sort of absolute or presumptive or mere suggestion or guideline. A lot is going to depend on what we build into it and I think a fair amount is built into the first one as a matter of fact.

DR. SHAPIRO: Okay. Thank you.

Let me make a suggestion, Alex, because we are jumping around a bit but there are certain issues I do want to get close to resolution and so we will come back if time allows either later this morning or tomorrow morning to some of the other issues both in Chapter 2 and Chapter 3 and Alex's suggestions regarding Chapter 1.

But I do want to move our focus now to another key recommendation and it really comes up under Recommendation 2 in Chapter 4. That recommendation, as you know, deals with obligations, post trial obligations, and it is important -- critically important, I think, to make sure that we agree with Recommendation 2 or some alternate

recommendation. And I would just like to open the floor now for discussion regarding Recommendation 2 on page 10 in Chapter 4 that deals with post-trial obligations and so on.

Eric?

DR. CASSELL: This is one of those areas where I am troubled by it. I really am because of several things. First of all, it does not say that we have to provide adequate food, which as I indicated before might make a bigger difference in that intervention. It does not say ongoing treatment of something like HIV to go two months or three months and then stop. It is just as bad as stopping after a one month trial.

It seems to specify -- it seems to me to be holding people to do something where it would be lovely but we do not -- why are they doing this? I mean, aside from the fact that it would be nice. And -- because the minute you specify limits to the doing then you have to justify, well, if those limits are there, why would they do it in the first place. Or those limits and why not these limits. So that it does not seem to me to be addressing an issue of having to do with the ethics of clinical trials as much as it has to do with what we think we might owe a deprived population and that is another question entirely or what we think the industrial might of the

United States should do rather than what it is doing.

DR. SHAPIRO: Other comments, questions? Steve?

MR. HOLTZMAN: I am not sure how I feel about this recommendation. I know it is a good aspiration but what I feel I do know is that the justification given for it in terms of the Daniels' like argument and justice is reciprocity and saying that it comes from the fact that whence in the trial you have established a new status quo from which it may not be diminished, I find that line of argument wholly unconvincing and that if I were to move forward and we were going to go ahead with these recommendations I would want to ground it in a different line of arguments, which is motioned towards here in terms of the special relationship that is established between the medical community and subjects of research, which imposes an obligation in order to keep intact the meaning of that relationship.

DR. SHAPIRO: Bill?

MR. OLDAKER: Like Steve, I am a little troubled by the justification. It seems to me that as a moral principle if we were saying universally that this had to be done in Watts or in poor parts of the United States, I would probably be empathetic with it. I mean but if we are dealing with it as

something that we are going to do in another country just because we are doing research there, it -- to me the ethical principle is not any different than dealing with an impoverished group here that would not have the follow up health care. I do not know that -- I have not thought enough about it to think about whether it should be kind of a universal principle and that we should be talking about it.

The second thing in the recommendation itself, I am always troubled by kind of open ended things, such as relevant parties and if you are going to negotiate this, and how you really figure it out, but I guess I am troubled by the underlying concept.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: I was comfortable with the original justification but I certainly share Steve's instinct that there is a second line of justification having to do with the special relationship between research subjects and the investigators, and would be happy to see that presented as well as an explanation for why some of us reach the conclusion that is represented in Recommendation 2, which I strongly support.

I am less -- I am not troubled as Bill Oldaker is by the open ended nature of it because that open ended nature was a result of compromise

since it used to have much more specific language that got people uncomfortable and so the recommendation was rewritten to loosen it up and allow for a process of negotiation among whoever seemed to be an appropriate party leaving it to the IRB and the investigator to discuss this when the research protocol was first being presented. And it seemed to me like the only compromise we could have rather than if we were not willing to lay down very rigid rules.

DR. SHAPIRO: Any other comments?

Yes, Laurie?

MS. FLYNN: I just want to offer kind of a two part thought. Like most of us here I think I kind of like the feeling of this that, in fact, we would want to be able to offer this. But I have some concerns that particularly in some of the situations in developing countries that we are familiar with that there is the great potential for further confusion around the therapeutic misconception that we have tried so hard to articulate and that there is some potential for this to be coercive and potentially exploitative depending upon the way in which this is presented.

So while I understand where we want to go and why we want to go there I do not think we have given sufficient justification to get there.

DR. SHAPIRO: Eric?

DR. CASSELL: Also even though Ruth does not like examples, my friends and hers, Stephen Toulmin and Johnson otherwise, here is an example -- here is an instance where an example would be very helpful to me. What drug are you talking about? What disease are you talking about? How long would you give it? What population are you talking about? Are you talking about only the clinical trial members or their families as well? After all, if the brother is getting it, why not the other brothers? And so forth and so on especially in a community where one person participates. In point of fact that is the community participating. It is different than it is here. And then we get into these issues and I would like to hear an example of it.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Well, actually, Eric, I thought there was a lot of language in this chapter that actually went exactly to all of that and the run up to the recommendation was saying you have got a lot of very complex situations. Some would say what is the relevant population? Is it everyone? Is it the family? What about the controls?

DR. CASSELL: (Not at microphone.)

MR. HOLTZMAN: So I thought -- but anyway, but I think maybe you could look for examples that

exemplify the different cases.

What struck me is that we do talk about wanting prior agreements, or whatever is the terminology that we would use, with representatives of the relevant country. And I wonder why here we are stipulating some specifics as opposed to just leaving it to that process.

DR. SHAPIRO: Let me make a comment on the recommendation itself and see if it might be of any help in at least thinking of some people.

With respect to the underlying rationale, it is my own view, as Eric and Ruth know, that the primary goods argument and so on really does not provide a solid basis for this nor does, in my view, justice as reciprocity because reciprocity can be expressed in many different ways. There is no particular reason it needs to be expressed in this way. It is only one of many possible ways.

But the recommendation as it is phrased has two sentences. The first one says they have to provide something but the second one says at some unknown price and some unknown period of time. It seems to me that you are then left with a recommendation that is not operable because it is not clear what anyone is supposed to do or expect because it could be zero price, high price, low price, short time, long time and so on.

It may be that you cannot get around the fact that these things need to be negotiated, as someone said a moment ago, in prior agreements.

One way to read Recommendation 2 would be say sponsors should continue to provide at terms to be negotiated, et cetera, et cetera, the research. That would just simply -- that is a much simpler, not necessarily adequate, not -- I am not trying to promote this recommendation, just looking at another alternative.

It would just say that this is something that really deserves some consideration and that ought to be part of some prior agreement or some other language like that and then you leave that to the people involved in a case by case basis to decide what is appropriate.

Bette?

MS. KRAMER: Picking up on the language you just suggested, what about the possibility of saying whether or not it should be continued -- a sponsor should continue to provide the research product. It should be a matter of prior agreement or discussion prior to the initiation of the research.

DR. SHAPIRO: Well, I do not think that is different in spirit from what I said. I have no view on the language. I have not thought about it carefully but I think that is -- I am not quite sure

what I am suggesting but, I mean, that -- I am just trying to move the conversation along but that is very consistent with what I just said.

Yes?

PROFESSOR CAPRON: Steve earlier pointed to a rationale which we have discussed at previous meetings, which is the fiduciary nature of the physician-patient relationship which carries over into medical researchers' relationship with their subjects. And the difficulty here, it seems to me, is whether we are establishing unreasonable expectations there which we do not expect are universal, that is to say they would not apply in this country.

And I am always -- and I think it is good when our looking at things abroad makes us look back at our practices here. There may be reasons why the rules would differ but presumptively they ought to be the same.

I do not think we have to worry about the researchers and we do talk in Recommendation 2 about sponsors rather than researchers. That is to say it is not a personal obligation of the researcher, although it arises out of their personal relationship. It is something that would be part of their agreement with their own research sponsor as to what the sponsor is going to provide.

But part of the difficulty I have with that is that an example which we mentioned in passing in the text leading up to this is the situation in which the intervention is not useful but the existing established treatment is useful and that is what the controls have been getting but maybe the controls would not have been getting it and do not have access to it or all of them do not from an ordinary medical system. And this would certainly be relevant if we were talking about trials in the United States as well if you have patients who are recruited, some of whom do not have insurance and so forth but they are in the trial and they are getting the effective intervention.

It is equally a breach of their fiduciary relationship to abandon, as it were then, just as it is not to turn around at that point, and to turn to the subjects who are getting the -- as it turned out -- an effective therapy -- research intervention and give them now the established effective treatment that the controls were receiving.

So I think we -- I mean, I do not think we can waltz around this. We can point out that those are issues that have to be done and if we do that then the solution that you and Bette just were coming up with is all that we can say, which is simply these are the considerations and people ought to have

thought about them in advance and negotiated them.

That is not what this says now and it seems to me that we just ought to have a show of hands or something. Do we believe that there is an obligation recognizing that sometimes it will not be possible to fulfill it? I am not sure what justification other than impossibility you would give there but if there is an obligation then it does not seem to me that it is something -- if it is based on this fiduciary relationship, it does not seem to me it is something that disappears in a week or a month or whatever. It becomes some notion of an ongoing obligation.

If that seems too impossible, that is to say there will be no circumstances in which a research sponsor would want to take on that potentially lifetime obligation, then we ought to just to take the weaker view and back away from this.

DR. SHAPIRO: Trish wants to say a few words in a moment.

With respect to the principle that gives rise to this obligation, Alex and others referred to the fiduciary relationship between the physician/investigator and the subject, and I think that is an important issue, although I have to confess that I am not sure just what the nature of that relationship is everywhere. I just do not know. I mean, it is just a lack of knowledge on my part but

I could believe that it is an important fiduciary relationship in many places.

There is another argument, which in fact I may be the only one here who has found it somewhat convincing, namely that someone is made better in the trial to -- as someone said to put it in an exaggerated way -- to have them abandoned at the end of the trial, represents in my view some kind of existential loss which cannot be anticipated in the informed consent process, not easily anticipated, since subjects do not know what it is to feel better in some sense.

And that is to me at least something worth some serious consideration. However, I do favor at the end of the day the weaker version of this recommendation for some of the reasons Alex pointed out because it is difficult and complex.

Second of all, I think that while we do not want -- sponsors are not simply pharmaceutical companies where that is a model which I think is in people's minds as we have a lot of discussion. And the U.S. government is a major sponsor, probably the major sponsor, and some very interesting -- it is not clear that depending on the results that even the government or at least some agency of the government has the capacity to deliver on this kind of thing and, therefore, they would be unable to proceed at

all.

It seems to me that one has to think about the incentives in a complicated way here. And so for those and other reasons that have been mentioned, I do not want to repeat here, I do favor the weaker version of this. I may not have the right language but I will not repeat it -- but language that is similar to that really might be as far as we can go and then point out these various issues.

Trish, you are next.

PROFESSOR BACKLAR: Yes. I actually favor the weaker version but there are two things. One is I think that you are moving in the right direction, Harold, because I was thinking that one also wants to say about research subjects that one does not wish to make them worse off than they were during the trial.

So you reach the -- they reach a certain point and then if you -- if they get nothing they are actually made worse off.

And we actually did discuss this to some extent while we were doing our capacity report and the issue of people with mental disorders getting certain kinds of medications during a trial and then not being able to give it to them afterwards, and at that time as -- if I remember correctly, I actually looked through the capacity report because I had in my mind that we had said somewhere -- I know that

Laurie pushed this quite hard -- that when people were in trials we should make sure that they were able to get the drugs afterwards.

But when I looked through the capacity report recently I could not find that anywhere so exactly what you are saying, Alex, holds. We were not able to do it here. How can we do it elsewhere? Or should -- is this an opportunity for us to revisit this problem because it is a real problem?

DR. SHAPIRO: My own view is that -- the fact that we do not do it here should cause us to pause and think it through but not necessarily stop because it may be after all something which we should be doing here and are not. It should certainly cause us to pause.

I have a number of people who want to speak. Larry, Steve and then Eric.

DR. MIIKE: In answer to Alex's question I do think we need to treat the trial participants differently from the host country inhabitants and so the discussion around 2 has to be linked with the discussion around 4. If we say that all we need to owe trial participants is a negotiated -- negotiation beforehand of whether they get anything or not, rather than a negotiation about what kinds of benefits they would get, then the discussion about the host country participants is useless because if

we are not going to have any obligation except a discussion before the trial takes place about what we -- what, if anything, is to be provided to the trial participants then nothing is owed. Not even a discussion to the -- what might be owed to the host country's inhabitants.

So I think we have to keep in mind 4 while we discuss 2.

DR. SHAPIRO: Yes. I think 2 and 4 in my view ought to be more closely integrated on a number of grounds, including what Larry has just said. There is a lot in 2 that is again repeated in 4 and so on. We need to bring that together.

Steve?

MR. HOLTZMAN: I would like to try to piece apart two different strands in Recommendation 2. The one that is, is something owed, and I think that ties very closely to 4. And specification of a process by which it is determined what form that which is owed should take.

That is distinct from the question -- a different strand which says certain forms of recompense would be inappropriate and the justice as reciprocity in the Daniels' argument, which I do not accept, I think is trying to drive at that. That is saying that only certain exchanges would be appropriate exchanges.

I actually agree that that is true but that is where I want to ground it in the relationship of the researcher or the medical doctor to the subjects and what they are doing and how certain forms of recompense would erode that. It would change the meaning of the enterprise.

So, for example, if we were talking here about consensual sex, we would say that it is okay and people can negotiate it. However, there are certain things we might say are beyond the pale such as money in exchange for the sex. Why? Not because it could not be -- it could be reciprocity there but we think that the nature of that reciprocity erodes what we hold to be as a value in the act.

And I think that goes to your points, Harold, also about the existential charge of the relationship.

And I think we are saying something stronger, wherever we are going to ground it, that says we think certain forms of exchange would be inappropriate and exploitative.

DR. SHAPIRO: Thank you.

Eric?

DR. CASSELL: You know, grounding it in the fiduciary relationship of physician and patient, I spent a lifetime in that relationship, and the one thing about it is you have to be very careful that

you are not Thidwick, the big hearted moose. I do not know -- Dr. Seuss fans aside, Thidwick allows birds to keep nesting up in his horns you see until finally he can hardly move because there are so many birds nesting in his horns.

Physicians learn very early on that that relationship has got to have boundaries. You are not a family member. You give what you can do. You are not expected to give beyond what is practical for you. You are expected on the other hand to be honest and, you know, constant and so forth within the limits of ability. So that is on the one hand.

The other hand is generally speaking when we talk about the relationship of researchers to subjects, it is not the same relationship. We would mostly like to see the relationship of the researcher to knowledge be the stronger of the two relationships. That is one of the things that comes up in conflicts in lots of clinical research.

So to move it over and call it the fiduciary relationship of a doctor -- the caring doctor and the patient is, I think, not grounded in the way things actually take place.

DR. SHAPIRO: Trish?

PROFESSOR BACKLAR: And leads to the therapeutic misconception we are so desperate to keep apart from research.

DR. SHAPIRO: I think I am going to go to Alex and Bill and then we are going to have to stop, and Jim. All right. Anyone else now because you get on the list now or you speak after lunch? So it is Alex, Bill and Jim.

Okay. Let me just say one thing about this therapeutic -- there is no getting around the issue that if you have post trial benefits for whatever reasons you have, it feeds into that, I think, especially if it is medical care or something close to it as opposed to some other benefit. But let's go. Alex?

PROFESSOR CAPRON: Yes. I want to disagree with that proposition and I thought Ruth articulated it well as I understood it before. There is a difference between inducements, which we may believe are under the circumstances so great that a person gets to the point where they cannot say no because they are just so desperate for all the ancillary things, which could include post trial treatments as well as nuggets of gold after. I mean, all sorts of things could be such inducements. That is different than the therapeutic misconception.

DR. SHAPIRO: Right.

PROFESSOR CAPRON: And I do not think that suggesting that you could have circumstances in which the relationship of a researcher providing a research

intervention to a subject which manifestly in a way that they both understand has made the subject's condition better is -- will seem to be comparable to a physician. Not because there was a therapeutic misconception going in but because coming out it has proven that this seems to have made a beneficial -- now it may be false.

It may turn out that you look statistically and the person is doing no better than the person getting the control but that there is that understanding. You are calling it existential, Mr. Chairman, and there is that understanding.

I like that to that fiduciary relationship in the sense that at that point it would be an exercise of the obligation of nonmaleficence not to withdraw that treatment from that person who is dependent upon it.

Now it is perfectly true, Eric, that we can say that the -- that there are reasons for treating the researcher-subject relationship very differently than the physician-patient relationship and that that relationship is time limited and it has to do with the research intervention and it ends when the research ends. I mean, it is possible to give that description.

I am simply saying that in -- as experienced -- maybe existential is the right word -- as

experienced by people that line -- that sharp distinction between those two relationships, I think, will not wash and there will be circumstances in which either the controls who did well on the standard intervention or the subjects who got the active research intervention who did well will feel, and other people observing it would justifiably feel that there has been an exercise of maleficence there in withdrawing it.

I think we have to address that and we have two choices. We can either say that is wrong and a strong obligation exists or we should say, as Bette and Harold were saying, we should say that this is a serious issue which needs to be thought through in advance, negotiated by the relevant parties and spelled out.

And, in effect, that would flip points 2 -- Recommendation 2 and 1 on page 10 because we would say first it needs to be negotiated and secondly you need to be clear to people about what the result of that negotiation is.

I just think at some point we should bring the conclusion to -- and give instruction to the staff by having a straw poll as to whether the negotiation or the strong ethical conclusion is the one that we favor.

DR. SHAPIRO: Okay. We will do that in a

few moments. Bill?

MR. OLDAKER: I will agree with that, too, but my -- and I agree that we should use a word like "negotiated" if we are going to do this. My fear is if we use "relevant parties" we will have created also a nullity because people will create whichever relevant parties they want.

I think that it -- and it also goes back into 4. I do not know if the right entity to be negotiated with is the Ministry of Health or someone else but if it is we should be trying to be somewhat more specific because it is -- I think "relevant parties" is just too ambiguous of a term to figure out who the sponsor is going to negotiate with, and we should be a little bit more specific.

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Just a second, Alta.

Jim, you are next.

PROFESSOR CHILDRESS: I think we have materials in the text and in the lines of argument that Steve and Alex and others have suggested to develop a kind of relationship model without falling into some of the pitfalls that Eric worries about in which we are really talking about a relationship in which we have a kind of partnership, reciprocity, fiduciary concerns and so forth and that would certainly clear the matters that we have already

talked about of not exploiting people and not making them worse off, of having some obligations that continue by virtue of what was established in that relationship.

I think that we have those threads in our discussion today and in the text and I think those threads got lost somewhat because in -- this is a version of a point that Steve was making earlier, too, the Daniels' discussion may mislead us. It is really brought in to indicate why in a justice is reciprocity mode we should be focusing on health benefits rather than other kinds of benefits.

The problem is that obviously food and other things could contribute to health benefits if that is the direction we are going. So really it is not so much that kind of outcome oriented concern but rather the nature of the relationship and that process of interaction.

So I think we could go in that direction and capture most of the concerns and themes that have been raised this morning. If we do that then I think we really are making the first step relative to the participants in the research and we still have the further problems to address with the other recommendations.

DR. SHAPIRO: Alta?

PROFESSOR CHARO: Since a challenge has been

laid down that we distinguish -- that we vote essentially on whether we think of this as an ethical obligation or something that is simply a matter of negotiation, I would like to remind us or urge us to keep this in some context.

If we were talking about research trials in France, I think negotiation might be the perfectly sensible way to go for a lot of these things. But when we are talking about research in totally impoverished countries where three or four percent of the GMP is spent on health at best, two percent is already going to AIDS -- you know, care for people who are HIV positive according to the latest stuff out of the AIDS conference in Durbin, I think we have got to keep in mind that the negotiating partners are not in equally powerful positions.

That no matter how the Ministry of Health in one of the impoverished countries -- of the country's own self interest, it is not in a position to push in a negotiation the way a country in Northern Europe might be.

I mean, if you look at the pharmaceutical pricing schemes, one of the reasons why pharmaceutical prices are lower in the European Union is because Union countries have a negotiating ability to insist on that. And you do not find that when you are talking about the Southern African countries.

And the same thing is going to happen with regard to every aspect of a trial, instruction, and the details of what will be made available afterwards, and the infrastructure that will be left behind.

And so for that reason because I do not think we actually have a level playing field that is background justification for going to a contractual model in which all parties negotiate and then shake hands, I think that there is a strong argument for laying down some basic conditions that strain the parameters of that negotiation.

Let's say that there are certain things that we are simply going to say have to be done if they are at all feasible because we cannot trust all parties to be able to effectively represent their own interests.

DR. SHAPIRO: Before we see how we feel on this, I do want to say that it is -- the choice is not between ethical approaches and negotiation by assumption and nonethical approach, that is simply not the choice that is in front of us.

Ethics deals with taking the interest of others into consideration and negotiation may or may not be the best way to do that. That is another matter.

But I do not think we should view ourselves as either taking an ethical or nonethical approach on

this subject.

PROFESSOR CHARO: That is not my -- Harold, I am sorry but that was not my implication but to the extent that what is being discussed is a move towards saying that everything should be a matter for negotiation rather than saying that there are some limits, that they feel that the position can be no worse than this. Right? That is what I am getting at. But I think we should put some constraints on that negotiation.

DR. SHAPIRO: All right.

PROFESSOR CHARO: If the negotiating partners are not equally well positioned to represent their own interests.

DR. SHAPIRO: Okay. We are going to break in 30 seconds for lunch. We do have public comments at 1:00 and, therefore, we should try to be back here as close to 1:00 as possible.

Let's take a show of hands right now as Alex has suggested --

PROFESSOR CAPRON: As I think about it, are there then three choices? There is -- that it is as strong ethical obligation, that there is an ethical presumption within which negotiations should take place. And, third, that it is a matter for negotiation that deserves prior attention and then -- but without stating in the recommendation any ethical

presumption as to what is the right outcome.

DR. SHAPIRO: It seems to me that the -- just since we are just trying to clarify how we think at the moment -- that -- you know, I take the recommendation as it stands.

It really is in some -- in my view the weak version because it says prices and time are unknown and, therefore, it is a negotiation although it does not quite say it that way. That is what it actually says. At least that is the way -- I should not say that. That is the way I interpret it. And I think what we -- let me just pose it this way and we may have to refine this as we get to talk about this further.

I had made one recommendation, namely that we look at Recommendation 2, which we will have to integrate with Recommendation 4 later on. We have to get to that. Sponsors should continue to provide at terms to be negotiated, et cetera, down to the end of that first sentence. That is what we have come to identify as the weak version of this and I do not mind if we call it that.

So why don't we just have a show of hands of those who would like that kind of a recommendation as opposed to the exact language versus something that is significantly stronger language to be developed? So let's -- those who would favor -- let's put it

this way: Those who would favor something significantly stronger than that?

(A show of hands.)

PROFESSOR CHARO: Hand up.

DR. SHAPIRO: Hands up. One, two, three.

PROFESSOR BACKLAR: Stronger than just --

DR. SHAPIRO: That is right. Right. Okay. Others?

DR. MIIKE: Let me ask a clarification. Both of these, the strong or the weak, is -- there is the assumption that something is owed to the trial participants, right?

DR. SHAPIRO: Correct.

DR. MIIKE: Okay.

DR. SHAPIRO: Correct. And what is exactly owed is to be negotiated. Exactly.

PROFESSOR BACKLAR: Through prior agreement.

PROFESSOR CAPRON: To say that the strong one -- to me the strong one also has to then lead to negotiation. It is whether you start off with a strong presumption that that would be the right thing to do.

DR. SHAPIRO: What would be the right thing to do?

PROFESSOR CAPRON: No, to provide --

(Simultaneous discussion.)

PROFESSOR CAPRON: To provide those things

which during the trial have proven to advance the health of the participants in the trial, that there is some --

DR. SHAPIRO: Free of charge indefinitely.

PROFESSOR CAPRON: There is some ongoing -- and that the -- I mean, I do not think it is impossible to say the exact terms of those are subject to the constraints of the ability of the sponsor to provide that.

As you say, some sponsors may not be able -- but there is different -- to me, that I though -- the real contrast with what I thought you agreed with Bette that there was a different way of going about this, which basically says the important thing is to negotiate these points out in advance.

DR. SHAPIRO: Correct, I agree with that.

PROFESSOR CAPRON: But that does not start off with a presumption that you ought to be providing it.

I mean, that seems to me a legitimate position that is an alternative. If we are all saying, no, there is a presumption and it is just a matter of negotiation then we are very close to what was already here. It is just a matter of moving --

DR. SHAPIRO: My own view is that we -- the reason we cannot vote on that is there is really no distinction here because if one does not specify

time, amount and a whole bunch of other things there is no obligation here.

PROFESSOR CAPRON: But we -- Harold, at other points I think we get to a point as we were just talking about the last set of recommendations, we try to set out criteria which someone will use in judging whether or not the outcome of a process is acceptable.

But we -- so we -- you could -- we provide an ethical stance from which you could look at a situation and say they met their ethical obligations or they did not. That still recognizes that it is subject to negotiation, judgment and individual determination.

There is a different view which is that this is just a matter that ought to be thought about and negotiated.

DR. SHAPIRO: Okay. I do not -- okay. I do not understand it but okay.

DR. MIIKE: What I am understanding us to vote on, let me just jump to 4 and it makes it clearer.

In 4 I would say that we have an obligation to trial participants and the negotiation is over whether -- what the price is and how long the time is but there is an obligation to provide something.

Whereas in the host country's inhabitants

the only obligation is to have a negotiation whether anything is going to be done about it. And I think that is a positive point in the sense that it raises the issue explicitly whether or not they actually do something about it.

So in the Recommendation 2 the distinction to me is about whether they are going to negotiate about some kind of benefit to be determined or whether they are going to negotiate about whether there is or not a benefit.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I think right from the beginning of this report we articulate as a fundamental principle that one ought not be conducting a trial in a population unless there is reason to believe that if successful the benefit will accrue to that population.

DR. SHAPIRO: Right.

PROFESSOR BACKLAR: Right.

MR. HOLTZMAN: So I think what we are trying to do here is state the presumption -- to start to flush that out. Okay. If it is successful what does it mean for that presumption to be fulfilled?

So, therefore, I think we can state it in terms of there should be a negotiation but there is presumption that if successful it will be made available in some reasonable time frame in some

relevant way and that people need to try to figure out how to do that.

So, therefore, I think that is a little more -- I understand your logical point, Harold. You are saying, well, it is just negotiating -- if you have not specified any parameters it is all in negotiation.

DR. SHAPIRO: Right.

MR. HOLTZMAN: But I think one can say -- but you are saying it needs to be negotiated as opposed to just saying it is irrelevant and I think that is the presumption we are trying to establish.

DR. SHAPIRO: Well, let's try to actually develop some actual language here rather than try to -- we all have a different kind of sense of what the language is so let's actually try to develop some language and we will see how we feel about it.

MR. HOLTZMAN: I also think that is what -- that again ties back to why certain forms of recompense are not appropriate because the precondition that it has to be fulfilled is that the stuff will be made available, that is why you are testing it in this population.

DR. SHAPIRO: Okay. We are going to have to break now and let's try to reassemble at 1:00.

(Whereupon, at 12:40, a lunch break was taken.)

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