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

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W O R K I N G L U N C H

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

CHAPTER 2 - INFORMED CONSENT

PROF. CAPRON: Let's turn to our brief discussion of the alternative language for the Recommendation 5 in Chapter 2, which we left off with yesterday.

Ruth and her team, in conjunction with Jim and Bernie, developed alternative language, which, as I understand it, comes after the first sentence.

Is that correct, Ruth?

DR. MACKLIN: Yes.

PROF. CAPRON: So let me read that for us and for the record.

It would now read: "Researchers should use the same procedures for recruiting men and women and obtaining their informed consent to serve as research participants. However, if (a) research on a common serious health problem that affects only women could not otherwise be done in the host country and (b) inability to do that research would have the result that potential substantial benefits of the research would be unavailable to all women in the country, their local custom may be adhered to."

And I suppose the implicit statement that is

intended there is that the local custom is one of not treating women and men the same in the recruitment.

The next paragraph says: "Researchers must provide evidence that (1) it would be impossible to conduct the research under the conditions stipulated in this recommendation; (2) failure to conduct this research would probably deny its potential benefits to women in the country; and (3) measures to promote or respect the woman's autonomy to consent to research are undertaken to the extent that this is possible."

The proposal is open for discussion.

Let's not worry about the language as such the thrust of it.

Yes?

DR. CASSELL: Just for clarification. Does that mean that if a serious health problem affects both men and women, this does not apply or that a serious health problem affects the population generally and would have to be done with men only?

PROF. CAPRON: Well, I would read this to say that if you could get results that are applicable to the women in the country by doing research on someone else, namely women in another country or men in that country, then you would not do the research in the waived fashion, that is to say you would not recruit

women by going to their husbands. It would exclude them as a research population.

Is that a fair --

DR. MACKLIN: Yes.

PROF. CAPRON: I did not rehearse this answer with Ruth so if that is the correct answer in her view --

DR. MACKLIN: Yes. I mean, it would certainly allow for, or result in, the exclusion of women from studies but it would not prevent them from having the benefits ultimately, because if the study had to be conducted in that country, in order to get regulatory approval in that country once the drug were approved, then it would be available for men and women.

So if it would end up excluding women from the study, even though on other grounds we like to see men and women represented in studies, it is the lesser of the two evils.

PROF. CAPRON: I have David and then Alta.

DR. COX: Well, we can --

PROF. CHARO: It is just a clarification.

DR. COX: Go ahead.

PROF. CHARO: Ruth, I am also assuming that in addition to this there is the additional provision -- I forget if it was in this recommendation or in a

different one -- that said nonetheless nobody can consent for somebody else and force them into a study, including her husband.

DR. MACKLIN: That is already in the first part of this.

PROF. CHARO: Right. I just wanted to make sure I remembered that correctly.

DR. MACKLIN: This, however, follows the existing one that says nobody can affirmatively put someone --

PROF. CHARO: That is fine. Thanks.

Sorry, David, I did not mean to take your place.

PROF. CAPRON: Well, while we are waiting for David, do we have Trish or Rhetaugh on the phone at the moment? Okay. I just wanted to know if they are here.

As of now, I have to note that we are in a discussion mode. The Commission meeting as a Commission meeting has come to a close with the absence of a quorum of our members. We are no longer an Advisory Committee as of this moment. We are just having a discussion, an open discussion, but one without a quorum.

David?

DR. COX: So should I talk anyway?

PROF. CAPRON: Yes.

DR. COX: So I would like to say that I am in favor of this language but I would like to ask that it be extended more generally. My view of this point is one that Ruth just, I think, nicely articulated, which is that this is basically exceptional language to avoid something that would be worse if the language was not there. And that this is in the context -- written specifically in the context of women.

Eric alluded to it. I think that there is going to be all sorts of similar contexts, where in the international setting our U.S. standards basically are not able to be met specifically as written, and so what we are -- I would like to endorse this but extend it passed the situation of just women or women's issues. That is not to say that I do not think the issues of women are important but I think that there is going to be numerous other situations that are exactly analogous to this.

And I am probably not being very clear. For me personally what I will do -- and that is what I did yesterday was vote for what was proposition 3, which was in order to uphold the basic principles of human subjects research in the U.S., I would personally uphold the -- even though it would mean that certain

types of research could not be done internationally.

But I see this as a way of saying we will still uphold them but that there is some flexibility in them to allow research that could not otherwise be done to go forward.

I will just say from an ethical point of view, though, how you weigh that -- the importance of that research over the ethical principles is one that is troubling me and how you weight them, you know, is always tricky but this does leave a trap door to make that at least a possibility, which we did not have yesterday, and I am very much in favor of that.

But I would not like it to be simply in the context of women's issues by itself.

PROF. CAPRON: Steve?

MR. HOLTZMAN: David, I do not think this is about importing U.S. notions about the regulation of research elsewhere because to my knowledge there is nothing in the regulation of research in the U.S. that says anything like this. Is that correct? Right?

So I want to -- I would like to conceptualize the problem somewhat differently, and it is going back to a formulation of Alta's yesterday. All right. And that has to do with whether or not with respect to any given sphere of human activity of which one such sphere

is research, we wish to be making a statement about whether we wish to conduct that in a way which can be compilcit in the violation of certain rights of people, in particular in this case women.

DR. COX: Perfect.

MR. HOLTZMAN: Right? Which we feel is in some sense a universal standard. All right. So the premise here is that there is a universal standard, that certain societal practices violate that standard, that we do not wish to be complicit in contributing to the violation of that standard, and that this is a particular area of human endeavor in which we wish to make that statement.

DR. COX: Okay.

MR. HOLTZMAN: All right. As opposed to -- because we are dealing with research. If we were dealing with commerce we could be making similar sorts of things. Right?

DR. COX: Yes.

MR. HOLTZMAN: Then the question is -- if you frame it that way, you can frame the question "is do we think that is important here, and subject to what conditions?"

And then the second is: "do we want to make a particular point about that with respect to a

particular area of oppression only that's relevant to women, or do we want to make it with respect to oppression per se?" That is the way at least I would lay it out to myself.

DR. COX: And that is because you are more an expert in this area, so I actually defer to you in that. I think I am happy --

MR. HOLTZMAN: It is not a question of expert. That is just the way I think about it.

DR. COX: No, but I am happy. It is a more actually rigorous explanation about it and I am happy with that.

My only problem is this question of universal, and that is one that I just wrestled with for myself, but certainly more global than just the U.S., I agree.

PROF. CAPRON: I hope that the discussion, which we are now going to bring to an end on this point, has been useful to Ruth and Alice because if others agree with the exchange that David and Steve just had, it does affect the way this recommendation is presented and the rationale that is used.

MR. HOLTZMAN: And that is exactly what I was going to, Alex. If we are going down this path, I think one has to be laying out that kind of -- the rationale for why this sphere of activity is when we

are choosing to make this statement, and why specifically we are doing it with respect to a particular class of oppressed people.

DR. CASSELL: And the class is married women. It is not women. The class is married women.

PROF. CAPRON: How about unmarried women and their fathers?

DR. CASSELL: Well, I do not -- that is one of the things I raised before and that did not come up, you see, unmarried --

PROF. CAPRON: Not minor women.

DR. CASSELL: -- women and their mothers.

PROF. CHARO: I would love to start first with married women but then acknowledge the comment that this seems to have something in common with the next two recommendations, which was pointed out by multiple people yesterday.

The next two recommendations deal with family and the implication was non-husband family, and then village leaders and community leaders, et cetera.

It strikes me that we do not have time scheduled to discuss, but could easily choose to discuss, whether we wish to follow exactly this model as a more general rule in which what we say is: “U.S. sponsored researchers should approach subjects

themselves, and if the subjects want to involve third parties, that is up to them." And that there will be a couple of -- there will be some occasions where the research cannot be done that way because of local custom and that we should not abide by that local custom unless these conditions are met and that we could apply it across the board to all third party situations.

We have never discussed it. We acknowledge that there are some differences among them, so I am not proposing it for a debate right now, but I am just saying that that is something that is still left out there for those that want to be consistent.

But for the moment I think limiting this to married women would be a great start.

PROF. CAPRON: Ruth?

DR. MACKLIN: It is also without having to elucidate it in the text, which we could, if necessary, point out that the concern is those conditions or diseases or circumstances that affect only women such as a whole array of things in reproductive health and, I guess, breast cancer would be another, and curiously enough many women in developing countries -- in fact, in almost all developing countries there is very poor access that unmarried women have to those reproductive

health services anyway. So to deny those particular individuals entre into research is not -- I mean, it is just a special trivial matter.

So I think we can try to deal with this in the context -- it is certainly different because if we are talking about other research that affects men and women, it is not that the entire class of women or group of women in any given society would be denied the benefits of research if, for example, they are developing a new contraceptive or a microbicide or something important like that.

DR. COX: So, Alta, I would just like to say that we cannot do it now but I would like to have further discussion on exactly this point in a more general way because I think we have not discussed it.

PROF. CHARO: If there is not opportunity before the public draft goes out, there is certainly going to be opportunity after it comes back.

DR. COX: Exactly.

DR. MESLIN: I mean, if you want to offer views informally over, you know, e-mail, you are welcome to do that, but this is the time to raise an issue if you want to raise it.

PROF. CAPRON: It has been raised in your absence.

DR. COX: I just did it.

DR. MESLIN: Okay.

DR. COX: It was raised, Eric. It may not be very articulate but it is my effort to raise it.

DR. MESLIN: Okay. Got it.

DR. COX: Not in the framework that Steve just laid out, but in these different settings.

PROF. CAPRON: As I understand the framework issue, there are two aspects to it. One is that this is not an exercise in American standards being used to try to change cultures abroad, but rather American researchers and American research companies following certain precepts which are widely, if not universally, held, and not engaging in research where they violate that unless certain special findings have been made as to the necessity of doing so.

The second question that was raised is to what additional categories of prohibited research would this kind of presumption overcome by special circumstances potentially apply? I think we can ask -- the first question we will tell -- when we see the next draft. Does the text explain it in a way that is satisfactory.

The second question we can all ask ourselves and perhaps Alice and Ruth will ask themselves as well: is there any way of looking at any of the other

recommendations that might get into this and asking the same question?

Earlier Eric announced that we would now, after this brief discussion of Recommendation 5 in Chapter 2, look at Dr. Shapiro's memo to us as an organizing framework for our discussion to make sure that the concerns that he had raised have been addressed.

Eric, since you were the one who, in effect, are the conduit to that, I turn it over to you.

DR. MESLIN: Certainly. Before we do that, I just wanted to be clear because I know there was a little bit of work done on Recommendation 11 in Chapter 2. We discussed yesterday 8, 9 and 10, and then there was some discussion about whether it would -- 11 would be dropped or changed or modified. Ruth reminded me that they have done a bit more work on 11.

Did you just want to say a word about that?

DR. MACKLIN: Yes. Just a word. What we did was "delete" a couple of words that seemed to be the offending words that created a lot of difficulty. So if you look briefly, it is on page 32, Recommendation 11.

We have deleted the words in Line 19, "during and after." Just deleted those words so the

recommendation now reads, "Researchers should develop and implement a process of community education and consultation to take place before the research begins." We added the word "begins."

Everything else is left the same. Since we understood that there was some confusion and uncertainty or lack of --

PROF. CAPRON: I think, Ruth, I would restate the consensus that we had, and others can correct me if I can have everyone's help on this. The sense was that we did not need the first sentence of 11, that that would be taken up under a revised 9. If we say, "Researchers should consult with community representatives in developing effective means to communicate the necessary information," and that one of those means might be face-to-face education of subjects, another might be pre-education of the community from which subjects would be drawn, about any number of topics, depending upon that community's consultation.

And that both 9 and 10 could benefit from the thought, which is encapsulated in the second sentence, that the steps that will be taken to implement that recommendation be made apparent in the protocol and that the IRB assure itself that the process is adequate

to the situation. So we did not see a need for a separate 11.

Is that okay?

DR. MACKLIN: Yes. I do not want to go further with that now. It is not important.

PROF. CAPRON: Okay. I am sorry that did not get communicated.

DR. CASSELL: So it is left with no second 11, no 11?

PROF. CAPRON: No separate -- that was our conclusion at the end of the day yesterday.

DR. CASSELL: Yes.

PROF. CAPRON: And, unfortunately, I did not realize that Ruth and Alice were going to work on that and they had said before that they would just consult the transcript since they were not here during that part of the discussion.

Eric, it is in your hands.

DR. MESLIN: Okay. Well, no, we are going to essentially spend as much time as everyone has. I really want to let Ruth and Alice go at this point. You have seen Harold's memo.

I think, Ruth, you have indicated that a number of the concerns that Harold had raised, certainly in one and two, et cetera, were already

covered.

So really the point of the memo where Harold has comments begin on page 3 of his memo.

DR. COX: When was it covered?

DR. MESLIN: I am sorry.

DR. COX: I am sorry. When was it covered, the first part of this?

DR. MESLIN: Well, I was speaking quickly. In the revisions to 1 and the discussion we have had in 2, and now what I think Ruth has suggested we are going to discuss for 3, which is where we are going to essentially -- we have now finished and we are going to go to 4.

Am I confusing you, Steve?

MR. HOLTZMAN: No, do not worry about me.

CHAPTER 3 - CHOOSING A STUDY DESIGN: ETHICAL AND METHODOLOGICAL CONSIDERATIONS

DR. MESLIN: We have done Chapters 1 and 2. We have had a discussion about the recommendations in 2. And now we have to spend what is essentially the working lunch part talking about Chapter 3. Then we will come to Harold's concerns about 4 and 5.

I was not really going to lead the discussion because the working lunch was supposed to focus on Chapter 3, which is where I believe we are now. Is

that fair? All right.

So in front of you should be --

PROF. CAPRON: Well, I sort of share --

DR. MESLIN: Steve's concern.

PROF. CAPRON: -- Steve's concern. I just -- could we just have a word about how and where the bullets --

DR. MESLIN: On 1 for 2(a)? Okay. I am sorry.

PROF. CAPRON: -- under 2, the first couple of bullets there are addressed because those are themes that Harold has sounded before.

DR. MESLIN: Okay.

PROF. CAPRON: And if Ruth and Alice feel that they are fully addressed by either what we have seen or what they have revised since we have seen it --

DR. MACKLIN: These are comments that do not refer to any particular chapter but maybe thread throughout the report. Most of these items, not all, but almost all pertain to Chapter 4 because that is where most of this discussion takes place. That is where patents takes place, that is where pharmaceutical industries are discussed, that is where --

PROF. CAPRON: So we will take it up when we get to 4 then.

DR. MACKLIN: These are -- even though they are more general than the specific points he makes line by line on Chapter 4, that is really what they deal with.

Now the only exception to that is the discussion we had yesterday when everyone cheered Alta when she volunteered to write something that would be included in Chapter 1. So that is still in abeyance but what I see us doing now once we get to Chapter 4 is these concerns of Harold's are in addition to the ones that he specifically identifies in Chapter 4 should be part of that discussion.

PROF. CAPRON: Okay.

DR. MESLIN: The only thing I should add, and in respect of Alex's raising this, is in Chapter 1 some of these issues are brought -- introduced for the first time. It is in bullet 2(a) -- there is no (a). 2 -- the first bullet of 2. And there is not a recommendation that Harold is asking for the Commission to consider. He just gives his own views that we focus on ethics of research in general, independent of sponsor.

And I think what you can read from that is should the discussion not make a distinction early on between industrialized pharmaceutical sponsored

research versus industrialized country, Federal Government, sponsored research. And that is an open question that he has asked.

His points in the second bullet flow in the same way but you are quite right, it gets picked up mostly in Chapter 4.

DR. BRITO: I think that first bullet does need to be discussed becasue that is -- it is introduced in that one paragraph in the first chapter and I am not sure that we finally concluded what we were going to do with that.

PROF. CAPRON: Well, Ruth had suggested to us that we sort of await to see the language that Alta comes up with and that they use in revising the chapter.

DR. BRITO: Okay.

PROF. CAPRON: So I think that the suggestion that we mostly deal with this where it is the central focus in Chapter 4 is probably a good one and we just have to make sure we turn to it then.

Are we comfortable then? So we are now going to turn to Chapter 3.

DR. MESLIN: Steve, are you comfortable with that as a strategy?

MR. HOLTZMAN: I was not here when you talked

about Chapter 1, so it is very hard for me to comment and I do not want send you guys backwards.

PROF. CAPRON: Thank you. We can do it well enough on our own.

(Laughter.)

CHAPTER 3 - CHOOSING A STUDY DESIGN: ETHICAL AND METHODOLOGICAL CONSIDERATIONS

DR. MESLIN: I will continue to be Harold's agent at the appropriate time but right now we should go to Chapter 3 and what Ruth and Alice and Elisa have done.

DR. MACKLIN: Are you waiting for me?

PROF. CAPRON: Yes.

DR. MESLIN: Yes. You are the Ruth.

DR. MACKLIN: Well, there are one major -- since you saw Chapter 3 -- one major change and then a lot of changes -- smaller changes in the text, mostly supporting the major change. So you should have now on the table what is called Chapter 3 recommendation. Chapter 3 is in blue. Maybe not everybody's is in blue. It says “recommendation.”

Now if you want to see what this replaces, please go to the end of Chapter 3 of the version you have and -- by the way, we have already inserted these as discussed yesterday, put these recommendations in

the appropriate place in the text, and I guess I can tell you in a moment where that goes. But right now the recommendation appears on page 40.

This is the second of the two recommendations from this chapter and we might as well look first at the former one which is now replaced. The old one said, "Research --" and by the way, just to remind everyone, we did discuss this quite fully at previous meetings, at least once if not twice.

The one that is now replaced reads: "Researchers and sponsors should strive to --" I am sorry. "Researchers and sponsors should provide members of a control group with an established effective treatment whether or not that treatment is and would continue to be unavailable in the country where the research is conducted."

That is the old one. That is the old one. It is on page 40.

We are replacing that, along with supporting text in the appropriate places, with the one you have in front of you now on the single sheet of paper.

MR. HOLTZMAN: Is there an extra around?

DR. MACKLIN: "Whenever possible, researchers and sponsors should design clinical trials that provide members of a control group with an established

effective treatment. This should be whether or not that treatment is currently available in the country where the research is conducted. In cases in which the study design does not provide the control group with an established effective treatment, the research protocol should include a justification of this design. The IRB should assess the justification provided as well as the ethical appropriateness of the research design."

PROF. CAPRON: Alta?

PROF. CHARO: Ruth, because it has now been two meeting days since I read this, so I am not longer sure I remember what is or what is not in the chapters, do we find in the chapter enough detail about what might be considered an adequate justification versus what might not be considered an adequate justification?

DR. MACKLIN: There is -- I am sorry.

PROF. CHARO: That an IRB would actually know how to handle this and that we also might even achieve some degree of consistency from IRB to IRB in how they handle these reviews?

DR. MACKLIN: I -- there is nothing that would even give a hint about how to establish consistency among IRBs since they remain inconsistent in many

things they do in other areas.

PROF. CHARO: Okay.

DR. MACKLIN: And I do not see how we could even begin to address that problem, which I see as a problem and other people do not.

However, there was not in the chapter you read anything that could support this but there is now, and let me explain just a little bit more. I could actually read aloud the passage. I know you do not have it in front of you but since this was woven into the text --

PROF. CHARO: Okay.

PROF. CAPRON: Why don't you do that?

DR. MACKLIN: I will. This came in response -- this whole change came in response -- you remember we mentioned yesterday that this chapter was sent out to several people for a pre-review before the general public review in order to ensure that it was both accurate and credible, both in the details of the research design as well as to reflect the practices as they ought to be conducted.

And one very thoughtful response -- one very thoughtful response had -- was the basis for this recommendation. This change in the recommendation, along with some supporting text. And since I did this

in red I am just going to look for that supporting text. It will take me one second to scroll through. And this will be the text that for the most part justifies this.

Anybody remember where this was?

MS. PAGE: It is towards the end.

DR. MACKLIN: Yes, it is towards the end. I know it is towards the end. Towards the end.

MR. HOLTZMAN: Around 38.

DR. MACKLIN: Pardon?

MR. HOLTZMAN: Your existing argument is on page 38.

DR. MACKLIN: Okay. All right. Here it is.

And here is the beginning. This begins -- this is a new beginning for the section that begins entitled "Ethical Considerations in the Design and Conduct of Clinical Trials."

PROF. CHARO: Okay.

DR. MACKLIN: It is that section and it begins as follows: "International collaborative research can be thought of as lying somewhere along a continuum. At one end is research in which a sponsor sees an opportunity to get rapid, easy, inexpensive answers to a research question, and then uses the information for its own purposes in the sponsoring country. The other

end is research intended specifically to address a health problem of little or no relevance in the sponsor's country but which is important for advancing the health of people in the host country. These two extremes frame a spectrum of political exploitation and clearly differ from each other. However, both might lead to research that could not be conducted in the industrialized country. An assessment of the ethical appropriateness of a particular study's design should include an evaluation of where it lies along this continuum."

That is the first new material. You know who we can thank for that.

PROF. CHARO: Yes.

DR. MACKLIN: Then there is another --

PROF. CAPRON: Was the language "political exploitation?" Did I hear you?

DR. MACKLIN: I think it did say political.

PROF. CAPRON: What is the meaning of that?

DR. MACKLIN: Presumably --

PROF. CAPRON: You took this whole cloth from someone so it was not a word that you chose? I do not understand "political exploitation" in the middle of that sentence.

DR. MACKLIN: All right. I do not -- we can

come back to the word, Alex.

PROF. CAPRON: Okay. All right.

DR. MACKLIN: The word is not important. We can change the word. We want to get the sense. We are looking for the justification.

The second point that comes in support of this comes later and let me see if I can identify later. It is just before the section that begins "Monitoring the interim results of the study." That is where the recommendation will go and immediately preceding the recommendation is this new text, which I will read.

"It is essential to recognize the tension that exists between the need for a control that has relevance as the optimal baseline against which the new intervention is measured on the one hand and the ethical mandate of beneficence on the other. In addition, ethical review should include an explicit assessment of the appropriateness of the study's balancing of this tension grounded in (1)..." and there are going to be four points here "...(1) an ideal that participants should receive an established effective treatment unless a case is specifically made that the only viable alternative to a lesser level of care is not being able to conduct the study at all or data that will not be useful in advancing the care of people in

the host country." That is the first grounding.

"(2) an explicit prohibition of over exploitation.

"(3) an explicit case that the study lies far from the end of the continuum of overt and obvious exploitation."

And far toward the other end of the continuum of advancing host country health.

"And (4) a clear case that controls are intended to simulate the current state of care in the host locale and thereby serve as a legitimate standard against which the new intervention is measured."

Now those four -- I mean, that is not going to guarantee IRB insurance, but those are the basis. I mean, they provide something like criteria for making those judgments. So it is mostly those two sections which may have to be suitably reworded that are supporting the new recommendation.

PROF. CAPRON: Okay. Discussion?

Alta?

PROF. CHARO: First, thank you because that is exactly what I was hoping that we would find in the chapter because that would fill out what an IRB does.

Perhaps in anticipation of being unsuccessful, I want to reiterate something I said on e-mail when we

first got a chance to react to recommendations.

And that is that there are situations where the best science would be done by using either a placebo control or a control that represents a rather ineffective therapy even though it tends to be the one that is provided locally.

And I had written that I thought that in the end that can be justified but that there will be situations in which, as a preliminary step, one might choose to test a new intervention against a gold standard or established effective therapy in order to get a first order approximation of whether the new intervention even has a hope of being useful.

And if it indicates -- if that experiment indicates that it might, only then move to the situation in which control groups have to be given placebos or manifestly ineffective therapies.

Not every time will this be the case and it has cost in terms of doubling the number of study subjects perhaps so there are balancing acts to be done here.

But I did not want to at least put out on the table the idea that the first claim that science is best served by a placebo control or by an ineffective therapy control should not end the debate when there

are interim measures that could be explored that would effectuate a somewhat different balance along the way, and I think that is consistent with what you were just writing in those criteria but not necessarily so obvious that an IRB would feel it is necessary to explore those options.

PROF. CAPRON: In order to have an orderly discussion, I think Alta has put forward a suggested addition to the points, and I would like to know if we can discuss that before moving on to some new thought or some other reaction to what is there.

Are there comments on her suggestion?

Yes, Steve?

MR. HOLTZMAN: I read that as consistent, though not explicit. The problem I have with it, which is the problem I had when I read it on your e-mail, is I felt totally unable to know whether or not what you were saying was true or false so to speak in terms of clinical trial design so you were making a claim about often it can be the case that one can proceed this way.

I personally do not know that that is true, how often that is the case, what are the conditions under which it would -- it is true and I felt like it was taking me into an area of expertise about clinical trial design that was not the business of an ethics

commission.

Whereas what I just heard Ruth reading is more up our alley.

So that was just my basic reaction to it.

PROF. CAPRON: Ruth?

DR. MACKLIN: Let me just respond. I mean, I am probably less of an expert than Steve on this but -- on trial design. What you propose might be ethically superior in that it is a kind of feasibility study but what we know about these designs, and I am going to turn to Elisa, is that any equivalency study, that is something that uses the effective established treatment and not placebo is going to involve many more study participants, it is going to take much longer to do, and it is going to be much more costly.

So if one of the priorities and one of the very reasons for using placebo designs anyway is to do it more quickly in the hope of getting an answer, and thereby provide to the population an effective treatment, that whole thing gets delayed with this mechanism and one might even argue that on utilitarian grounds ultimately there is a greater delay because first you do this very long established effective equivalency study, then turn to the placebo controlled study in which you have actually taken much longer than

just initiating the placebo controlled study.

PROF. CAPRON: Alta?

PROF. CHARO: Yes. I am sensible to both of these concerns, although on the study design I think the presentation we got three years ago indicated that this is one form of study design that has limited usefulness in terms of the data it generates. And that is why I was never suggesting that it ought to be the case that you have to do this before you can move to a placebo or an ineffective treatment as the control.

I was simply proposing that IRBs have to at least ask if this is, in fact, a sensible intermediate step. For some diseases, with some populations, with some numbers and some budgets, it may be a reasonable option.

I guess what I am trying to get at is that I think of placebo as an ineffective therapy control as something that should be acknowledged as a last resort when you need it in order to accomplish your primary goal, which is scientifically defensible, efficient movement towards a benefit -- a hoped for benefit but that it should not be a first resort. Other options should be explored and discarded first. That is my only goal in proposing this.

PROF. CAPRON: I am now a little confused by

your suggestion because if the notion is that you would provide effective, established treatment as the control, that I take to be the starting point of all of this discussion. Is that not correct, Ruth?

DR. MACKLIN: Yes.

PROF. CAPRON: So that if that is the reason for doing it then what you have said is just what is in the recommendation here. That is to say you would do that but you have a however, a waiver if the following -- if certain criteria are met.

I thought you were suggesting something else when I first heard your suggestion which is before researchers engage in a situation in which they are exposing the control group to the new intervention -- excuse me, the active group to a new intervention of possibly unknown efficacy and maybe not as great efficacy as they would require to do the study in the United States where they would have to be comparing it against the gold standard, and the control group to nothing, you ought to have greater assurance that the intervention has some likelihood of working.

Was that not what you were trying to say?

PROF. CHARO: It is but now I am completely confused.

PROF. CAPRON: Okay. Well, if that is the

case, if that is the case it seems to me what you are talking about is saying, "Gee, preclinical studies are not adequate."

In other words, you want some higher level of assurance in this circumstance because the tendency would be to say since we are comparing this to the nothing that people usually get, there would be some risk of being willing to test things of marginal utility.

The reason I thought you were suggesting, therefore, to do the other was let's have a run against -- let's do some preliminary work to compare it to the gold standard.

But why do you need the gold standard at all there? I mean, why aren't you saying that this is just a form or sort of a more elaborate Phase II where you are giving a limited number of patients something, not to prove it as you would in Phase III in a controlled clinical trial, but simply to measure and have some, not conclusive, but supportive data that it has some effect on a metabolic or other basis that you are -- in other words, you are just --

PROF. CHARO: So you do it without any controls at all?

PROF. CAPRON: You do it without controls

because you are not trying to show that it is better than anything. You are just trying to show that it, indeed, has some of the effects that you hope to accomplish and that seems to me to be sort of a boosted up Phase II. And that kind of suggestion, Alta, actually does appeal to me. The sense that we want to guard against people saying, "Because the study is comparing this to nothing, we do not have to have very strong evidence that it will have any effect," and we will go ahead and do a study and then it turns out that, indeed, it is useless and you have put a lot of people through a study.

Granted the controls got what they would have gotten anyway but they have been put through a study, you know, and it is just you are using people.

So you want to say just to guard against that slight inclination, we ought to -- we ought to insist that we go through a process, a Phase II process in which we have some stronger indications that this intervention will, indeed, have some effect.

PROF. CHARO: I would take that as a friendly amendment although I would still say that as with my original notion where I was assuming controls had to be in place, I would not want to suggest that this is required under all circumstances but simply that it is

something that IRBs should be urged to explore before leaping to the placebo control.

PROF. CAPRON: I entirely agree with that.

PROF. CHARO: Then I have nothing further to say.

PROF. CAPRON: And I would ask that we send this particular notion in memorandum style, as it were, so they do not have to re-read the whole chapter, to the people who commented and have them -- those who are familiar with research design and FDA approvals and so forth, have them comment whether they think it is appropriate or unnecessary, already accomplished by some other means.

Could we do that, Ruth?

DR. MACKLIN: Well, if Alta is willing to write it up.

PROF. CAPRON: Okay.

PROF. CHARO: Sure. I mean, I will be happy to do that.

DR. MACKLIN: I still think, though, it is going to be viewed as highly unrealistic and I guess the one other -- the one other problem, Alta, though, is that putting that burden on the IRB puts the IRB in a position of telling researchers how to design their research, which first of all is a -- the research comes

to the IRB already designed.

It may come from an NIH design in a multi-center trial. It may come from an industry sponsor trial. So sending the researcher back at that point is a little bit late in the process of protocol development so I think if you want to write it up you have to address those questions, too, and the appropriateness of the IRB at that fairly late stage, especially if somebody is going to submit something for an NIH grant that is quite close to the deadline, the IRB says, "Oops, we want you to go back and try to design an equivalency trial."

So all those things I think have to be taken into account.

PROF. CHARO: That is fair, but if the bottom line message that gets through is that before studies are designed everybody in the research world is on notice that all options will be explored as a way to minimize the number of times we have to go into these kinds of controversial placebo controlled trials to look at locally viable options.

Then slowly the research community will begin to make their designs with that in mind, use it where appropriate, explain why it is not appropriate, and the many circumstances where it is not, and the problem

will slowly iron itself out.

PROF. CAPRON: Now I had Arturo and David who were deferred while we discussed Alta's point.

DR. CASSELL: I just wanted -- I mean, there has been so much --

PROF. CAPRON: I have Arturo or --

DR. CASSELL: No, there has been so much conversation --

PROF. CAPRON: Yes.

DR. CASSELL: -- since Ruth read those that the wording has gotten lost to me so I would not mind if she would read them once more.

DR. BRITO: And my comment has to do with that first sentence so I would like to hear it again.

DR. MACKLIN: Is this -- this is the -- are you talking about the recommendation itself?

PROF. CAPRON: No.

DR. CASSELL: No.

DR. MACKLIN: The justification?

DR. CASSELL: The justification.

DR. MACKLIN: Okay. The first one. I must apologize profoundly here. I misread a word. The word that came out as political was suppose to be potential. Okay. So that settles that one. I will read both of these passages again.

The first passage appears after the heading, immediately after the heading, "Ethical Considerations in the Design and Conduct of Clinical Trials."

PROF. CAPRON: Slowly and with feeling.

DR. MACKLIN: Not slowly. I am going to move on.

"International collaborative research can be thought of as lying somewhere along a continuum. At one end is research in which a sponsor sees an opportunity to get rapid, easy, inexpensive answers to a research question and then use the information for its own purposes in the sponsoring country. The other end is research intended specifically to address a health problem of little or no relevance in the sponsor's country, but which is important for advancing the health of people in the host country. These two extremes frame a spectrum of potential exploitation and clearly differ from each other. However, both might lead to research that could not be conducted in the industrialized country. An assessment of the ethical appropriateness of a particular study's design should include an evaluation of where it lies along this continuum."

Now that is just an introduction to the whole section and the specific justification that comes

immediately before the recommendation is as follows:

"It is essential to recognize the tension that exists between the need for a control that has relevance as the optimal baseline against which the new intervention is measured on the one hand and the ethical mandate of beneficence on the other. In addition, ethical review should include an explicit assessment of the appropriateness of the study's balancing of this tension grounded in..." and now there are four items "...(1) an ideal that participants should receive an established effective treatment unless a case is specifically made that the only viable alternative to a lesser level of care is not being able to conduct the study at all; or data that will not be useful in advancing the care of people in the host country;

"(2) an explicit prohibition of overt exploitation;

"(3) an explicit case that the studies lies far from the end of the continuum of overt and obvious exploitation and far toward the other end of the continuum of advancing host country health;

"And (4) a clear case that controls are intended to simulate the current state of care in the host/locale and, thereby, serve as a legitimate

standard against which the new intervention is measured.

PROF. CAPRON: Did you do the translation from the German yourself or was that a --

DR. MACKLIN: We may have to break up a few --

PROF. CAPRON: -- it is a very --

PROF. CHARO: It is true that the person who wrote it is not a Native American speaker.

PROF. CAPRON: No, that is -- in any case, a lot of complex ideas is what I am trying to say. It is like listening to the Kant. Okay.

You wanted to focus on that first sentence of the second --

DR. BRITO: Of the second --

PROF. CAPRON: Yes, I thought so.

DR. BRITO: Well, when I heard it the first time and maybe now hearing it again, it is rather complex but what I heard and what I worry about is the implication -- and maybe it is because of the recommendation -- reading the recommendation first. But the implication that a placebo controlled trial is necessarily an unethical or creates that tension because sometimes doing a placebo arm when there is no effective treatment is the most ethical thing to do so I do not know if I am hearing it right. I have to see

it written down.

DR. MACKLIN: But that is -- Arturo, that is handled elsewhere in the chapter. I mean, there is a section. I mean, you cannot say everything in one sentence.

DR. BRITO: No, I understand.

DR. MACKLIN: There is a section that discusses placebos when they are clearly justified, when they are clearly unjustified, and maybe we could find the page --

DR. BRITO: Okay. No, that is fine. But then that first sentence -- but the way the first sentence is written, what I am hearing is this tension and I am imagining this tension that is so extreme that it implies that the placebos are at one side. Am I hearing this wrong?

PROF. CAPRON: Why don't you read that sentence --

DR. BRITO: If you read just that one sentence -- the first sentence again.

PROF. CAPRON: The first sentence of the second --

DR. MACKLIN: "It is essential to recognize the tension that exists between the need for a control that has relevance as the optimal baseline against

which the new intervention is measured..." That is the sound scientific criterion. "...on the one hand. And the ethical mandate of beneficence on the other."

And what beneficence simply means here is --

DR. BRITO: Okay.

DR. MACKLIN: -- if there exists an established effective treatment, you are optimizing beneficence to give that to the people in the control arm.

So the tension is between the scientific reasons for the placebo control on the one hand and on the other hand the optimal beneficence, which is to try to give everybody something beneficial when it exists even though there are these other short-comings.

PROF. CAPRON: Well, isn't the tension with beneficence beyond that though because it is the question of giving the people who are getting the active intervention, which is on its face a lesser intervention, and intended to not believe to be as effective as the gold standard in the U.S. as the effective established treatment in the U.S., so that the beneficence issue applies to them as well . Is that right?

DR. MACKLIN: Well, yes, it does but I mean we -- you cannot get into the nuances of beneficence. The

other part of the beneficence is, of course, it is the benefits to the research participants and to others. And since the benefits are hoped to accrue to the entire population, which they would never get from the established effective treatment because it is unaffordable or it cannot be introduced, then you have got to weigh that part for the beneficence, too.

I mean, if you want all that analysis in here, we can do it, or we can change the words so we do not have to -- it does not --

PROF. CAPRON: Well, I just wonder if that encapsulation of the word "beneficence" rather than spelling out -- I mean, when you spelled it out it was to me easier to understand than the code word was.

DR. MACKLIN: Yes. Let me only say --

PROF. CAPRON: Which brings in more and you do not want it here.

DR. MACKLIN: Yes, it brings in -- it brings in but it is in the preceding paragraph, Alex.

PROF. CAPRON: Oh, okay.

DR. MACKLIN: You know, we are not reading the whole thing. The preceding paragraph begins by saying --

DR. CASSELL: Well, can't we print this out so we can look at it, you know, instead of doing this? It

is in the preceding paragraph -- it is in this -- I mean, this is a crucial wording.

DR. MACKLIN: Well, the preceding paragraph -- I am sorry. The preceding paragraph is the text you have. It is the text you have.

PROF. CAPRON: Page 48.

DR. MACKLIN: All I did -- wherever it is that starts "The relevant principles are familiar ones," and then it describes beneficence. It says maximize them. I mean, all of that text that is in there is -- was there before.

In the interest of time and also not printing out 40 pages multiplied times everybody in this room --

DR. CASSELL: Just what you have written, that is all we are talking about, just the new material.

DR. BRITO: Just the last --

PROF. CAPRON: Well, look, we are -- I think the purpose now is to see whether the direction which has been sketched here by the changes that Ruth is talking about we are comfortable with.

And I realize that we cannot endorse it until we have had a -- particularly complicated language until we have had a chance to read it.

We are not in session now. We are having a discussion now so nothing we can do -- we do not need

the text if it is now going to be complicated and time consuming to print it out.

I mean, ideally I agree with you, Eric, but I think it is less than ideal.

Steve, and then Bernie.

MR. HOLTZMAN: So I take the suggestion on the table to have two essential parts. The first I very much like, which is introducing that we need to look at why the study is taking place because a lot of the discourse comparing the AIDS trials to what the Nazis did totally left out that these were trials that were trying to do something to benefit the local population. So that formulation of take a look and why is this thing taking place, for whose benefit before you start your analysis, I think, is absolutely essential and is very good.

The second then is this weighing off of -- in shorthand -- the demands of beneficence versus the ability to actually conduct this in a way in which it helps the people.

So the question I would have is as you are thinking this through your paragraph that is preceding it, right, where it starts with "The relevant principles are familiar..." one -- isn't -- I think you need to look at it again and whether the way you have

structured it leaves room for a “however” or not.

I am not sure -- I think it is going to take -- you just need to test it. Okay. Because you came out really, really strong here in support of the other -- the way we had it before.

And then some other time off-line we can talk about whether in a trial, for example, the same principle of beneficence requires you, for example, to feed people who are malnutritioned or do not have enough food because I do not understand -- that is something -- that is just a personal -- something I have never understood about why beneficence drives you to this one particular action.

PROF. CHARO: Eric?

DR. MESLIN: I am going to insert myself to speak for Harold when there is relevant items. Harold made a note on that same page 38 -- I mean, in text, not in his memo, marked up text -- that may speak to Steve's issue. It is the last -- however, people's pages are printed out. The sentence that begins, "Therefore, the principle of beneficence is defined, et cetera, et cetera, and widely recognized."

Harold wanted to add before the word "entails" -- do you see where I am?

DR. CASSELL: Yes.

DR. MESLIN: "Could be interpreted by some --"

DR. EISEMAN: Just to mention that we actually made some changes in this paragraph that Ruth has not mentioned yet and one of those changes is we deleted that last sentence that starts with "Therefore, the principle of beneficence is defined in the Belmont Report."

There is also one other sentence that was deleted which in my version starts on line 20 that says, "To withhold an established effective treatment from a control group even when that treatment is not available outside the trial violates the principle of beneficence."

DR. CASSELL: Yes.

DR. EISEMAN: That sentence also was deleted. So we have at least tried -- and we can look at it again but have tried to soften the language in that paragraph to make it consistent with our recommendation -- revised recommendation.

DR. MESLIN: I withdraw my editorial comment on Harold's behalf. I have others but not at this time.

PROF. CAPRON: Thank you.

DR. BRITO: Eric, which of Harold's points were you going to refer to just to make --

DR. MESLIN: What I was going to say was the softening comment. It was to modify the "entails an obligation" to "could be interpreted by some as entailing an obligation." It is not simply a linear. It is a Haroldism that you are all very familiar with but in this case it would have been relevant but now it is no longer relevant.

MR. HOLTZMAN: Thank you for that irrelevance.

(Laughter.)

DR. MESLIN: Oh, it is nothing.

MR. HOLTZMAN: We are in conversation without accession.

DR. MESLIN: All the best to you, Steve.

PROF. CAPRON: All right. Staying in focus then on the recommendation as revised and as justified by the language, are we in our informal fashion telling staff to go ahead with that?

Yes, Eric?

DR. MESLIN: Not until -- this is the time where I have to introduce part of Harold's memo so if you go to page 3 of Harold's memo, page 3 of Harold's memo, the third bullet of page 3 of Harold's memo that begins, "I believe Chapters 3 and 4 --"

So if you look at the end of that bulleted paragraph you have made the recommendation different

but his concern is about the line on page -- lines 17 to 23 in the old text of page 3, before "RESEARCH DESIGN METHODOLOGY" in caps just to give people a landmark. The paragraph begins "One question that is related to the study design." Do people see where that is? So the sentence is the last clause of that sentence.

PROF. CAPRON: Just read the whole thing.

DR. MESLIN: "Although it is surely true that researchers and sponsors have obligations to subjects during a trial, the obligation to provide clinical care cannot overwhelm the overriding justification for conducting the research in the first place, that is to obtain results that are potentially beneficial in the country or community where the research is carried."

I think what -- the nice new language that Ruth has introduced showed the tension but if -- unless that has been changed, 17 to 23, then this -- no, that is not -- yes, this. Then it may say more along one end of a spectrum than you are intending to in the recommendation.

I am sort of re-interpolating Harold because his concern was how that statement squared with the original Recommendation 2. Now we have a new Recommendation 2.

PROF. CHARO: Right.

MR. HOLTZMAN: This language squares with the new recommendation.

PROF. CHARO: Yes, it does.

DR. MESLIN: That is why I just want to draw it to your attention. If you think it does --

DR. BRITO: It does.

PROF. CHARO: It does.

DR. MESLIN: All right. I am not quite sure.

MR. HOLTZMAN: Well, express your concern if you think it does not.

DR. MESLIN: Well, it is -- this is me, not Harold speaking now.

MR. HOLTZMAN: Right.

DR. MESLIN: the overriding justification for conducting research in the first place -- this puts it on one end of the spectrum. "Obtain research potentially beneficial."

Ruth's description was there are two extremes that relate -- from which will flow Recommendation 2 and it is the combination of that dealing with the tension between on the one hand doing research for the sponsors -- I am paraphrasing here -- for the sponsor's benefit and on the other extreme doing research for the subject's benefit. It is that tension that we are

trying to describe in Recommendation 2.

Is that a fair -- and then help me --

DR. MACKLIN: The tension is described a little differently and I think we probably have to just play with these words a little bit. I am going to re-read the sentence that has the tension in it.

It is essential to recognize the tension that exists between the need for a control that has relevance as the optimal baseline against which the new intervention is measured, which is the scientific --

DR. MESLIN: Scientific justification.

DR. MACKLIN: -- on the one hand and the ethical mandate of beneficence on the other, which is maximize benefits. And I think that is neutral with regard to maximize benefits to the subject, maximize benefit to the subjects and to others.

DR. MESLIN: I agree entirely, which is why the line -- all I am referring to is the line that says the overriding justification for conducting the research in the first place only speaks to one of those, which would be the -- in your -- what you just read -- the second pole of the tension.

MR. HOLTZMAN: No. No. No, I mean, because what is going on here is that it is -- in this text, right, it is reminding you the reason you are engaged

in research is because you are trying to come up with a finding.

Now beneficence says be good to the people in the trial and provide them with care but if you take that to the logical extreme where you blow away the potential for doing the study it does not make -- you have eroded your starting point, right.

DR. MESLIN: Right.

MR. HOLTZMAN: And so I would take the way we have redrafted the recommendation and the text is now recognizing precisely that because of the notion of "all relevant baseline" where relevant is not just scientific by the way, it is scientific and also is making reference to the relevant population. Right?

PROF. CAPRON: I did not think this paragraph was talking about that at all and that is why I am just totally baffled, frankly, by this discussion.

Go ahead, Elisa.

DR. EISEMAN: Well, also, what I wanted to say is there is actually --

MR. HOLTZMAN: You need to get up to your mike.

DR. EISEMAN: -- there is two -- I am sorry. There is two sets of conditions that we are looking at. One set is the continuum of on one end, only benefit

to the sponsor country or what can be called exploitation. The second -- the other end of that continuum is benefit to the host country, which is what this paragraph is referring to.

The second set is the tension that Ruth mentioned between setting up a scientifically sound experiment versus ensuring beneficence to the research participants. So this first -- this paragraph on page 3 really refers to the continuum of trying to provide benefit to the host country, not the second set where you are talking about the scientific soundness of the trial versus beneficence to the research participant specifically.

PROF. CAPRON: Let me express my puzzlement here and Elisa and Ruth can answer it.

There are three sentences in this paragraph. The first one simply says there is an ethically problematic issue here. Then the second one, as I understood, told us what that is.

It arises when researchers provide so much by way of clinical care for subjects during the trial that the results are less relevant to the country at the conclusion of the trial where such, as I understood it, clinical -- level of clinical care is not generally available.

I did not understand that sentence to be referring to the controls only or to the active subjects only but rather the background level of clinical intervention that they get.

DR. EISEMAN: That is right.

PROF. CAPRON: So that Recommendation 3 or Recommendation 2, excuse me, the second recommendation, the one we have been talking about, and modifications and all the elaborate -- are unrelated to this, aren't they?

MR. HOLTZMAN: Well, actually I took Recommendation 2 and the treatment of the control under the demands of beneficence as a species of the genus of the care you are giving these people precisely because they are in the trial as a demand of beneficence.

PROF. CAPRON: Yes. But doesn't -- I understand what you are saying.

MR. HOLTZMAN: That is why I think it was more -- bore on it directly.

PROF. CAPRON: It may have some -- I mean, what we say about one may have some bearing on the other but to me this was a different problem. I found the wording in the next paragraph confusing. "The cannot overwhelm," which I gather to mean cannot be allowed to overwhelm. Is that what that means?

DR. CASSELL: Should not overwhelm, I think.

PROF. CAPRON: Should not overwhelm. Should not.

DR. CASSELL: Yes.

PROF. CAPRON: But it should not be allowed to overwhelm. Is that what is meant or intellectually cannot. I just -- the phrase "cannot overwhelm" just left me puzzled as to what was being said here.

DR. MACKLIN: All right. Could I just ask this: I mean, my understanding of the way the process of the actual revision of the text is supposed to work in this Commission is that when people have this kind of question about a "cannot" or a "should not," that is what we do at a later stage over e-mail.

PROF. CAPRON: No. Excuse me, Ruth. This is --

DR. MACKLIN: I mean, this is not a very difficult thing. If we say, well, maybe we mean "should not" and then it is okay, can't we do that?

PROF. CAPRON: No. I do not understand what is being said here. It has nothing to do with whether it is "can" or "should." I do not understand what is being said here.

DR. CASSELL: I do not either because it seems to nullify the requirement for the active treatment in

the control group since no such thing is available. It is a standard of care much higher than would be available so you are saying one thing here and a different thing somewhere else.

DR. MACKLIN: Well, I can tell you if the person -- the Commissioner is willing to stand up to this claim, otherwise will eliminate these two sentences, that at a previous meeting one of our -- one of the Commissioners made this claim and our efforts to try to incorporate the views of the Commissioners in the text that we write and make sure that all of the voices and the comments and the observations are in here yielded this sentence that begins "Researchers could provide so much by way of clinical for subjects during the trial that it would make the results less relevant to the country at the conclusion of the trial."

PROF. CAPRON: I understand that.

DR. MACKLIN: Bernie used those words and gave us some very nice justification for why he said that at the meeting at which he said it. Okay. We included his words, his comment because it seemed relevant and appropriate, and correct.

And so now I am not sure whether you want to take those words away from Bernie --

DR. CASSELL: Oh, no.

DR. MACKLIN: -- or you want Bernie to say more about them?

PROF. CAPRON: Well, I had no question -- the first sentence that you just read, the second sentence of the paragraph, I understand. It is a factual description of a problem. I do not understand the sentence that follows it. Is it being stated as an ethical precept that demands a certain outcome or as --

DR. MACKLIN: Look, it goes like this: If you provide so much care by way of clinical care that it would make the results less relevant then you are not accomplishing the other goal of doing research, the results of which are potentially benefit to the country or the community.

I mean, the first statement says you can give them so much care, the results will no longer be relevant.

The third statement says it has got to be relevant. That is one of the requirements.

So this is a little ethical problem that has to be dealt with. It is some sort of laying it out.

DR. DUMAS: May I say something?

PROF. CAPRON: Rhetaugh, go ahead, Rhetaugh.

DR. CASSELL: Good morning.

DR. DUMAS: Hi. It seems to me that that second sentence that people find confusing is an elaboration of the first one. It is the conclusion. It is therefore, "although researchers and sponsors may have obligations to the subjects that the obligation to provide clinical care should not take primacy over the justification for conducting the research." That is the way I read it.

PROF. CAPRON: Well, as you are stating it, it is clear.

DR. DUMAS: It is the same thing at the top. It says they can provide so much that it will make the results less relevant so, therefore, they should not provide so much clinical care that it would make the results irrelevant.

PROF. CAPRON: Okay. Well, I will count on your comments and others leading to a clarification of the sentence. I understood that what we were talking about here is that there -- we are setting up an issue and what we are talking about is a tension between the two. And again a recognition that as you -- if you move too far in one direction or the other you either slight what you owe the subjects by not giving them appropriate care or you defeat the research. And that is a proposition I can understand put that way.

DR. DUMAS: Yes. I would rather have it that way, too.

DR. MESLIN: Can I just make a proposal since I raised this on Harold's behalf? I think that the explanation that Steve and Elisa gave would allay, speaking somewhat on Harold's behalf, those concerns. There is a new recommendation. It is very clear that there is these two issues going on at the same time. If Elisa with assistance from Rhetaugh or others can produce that more clear description, I think speaking for Harold it would be fine. I mean, let's not make more of this than -- that part than it is. And I do not mean to --

PROF. CAPRON: That is fine.

DR. MESLIN: -- but I really think that that was his major concern. It was the "overwhelm" line. It was not the previous "although" line. So I would propose that we move along.

PROF. CAPRON: Okay. Do you have further things you want to raise then on Chapter 3?

DR. MACKLIN: No, actually it should be open for any other comments about Chapters 3. The only changes we made are the ones that we have just now addressed. And I apologize, these chapters were all sent out before we made these changes because I only

got the e-mail from the person to whom this was sent for comments on Friday night, and that is why you did not see it before because everyone was leaving and there was nobody to send it out to everybody.

So we worked on that here and that is why you saw it in this form, and I apologize. It is just when we got the information. So anything else in Chapter 3 is the question.

PROF. CAPRON: Okay. Let's spend just a moment and look at the other recommendation just to make sure that there are no issues there on page 40.

"Researchers and sponsors should strive to involve representatives of the affected community in early stages of the design and implementation of research projects and promote their sustained involvement throughout the research activities."

MR. HOLTZMAN: I am sorry.

PROF. CAPRON: Yes.

MR. HOLTZMAN: Did we just move on from the recommendation about --

DR. MESLIN: Recommendation 2?

MR. HOLTZMAN: Yes.

DR. MESLIN: Yes.

PROF. CAPRON: You can bring us back.

MR. HOLTZMAN: Well, one thing that struck me

-- can I bring us back?

PROF. CAPRON: Yes.

MR. HOLTZMAN: On page 16 when it talks about the ICH guidelines. It created -- under the ICH guidelines, it struck me that there it says you can depart -- effectively what it says is you can depart from -- what is our phrase? -- an existing --

PROF. CHARO: Established.

MR. HOLTZMAN: -- an established existing effective -- an established effective treatment and go with the placebo as the control provided that the only down side risk is some minor discomfort. And it does not seems to me something reasonable about that. And in the way we have been attacking this and because I am thinking of the cases we have in mind, we are thinking about the down side risk is not merely discomfort.

So I am just wondering again as we look at what is the recommendation and what we should be thinking about whether we want to take into consideration what ICH is kind of thinking here.

PROF. CHARO: So an example -- I am sorry.

PROF. CAPRON: No, I was just -- go ahead.

PROF. CHARO: An example might be for studying topical ointments for rashes. I am trying to keep something in mind that would be biomedical but

discomfort focused. There is a topical ointment that is not sold locally. It is expensive.

MR. HOLTZMAN: Analgesics.

PROF. CHARO: Huh?

MR. HOLTZMAN: Analgesics.

PROF. CHARO: Or analgesics.

MR. HOLTZMAN: Would be the classic example.

PROF. CAPRON: Well, discomfort and pain are not the same. Are they?

PROF. CHARO: So stick with my rash. All right.

(Laughter.)

DR. CASSELL: Anesthesiologists use them interchangeably. They do not ask you does it hurt. They ask are you having discomfort?

(Laughter.)

PROF. CHARO: And what you are suggesting, if I understand, is that the recommendation about when you offer an established effective treatment versus when you may offer a placebo control should be tweaked to distinguish between things that are more than discomfort and things that are mere discomfort. Am I understanding your suggestion?

MR. HOLTZMAN: That is a questions more than a suggestion.

PROF. CHARO: Question, okay.

MR. HOLTZMAN: I was struck as I read that that there seems something very reasonable about the approach there and it made me think that as long as I have the AIDS trials in mind --

PROF. CHARO: Right.

MR. HOLTZMAN: -- I was never thinking about the case where the down side was some minor discomfort.

PROF. CHARO: Dare I ask whether you would want to use the phrase "minimal risk versus more than minimal risk" to express the concept of discomfort and more than discomfort just so we all know what we are talking about? Knowing how much all of us dislike the language of minimal risk and more than minimal risk but knowing how well we are stuck with it.

PROF. CAPRON: But doesn't that get us right into the question of whether you are talking about the subject's preexisting condition, too?

PROF. CHARO: It gets us into all of that headache.

PROF. CAPRON: Why do we use it then?

DR. BRITO: Doesn't the recommendation take care of that, though, the way it is written now? When it says -- basically it says whenever possible, right, and it goes on and then if not the research protocol

should include justification of its design.

So if you have something that has minimal discomfort as a side effect then maybe that might be a time when you cannot have --

PROF. CAPRON: I think that sounds like a very good response, Arturo.

DR. BRITO: Yes. You do not have to have a control -- I mean, you could opt to have a placebo trial if it is, you know, something minimal risk. It is implicit in there so I think it is taken care of without muddying the waters here a little bit.

PROF. CHARO: Okay.

PROF. CAPRON: Yes, Bernie?

DR. LO: I am sorry, Steve. Were you done?

MR. HOLTZMAN: I was done.

DR. LO: With regard --

PROF. CHARO: Microphone.

DR. LO: With regard to this chapter, I have always sort of had trouble clarifying for myself what we mean by established effective treatment and I suggested, in what I think was distributed, some language that I would like to see incorporated in the chapter saying that it is often controversial whether an intervention is, in fact, established and effective. Particularly when it has been shown to be effective in

one population but it may or may not be accepted as effective in another population that differs.

With the caveat that there may be genuine controversy and, therefore, if there is controversy you do not necessarily consider it established and effective -- I do not have a problem with three. A lot of it is then the definition or the strictness of which we construe the term.

I would not be happy with the idea that just because it is considered established and effective in this country means that it necessarily is in another country.

DR. MACKLIN: Can I read you what we wrote in response to your expressed concern? A new section in the chapter.

"We acknowledge that it can be difficult to determine whether an intervention constitutes an established effective treatment. An example of one difficulty is the question of whether an intervention shown to be effective in one population is likely to be as effective in another population." Okay. It is all in here.

DR. LO: I like that.

DR. MACKLIN: Okay. You like your words.

(Simultaneous discussion.)

DR. MACKLIN: "Scientists may disagree on this issue. Examples include differences between the U.S. on the one hand and Canada --" it is in here now because see I am reading from the computer. Okay.

DR. MESLIN: We have never seen him smile so much.

(Laughter.)

PROF. CAPRON: She just deleted it. I saw her.

(Laughter.)

DR. CASSELL: Are we still on the same --

PROF. CAPRON: Yes, we are still on the same. Go ahead.

DR. CASSELL: Ruth, does the word "exploitation" appear earlier in the chapter since that really is a central issue that we are discussing?

DR. MACKLIN: The word "exploitation" and a definition of it and some examples of it occur in Chapter 1.

DR. CASSELL: Right.

DR. MACKLIN: Maybe we only need to cross reference it. The word "exploitation" does appear at the very beginning or in the place of the new material that I just read that describes what that is.

DR. CASSELL: Yes, I know that.

DR. MACKLIN: But the place in which it is laid out most -- in most detail is in Chapter 1, which we looked at yesterday.

DR. CASSELL: Right.

DR. MACKLIN: Maybe we should cross reference the chapter.

PROF. CAPRON: Just a very small editorial suggestion. Let's get rid of that "whenever possible" at the beginning of the recommendation. The recommendation already, in effect, provides this escape clause. We do not -- and that does not tell me anything except -- so we start off --

DR. CASSELL: Well, we are on Recommendation 1. Actually we made the whole issue a negotiation between host and sponsor a very important part of the thrust of our work and so it should really be stronger than strive to involve. "Strive to involve" implies, well, maybe we will not be able to, we did our best, they did not answer the phone. I mean, we are now saying that they -- we have been saying throughout this report we are talking about the importance of working with the host. It is not strong enough.

PROF. CAPRON: Other people's reaction to making that a "should involve" instead of "should strive to involve." Bernie?

DR. LO: Yes. I agree with Eric on that and, also, I just wonder if involvement is strong enough as opposed to something like collaboration.

DR. CASSELL: Yes.

DR. LO: I mean, involvement -- you can involve someone in a very marginal way but I think what the scientists in these countries are asking for is true collaboration, which is more of a partnership.

DR. CASSELL: Yes, right. In all stages of the design and implementation of the research, the sponsor should collaborate with the host, whatever, in all stages.

PROF. CAPRON: At all stages?

DR. CASSELL: Yes, at all stages.

DR. MACKLIN: I know you want to take out strive. So what --

DR. CASSELL: At all stages of the design and --

DR. MACKLIN: You want to take out strive, too?

DR. CASSELL: Well, we are going further. At all stages of the design and implementation of research projects the --

PROF. CAPRON: Researchers and sponsors should involve --

DR. CASSELL: -- should collaborate with the host or should involve collaboration with the host. And the implication is that right from the start the host is involved collaborating and making -- helping making the decisions. One of the biggest ones has to do with this issue of placebo control but it certainly has to do with the problem of exploitation.

PROF. CAPRON: We have heard from Eric. What is our consensus on this if there is one?

DR. BRITO: I agree.

PROF. CAPRON: Harold's view? Let's have Harold's view.

DR. MESLIN: Well, Harold liked the recommendation as it was and the reason that he did was for reasons of not being too directive in telling people what has to happen but I am just giving you an interpolation.

PROF. CAPRON: That is the last point on page 3 of his memo?

DR. CASSELL: But not specifically about this recommendation but generically.

DR. MESLIN: His recommendation as is, is the only thing I can convey.

DR. CASSELL: Well, let's see how he feels about the idea of moving collaboration up front first

further.

DR. EISEMAN: I would just like to mention that not all research in developing countries is done as a collaboration. It may -- there are very -- there is a lot of different ways that research can be set up to involve people from the developing country. So it might have to be softer than what you say because if you say they have to develop a collaboration, that may not be possible in all cases.

DR. CASSELL: You mean we just sort of go like a beach head. Get up the beach and use the natives. How would you do that?

DR. EISEMAN: No, that is not what I am saying. But there is --

(Laughter.)

DR. EISEMAN: Collaboration means a very specific type of arrangement where you have joint efforts between both parties and it may very well be that you have -- and this happens all the time, you have American researchers who go into a country to do research with people in that country and it does not always necessarily entail a true collaboration in the terms that we think of on a scientific or a medical basis. That was the only comment I wanted to add.

DR. CASSELL: Can you get a different word

then that shows that I am in involved with a host and I am not doing something without discussions with the host and so forth?

DR. EISEMAN: Yes. That is the point I was trying to make.

PROF. CAPRON: What is wrong with the word "involved," Eric? I mean --

DR. CASSELL: It is not strong enough.

PROF. CAPRON: -- I take Elisa's point that the word "collaboration" is a very specific phrase in which people are collaborators, they are joint authors of papers, et cetera, et cetera, and that may or may not what is needed or is appropriate in every case.

It seems to me that the statement would be quite strong if we said at all stages in the process researchers and sponsors should involve representatives of the affect community in the design and implementation of their research project.

DR. CASSELL: That is fine. I find that satisfactory. That is fine for me.

PROF. CAPRON: Okay.

DR. DUMAS: I have a question.

PROF. CAPRON: Yes, Rhetaugh.

DR. MESLIN: Make it quick.

DR. DUMAS: Does that mean that the

representatives from the country affected communities would actually be involved in decision making about the design and the implement of the project?

PROF. CAPRON: Yes.

DR. CASSELL: Yes.

DR. DUMAS: Or does it mean that they would be informed and consulted with? What does the involvement entail? We say that collaboration is misleading. Do they help design the study?

DR. BRITO: Sometimes.

PROF. CAPRON: I think the answer is sometimes, yes. Could we have Ruth --

DR. DUMAS: But is that what the intent is of this recommendation?

PROF. CAPRON: Ruth, could we be pointed to where you have placed this in the chapter so we might look at the surrounding text?

DR. MACKLIN: Yes.

PROF. CAPRON: Do you know where --

DR. MACKLIN: It is immediately before -- I mean, I cannot give you a page number because it is all changed around. It comes immediately before the section entitled "Inducement to Participate in Research." It is the last --

PROF. CAPRON: Page 32, that is where that is

on our preexisting drafts.

DR. MACKLIN: It could be.

DR. EISEMAN: Right. It is in the section entitled "Involvement of Community and Study Participants in the Design of Research."

DR. MACKLIN: Yes. "Involvement of Community and Study Participants in the Design of Research."

DR. DUMAS: In the first part of the draft we have or towards the last part? I do not know how to find it.

PROF. CAPRON: That begins at page 30 and the recommendation apparently would come at line 5 on page 32.

DR. DUMAS: Okay.

PROF. CAPRON: If you have the printed --

DR. DUMAS: I have the printed.

PROF. CAPRON: And certainly the examples given here from the U.N. AIDS are examples of a strong degree of participation and endorsement. For example, at the bottom of page 31, the quote is "to ensure the ethical and scientific quality of proposed research, its relevance to the affected community, and its acceptance by the affected community, community representatives should be involved in the early and sustained manner of the design, development,

implementation and distribution of the results of HIV vaccine research." So that is a fairly strong --

DR. DUMAS: You know what I would feel more comfortable with, is just changing that "in" to "during."

DR. CASSELL: During all stages.

DR. DUMAS: Huh?

DR. CASSELL: During all stages.

DR. DUMAS: No. Community representatives should be involved in an early and sustained manner during the design, development and implementation.

PROF. CAPRON: Yes. Actually, Rhetaugh, listen to this wording, which I read and got nodded heads to before. "At all stages in the research process researchers and sponsors should involve representatives of the affected community in the design and implementation of their research projects."

DR. DUMAS: And I am saying I would feel more comfortable with "during" instead of "in."

PROF. CAPRON: Well, we will circulate the wording and people can comment on it when they see it.

DR. DUMAS: The concern that I have is that it might give the expectation that the people from the host, the community representatives should help design, develop and implement the project and distribute the

results.

PROF. CAPRON: Okay.

DR. MESLIN: Rhetaugh, I think because of timing we really want to move on to Chapter 4 and since we are not in quorum what we --

DR. DUMAS: Go ahead.

DR. MESLIN: -- what I think we will do is just send comments around on some e-mail and people can react if that is okay.

DR. DUMAS: Okay. That is fine.

DR. MESLIN: All right. I think we should move on to Chapter 4 unless there are --

PROF. CAPRON: Arturo, one more --

DR. BRITO: Since we are -- just on this same recommendation, just one other word that -- and I understand it is going to go in the -- following the text but I do not know if it is late in the day, second day here, and I am thinking too much here about this, but the "affected," the adjective "affected" is starting to bother me a little bit because the -- we are talking about the community where the research is going to occur.

DR. MACKLIN: Not necessarily. A community can be -- I am not sure how much of this is in here. A community can be the community of sufferers. It need

not be a geographic community.

So, for example, if we are talking about HIV, members of the community of people who are afflicted with HIV need not be specifically members of the geographic community. If we are talking about the geographic community that can also be a community but there is a vast literature out there on what constitutes a community and we just cannot get into that.

DR. BRITO: No, I understand that.

DR. MACKLIN: Yes.

DR. BRITO: But that is my point. You can have an affected community of sufferers, people that have the disease you are studying, and if you read this it would -- those would be the people you would consult with, but yet you can go and do the research in one part of that country where the community people had no say in it.

PROF. CAPRON: It would seem to me that the term --

DR. BRITO: Where geographically you would have people that were not involved in the process of --

PROF. CAPRON: Okay. Let's attend --

DR. BRITO: The way -- here is a suggestion. The suggestion is to -- where the community wherein

which the study will occur, something to that nature.

DR. MACKLIN: Well, all I can say is that the earlier -- I mean, I hope that the context could help make it clear. Otherwise, we could say it is specifically because the discussion of community involvement and impact that immediately precedes the recommendation talks about local researchers, potential participants, other community members, et cetera, and it implies there that it is the geographic community.

PROF. CAPRON: I think, you know, the way to handle this, it would seem to me, would be language of the explanatory sort that follows a recommendation where we could say the affected community may be the community of suffers of a nongeographic sort whose advice is sought. It would also include the geographic -- people in the geographic community in which the research was being conducted.

This is not regulatory language. This is an explanation of the multiple meanings of affected community. They are not exclusive. Okay?

DR. BRITO: I am not going to belabor it. I will -- on e-mail I will make some comments but I am just concerned that the actual community where the research occurs is not the community that is affected necessarily. That is all I will say.

PROF. CAPRON: All right. May we go on to Chapter 4 then? Are we done?

DR. COX: I have one quick comment on Chapter 3 because it is the whole summary and the whole point of it, that, in fact, we are recommending that an effective, okay, treatment be supplied to the controls. Okay. That means that an effective treatment is being supplied to the experimentals, too?

PROF. CAPRON: We went through that when you were away.

DR. COX: I understand. I just wanted to say that it is not stated there that it is. Okay.

PROF. CAPRON: Well, it will not be. I mean, if the experimental -- I mean, if, for example, you were to have concluded that you were in a circumstance where the 076 is the effective and you wanted to try something else --

DR. COX: Yes.

PROF. CAPRON: -- then the subjects who are getting the something else are not getting the 076.

DR. COX: I understand. So I am just pointing out that what we are doing is we are making sure the controls get an effective treatment --

PROF. CAPRON: Yes.

DR. COX: -- where the experimentals do not.

PROF. CAPRON: Yes.

DR. COX: Okay. Just so people realize that is what we are saying.

CHAPTER 4 - OBLIGATIONS TO SUBJECTS

PROF. CAPRON: Okay. We are going to Chapter 4. Any introduction from you, Eric, about the Chair --

DR. MESLIN: Well, I think you have just seen the memo. Harold's basic points on Chapter 3 are what you see before you. He has got some questions --

PROF. CAPRON: Chapter 4.

DR. MESLIN: I am sorry. On Chapter 4. Page 3 of his memo regarding justice as reciprocity. I think the tonal questions that he has at the bottom of that same memo can be handled by writing and I am not going to comment on those items.

The one item that I think is worth picking up is the notion of the health as a primary good that he wants to get some discussion no and then I will come to his recommendations and comments in a bit.

PROF. CAPRON: And this is where we were also going to turn back to the first page of his memo, is that right?

DR. MESLIN: Yes.

PROF. CAPRON: Alta?

PROF. CHARO: Sorry, Eric.

DR. MESLIN: No.

PROF. CHARO: Alex, stop me if I have go this wrong. I wanted to respond to his comment that he did not understand why it would be a problem to carry out trials in the most economically advantageous location provided that it is relevant to the health needs. Is that okay to respond to?

DR. MESLIN: Yes.

PROF. CHARO: I thought that an adequate answer is provided by Leonard Glantz's testimony and writing, which is cited throughout the chapter. Specifically, he says that it is okay providing it is relevant to the country's needs, but "relevant to the country's needs" means that, in my opinion, there has to be some prospect of actually getting and using any successful interventions so that if there is little or no expectation that the stuff would ever wind up -- if it turns out to be effective, little or no expectation that effective interventions would ever wind up in the country, then the research cannot be considered relevant to their needs and, therefore, his condition is not met and, therefore, you cannot do it.

PROF. CAPRON: Comments?

MR. HOLTZMAN: So effectively what you are saying if I look at Harold's letter is that you are

building it into the sense of relevant --

PROF. CHARO: Yes. I am building the prospect -- unlike Leonard Glantz, not the guarantee, but the reasonable prospect, the active contemplation, something like that, that any intervention that proves successful will eventually wind up being used in that country as the mark that the research, indeed, is relevant to that country. If it could never be used there, nobody expects it is going to be used there, then the research hardly seems relevant to them. It might be scientifically interesting. It might be scientifically relevant but it is not particularly relevant to their health needs.

PROF. CAPRON: Or in the reasonably foreseeable future.

PROF. CHARO: Yes.

PROF. CAPRON: I do not think one ever should say --

PROF. CHARO: Right. You know, properly qualified. What I am trying to say is it is somewhere between, I think, where Harold was talking and where Leonard Glantz came from where he was looking for hard and fast guarantees.

PROF. CAPRON: Which passage of Harold's are you referring to?

PROF. CHARO: This is where on page 3 in his comments on Chapter 3/4, toward the middle of the page, there is a bullet that goes, "As you know from my previous e-mail, I have no objection to carrying out trials in the most economically difficult..." and I think he meant advantageous.

DR. MESLIN: He did.

PROF. CHARO: "...location provided that (a) the trial was relevant to the health needs of the host country and (b) all substantive ethical requirements are met.

DR. MESLIN: Right.

MR. HOLTZMAN: Right. And where this hits in the chapter is page 2, the top of the page, ending in lines 7 and 8 where you say, "However, cost alone cannot be the only..."

DR. MESLIN: Correct.

MR. HOLTZMAN: Which I actually found that a little bit --

DR. MESLIN: I was going to -- I interrupted you. Please finish.

MR. HOLTZMAN: -- just ambiguous because I think maybe, Ruth and Alice, you might read that and see whether there is an ambiguity introduced there because I think we are agreeing with Harold's

observation with Alta's amplification.

DR. MESLIN: I have some marked up text from Harold. He is prepared to accept lines 1 to 8 on page 2, which is where you are, Steve.

MR. HOLTZMAN: Right. Which is relevant to this point.

DR. MESLIN: Correct. With the following insertions: On line 3 after the word "burdensome," the words "but ethically, substantive regulations," and then in line 7 after the word "however," "from an ethical perspective cost alone. So those -- I could read that again if you wanted but it is a qualification. And his note is he would accept those lines with those changes for your consideration.

MR. HOLTZMAN: Again I am struck -- I am thinking through some real live cases where the paradigm you have in mind, the one is where you are using someone as guinea pigs and that is clearly wrong. And then another is when you are again -- I know you -- minimal risk sorts of things where I can think of a trial I know of where bone morphogenic proteins are being tested in nonunion fractures which occur in largest numbers where people get into lots of motorcycle accidents. Well, it so happens that in certain under developed nations you will find a lot of

those. What is the prospect? And you can rapidly do the trial.

Do I see -- if that trial is successful will those BMPs be readily available as quickly there? No, they are not going to be. And yet it is a very low risk sort of trial and whatnot. It just does not feel like it has the same kind of notion of exploitation that one would be thinking of as things -- trying a very dangerous -- potentially dangerous medicine where there is no relevance to the population merely because you bought them off.

PROF. CAPRON: Bernie, did you have a comment?

DR. LO: No.

PROF. CAPRON: Alta, you wanted to respond to that?

PROF. CHARO: Well, yes. I understand your point, Steve, and I am not unsympathetic to it because I tend to approach these things not only from the point of view of what seems to be ethical or from a more physical point of view of what turns out to risky but also from a more political point of view.

I still have a concern, in general, under kind of overriding all of this area about the phenomenon of taking advantage of situations that are regrettable.

You know, I play poker and those of you that

play poker and ever play high/low games know that you can find yourself sitting in a situation at the end where one person has gone high and everybody else has gone low, and if there are no limits placed on the game you can keep maxing out on the bets and forcing the other players to spend a lot of chips and you know you are going to collect half that pot.

It is considered unsportsman-like, and a lot of poker games set a rule that says you may not, and in a sense that is what this is about. It is almost like unsportsman-like behavior on an international scale, that there is something simply unseemly about taking advantage of the circumstance that makes that injury more frequent in that country in order to try out something that is predominantly going to be used in the reasonable future in industrialized settings.

And although I understand the cost to people back in the industrialized settings, from a political standpoint I actually would prefer to stay away from that even though it does not actually convey significant risk to that population.

PROF. CAPRON: This chapter we call "Research According to Hoyle."

(Laughter.)

PROF. CAPRON: What other --

MR. HOLTZMAN: Just what it is worth, though, of course, right. I could also name you the hospitals we would do it in -- that same study in the United States. All right. And that most of the people who were getting in those crashes also are probably people who are not going to get the protein as well.

PROF. CAPRON: Bernie?

DR. LO: What strikes me about Steve's example is this is a short-term condition for which you give one round of therapy. It is not like the going into a country where there is a chronic disease like osteoporosis in China, testing a drug and then sort of -- if the drug is proven effective, say, "Thank you very much. We are going to pull out and go home but we have left you a nice CD player and a centrifuge."

So I mean elsewhere in the report we make a big deal out of kind of not fulfilling justified expectations for continuing care but in an acute setting -- I guess, you know, a new kind of suture that is self-reabsorbing or something, I mean it is hard to argue -- it is hard for me to envision that you are hurting people by trying -- letting some of them try a product and there is no sort of sense of an ongoing obligation to treat those very people.

PROF. CAPRON: Alta?

PROF. CHARO: I absolutely agree and I do sense how difficult this is. And yet the imagery that keeps coming to my mind is still a little bit different. It is that we are talking about situations where we really do now want to simply hire people to be the guinea pigs. And not that it is a dangerous thing, and as Harold might point out, not that a rational person in their position might not think that is a good idea. Be hired as a guinea pig rather than be hired to do some other work that may not pay as well or be as low risk. And I understand -- I understand that operation within the United States and, in fact, as I have said before on the record, I have hired myself out as a guinea pig when I was in a position of severe cash restraint. But because I am within the same political system, roughly within the same health care system, I mean even though our social compact is imperfect, I was still within our imperfect political social compact within this country. It seemed and still seems less politically inappropriate than when one goes to a population that is entirely outside our social compact and says, "Wouldn't you like to be hired to take on this task for us?"

You know, it is obviously more dramatic when there is bigger risk but we have seen this in the

environmental area also where we have exported hazardous wastes to Nigeria and Brazil and that was a high risk area, and we got very sensitive then to when we were exporting risks of any sort, even low ones, and began a discussion in general about the exportation of risk.

Maybe it is about whether or not being a guinea pig really is different than being a Nike sneaker worker. I mean, maybe we are back again to whether or not there is something special about hiring people to be in medical experiments as opposed to hiring them into any other economic activity.

PROF. CHARO: Yes, Bernie?

DR. LO: Alta, is part of your objection that the company sponsoring this is going to save a lot of money by doing it abroad and paying subjects less in that country than they might in this country? So if you got, you know, University of Wisconsin football players to test this sort of fracture medicine, you are going to have to pay them more money than you would people in developing country or people who get taken to the county hospital with major trauma. Is part of your concern that sponsoring company is making -- getting an economic benefit by saving money on how much it would cost to pay subjects?

PROF. CHARO: No. I mean, I do not mind them making money. That is okay. They are allowed. It is the image of people being -- the Kantian language is being used as means rather than an end, and that is not a perfect analogy because of course since they are being paid they are getting an exchange of value or they are getting something. I mean, presumably people are not just volunteering for this. They are getting something.

But, you know, it does keep coming down to that imagery of hiring people to be the guinea pigs. It really is.

Feel free to persuade me that this is not a big enough problem that we should worry about it.

MR. HOLTZMAN: You are right. First off, for the purposes of the report, in general, let's get clear on the economics of clinical research. All right. This notion that you go to other countries because it is cheaper is nonsense. All right.

What you -- the thing that you are trying to get it done as fast as possible because the real value is getting it done so you can get out on the marketplace with a good sound study. So the key thing that slows down trials is rates of accrual of patients.

So the example I gave is the choice of --

PROF. CHARO: High frequency.

MR. HOLTZMAN: Right. Is literally you choose that place becasue there is more people with the relevant cases. I choose that hospital at that intersection cloverleaf at I95 and 75 in Georgia because that is where the --

PROF. CHARO: Right, the high frequency.

MR. HOLTZMAN: High frequency. Okay. So that is the reason you go. Now to your point, you are absolutely right. It is the notion that it is if the treatment really is not in any relevant sense going to be available to them in the foreseeable future, they are being treated only as an ends or as a means, and there is no sense of an end as well.

And then you -- you know, the oddity there is you look at what the risk is involved. So I can make the argument that a benefit that comes out of it is involving those clinicians in that country in advance medicine.

Now is that good? Should they be able to choose to involve a third party to that end? Probably not. On the other hand, if it was a matter of de minimis risk maybe it does not bother you so much because to what extent were those people truly used as

means.

PROF. CAPRON: Is there a passage in the report that we are now addressing? I mean, I recognize that this began with a particular comment of Harold's and picking up the phrase "relevant to the health needs of the host country" but I am not clear whether we are now on Chapter 4 or not. I mean, we are on the area of 4 but is there an objectionable discussion here?

PROF. CHARO: I thought there had been a recommendation some place but I can see now it is not in Chapter 4 that had to do with one of the ethical requirements of doing research in these countries being that the research was relevant to the needs of the host country. That was some place in there somewhere in some chapter.

DR. MACKLIN: It is in the first chapter. There is a whole section in the first chapter that says that is the basic premise on which everything else is built.

PROF. CHARO: Thank you. And that is what Harold's comment --

DR. MACKLIN: And we refer to it --

PROF. CHARO: -- goes to. Doesn't it?

MR. HOLTZMAN: Yes.

PROF. CHARO: Harold challenges that comment,

but Harold essentially challenges that point of view with his comment, which suggests that --

PROF. CAPRON: No, I do not think so at all. He endorses it. "I have no objection to --"

DR. MESLIN: Harold is in agreement.

PROF. CAPRON: "-- carrying out trials in --"

PROF. CHARO: Well, but --

PROF. CAPRON: "-- the cheaper places provided that the trial is relevant to the health needs of the country."

PROF. CHARO: Right. But you see -- but later on he talks about why he does not think that you need to actually make sure that there is going to be some kind of benefit to the population of the country. So it is a two step dance here. If it is not going to be made available to the population of the country, which is a recommendation that Harold has had difficulty endorsing, in my view it means that the product is no longer relevant to the health needs of that country.

And, therefore, if he sticks to his guns, saying you do not have to make sure that it is going to be available to that population in the future, he is, for 4, saying he does not think that research has to be hinged on relevancy to the health needs of the population.

DR. CASSELL: No, that does not follow at all. You mean that kind of relevance. It has to be related to the health problems. But you are specifying what the relevance will be. They have to provide this -- that means you are taking care of the health problems but there are other ways also.

I mean, for example, I find a treatment for malaria and we did this thing now -- it is going to be 25 years before that really comes to be but all that time we are working with that country to help develop capacity and so forth to go on. We have not provided a single drug. We do not even know if the drug will come out. But we know that the problem of malaria is strong there and we are going to continue working with that group but we are not providing any medication. We may not even be providing care but we are still involved in that specific health problem which is so important to them.

I do not think you can pick the relevance. Just like I do not think you can say as we do in other -- does in another point that it is okay to negotiate until you come to a point where you do not like it because they may not be democratic. You just cannot do that.

You are going to negotiate in one place and

then you are going to negotiate everywhere else also.

I mean, we are hearing a problem of trying to specify what sponsors must do instead of the general issue which we have some concerns about. I also have concerns about the business of providing health care afterwards because I do not know what it means. I do not know how long it goes on. I do not know what the drug is. I do not know what it means.

MR. HOLTZMAN: But, Eric, let's put aside Harold for a second and let's take -- Ruth has said this --

PROF. CAPRON: I think we need Ruth not to be interrupted right now.

MR. HOLTZMAN: Okay. As Ruth points out, a fundamental premise in Chapter 1 that everything hinges around is a protocol ought not be undertaken unless there is a belief that it is relevant to the population.

DR. CASSELL: Yes, agreed. Absolutely.

PROF. CAPRON: Relevance is there defined as --

MR. HOLTZMAN: That is the question.

PROF. CAPRON: -- providing a benefit in terms of that disease being ameliorated by the outcome of the research potentially.

MR. HOLTZMAN: So it is a thin definition of relevance.

PROF. CAPRON: Am I correct in that --

MR. HOLTZMAN: That is my question, right. Because --

PROF. CAPRON: Ruth, is that a correct description?

DR. MACKLIN: I am looking. I am looking to see exactly what it says.

PROF. CAPRON: Okay.

MR. HOLTZMAN: So in that example, those BMPs since they do suffer fractures there would be relevant even if they may never see them. That is the question that is in play.

PROF. CAPRON: Because that would not end up ameliorating their situation. Now obviously -- I mean, I thought Eric just now was raising the point that you could have research which we naively or rather simply say is successful, a successful product. And the point is that success in a research study may provide you one building block towards an eventual marketable, manufactured, distributed and approved product.

And his take on it was we ought not to have language which suggests that it is illegitimate for sponsors and host countries to work out an arrangement

where it is understood that what they are really going to do at the end of this research is continue capacity building and training scientists, and so forth because it is going to be ten years before that drug is manufactured and available in that country.

And the question is does that still meet our definition of relevance, which is necessary for a favorable benefit/risk ratio, which is necessary for approval of the research.

And, frankly, it is described by Eric. I can imagine a situation in which I would answer yes to that, that the sine qua non is not the day the research ends you start shipping the drug to the population. I do not think anyone really thinks that that is the requirement.

So how far you move away from that and what other things you do in place of that is an open question. That view also, to me, has the advantage of saying that if you take that view that this ought to be a normal part of the negotiations that research which is not narrowly successful, that is to say it shows that a particular approach does not work, does not eliminate the notion that the sponsor should be doing something for those people.

DR. CASSELL: Correct.

PROF. CAPRON: And that should have been negotiated in advance and it should not be contingent on our having a million dollar product at the end.

DR. CASSELL: Correct.

PROF. CAPRON: Because who knows serrendipitously what good that research result will be to the long-term project of actually finding the vaccine or the drug that is responsive to the situation.

Ruth is going to tell us what it says and then Alta is.

DR. MACKLIN: Well, I mean there is a long section in Chapter 1 that quotes and cites everybody from the CDC and the NIH and the CIOMS and everybody else talking about the need to make the research responsive to the health.

Ultimately it says on page 19, line 24, "The justification for the requirement that research be responsive to the health needs of the population rests on a conception of justice. This conception is articulated in a cornerstone of U.S. research ethics, the Belmont Report, and then it quotes the Belmont Report.

"Whenever research supported by public funds leads to the development of therapeutic devices and

procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research."

Now that is pretty clear. It says, "Subsequent applications of the research." This comes from the Belmont Report, which is a pretty old document. It is not yesterday's revision of -- so this is in those words -- this is not you can build some roads or you can do a little capacity building. It seems to me that these words are clear on their face and that is why for the United States this counts as a pretty good justification for -- couched in terms of justice, both an explication and a justification for why it should be responsive, and the particular way in which it should be responsive.

DR. CASSELL: I thought one of the things that was important about this whole project was the understanding that the ethical things that we do in justification of ethical requirements in the United States may not go over in the same form, that is a kind of a paternalism just as you pointed out for something else, and that what we are trying to do is make sure that our research does not exploit certainly and

absolutely that it is related to the health needs of the country. And that we are not the final arbiters of that. Who are we to be the arbiters? Just as I would not do that for an individual I care for, I do not see how this country or a sponsor should do that for another nation.

DR. MACKLIN: This is a principle of justice. It is not a particular forum.

DR. CASSELL: Do not give me --

(Simultaneous discussion.)

DR. CASSELL: Please, we are talking justice but your definition. Justice -- the way you have justice of reciprocity, that is fine. But you are deciding what is reciprocity. Who are you to decide? Don't you think that is a matter for the host country?

PROF. CAPRON: Alta?

PROF. CHARO: Well, let me --

DR. CASSELL: No, you do not but I do. How is that?

PROF. CHARO: I am going to take a page out of Bernie Lo's book and I am going to use a concrete example.

You have seen references to the infamous Love protocol at the University of Wisconsin scattered

throughout this report and it actually exemplifies in some ways this very debate.

It involved the decision to test ovariectomies or oophorectomies in women to prevent the recurrence of breast cancer in a population that was unable to get access to chemotherapy and taxol, which would be the approach in the United States for that population, as I recall.

And it was something which if successful would have been transferable back to the United States for the population of women here should it prove to be as effective or even more effective than what we were doing here but it was untestable in the United States because -- not because of a lower frequency in this case but simply because we have now a standard therapy and this was an unacceptably risky alternative to standard therapy for American trials to go ahead with. Nobody in the U.S. was willing to go with it.

Now the Vietnamese population was not chosen because women there are particularly appropriate from a medical standpoint. Indeed, in some ways they were not medically appropriate since being Asian women they have a higher frequency than other populations of osteoporosis and the premature menopause that this brings on actually put them at increased risk of

osteoporosis.

Nor was there any guarantee or even strong expectation that many or most Vietnamese women would have access even to oophorectomies as a therapy in the future.

One of the things that in my opinion made it most controversial when it was discussed is that the reason the Vietnamese population was chosen, and I say this believing it to be true and perhaps it is not, is reflected in an exchange of letters demonstrating that Dr. Love happened to have professional ties to a number of Vietnamese physicians and researchers, had wanted to deepen those ties, and that the Vietnamese Ministry of Health saw here an opportunity for capacity building. And the exchange of letters specifically contemplated training in medical procedures and in research management by Vietnamese professionals with long-term gains to the public health of the country over the long run by virtue of capacity building in its professional class.

It is not, however, as if anybody looked around the world and said, "Globally speaking, what is the population that is most medically suited and likely to benefit from this alternative to gold standard therapy." It was the haphazard incidence of a

professional relationship coupled with a host country's interest in seeing its professional class furthered in its education.

And that was the benefit along with the faint possibility that oophorectomies might eventually get introduced there that was used to say that this was relevant enough to the health needs of that country to be justifiable research.

Now reasonable people differ on whether that protocol should have been approved. I have to say that because reasonable people differed for months on my campus. But I, for one, find myself made very uncomfortable by that particular scenario and yet the way it was spelled out makes me think it is actually not that atypical a scenario.

And it does seem to go right to the heart of what we consider to be a benefit that makes something relevant enough that it satisfies the conditions laid out in Chapter 1 and really forces us to then discuss whether benefits in the form of the medical intervention being tested, narrow as it may be, is the relevant definition -- is the appropriate definition to be used here or not.

MR. HOLTZMAN: And that is exactly -- this is the crux of the matter because if you go up on page 19

of the text, the paragraph at line 7, you will again pull the tight connection that relevance is equal -- that it is likely that the particular intervention being studied will be used. So that other concepts of a benefit are not allowed in play at all. All right. That is the way this has been drafted and I think Harold's question is specifically asking us what is relevant.

It branches out into Eric's discussion. It branches out into the requirements of reciprocity but it is a -- even -- before you even get to those kinds of very global issues, issues -- take my simple example of the BMPs, is it good enough that it may be available to a few people in 20 years or does it have to be available immediately? All right.

To your example, you are very uncomfortable when the example is an oophorectomy, right. If I make it a minimally invasive treatment you would probably get less uncomfortable. Right?

PROF. CHARO: Yes, I would -- of course, I would be.

MR. HOLTZMAN: Right. Okay. So it is not --

PROF. CHARO: I might still fuss with you but I would certainly be less --

MR. HOLTZMAN: You would fuss but all of a

sudden your Kantian principles of means only -- you are willing to start to give it up if there is a benefit, an ancillary benefit.

DR. CASSELL: I have the disadvantage of having a history in the United States providing medical care across boundaries after the Second World War in which we determined what were the health needs of those nations, and we were wrong repeatedly, and we were wrong because we were sure -- I mean, there are endless numbers of cases in which we just made a big mistake because we just did not know and we were so sure we did know.

And this is the same kind of thing. You have to have respect for other people and the respect requires -- just like individuals, it is a question of respect. Respect for persons, respect for their communities. Of course, it is -- and you can find another anecdote. Of course, you can.

But this is an issue in which in the very beginning of the whole process, we have a problematic protocol about HIV, problematic and we are still arguing. But we are hoping -- but by the end of the number of years these things are much less problematic because capacity has been built. There are -- people begin to know about ethics. Researchers are there.

And the real advantage of our going over there for them becomes much clearer.

In the short-term we may have things like you are discussing. They are uncomfortable anecdotes although, as you point out, there was a lot of debate about it. I do not know enough about it myself to have an opinion about the protocol but I can understand the debate for sure.

PROF. CHARO: Right. And, in fact, it would be interesting to know how you would like that debate to be resolved because that is an indication of how you would like these recommendations to be written.

PROF. CAPRON: If I --

PROF. CHARO: Yes.

PROF. CAPRON: If I may, Eric, it seems to me that the -- excuse me. One of the things that we hoped that the International Report would do was to shine a light on domestic practices. It was not a one-way street.

And I think that this discussion provides a good opportunity in this report for us to comment that that particular aspect of the three principles of Belmont, the justice part, is by common agreement the most widely ignored by U.S. IRBs, the one that makes them scratch their heads the most, and to the extent

that this particular problem is highlighted by the recognition of this issue as research would be done along the far end of the spectrum of benefit to the sponsoring country and little benefit, if any, to the host country, as a reminder that this is an ethical issue.

I think we should take the occasion of the material in Chapter 1, Ruth, to actually draw a little bit of that lesson and not just recite that vis-a-vis its international implications.

On the international implication, Eric, certainly the short-term -- short-course AZT treatment African experiment is not a problem of this sort. Quite the opposite. I mean that was something which was designed to be relevant in that country.

And if the thought was that they wanted to give women in San Francisco a short-term treatment and they could not test it here because all the women were already getting the gold standard and would not accept it -- it would be unethical or impossible to conduct the research and so you go abroad to see if you can do something cheaper and then import it here but with no intention of making it available there. That seems to me it would raise questions.

And the questions would not be fully resolved

by saying, well, they are going to get something out of it because we are going to bring a few of their people over to study with Bernie Lo at UCSF and that is San Francisco's contribution.

It does seem, however, that we have perhaps made this too much of a dichotomous situation. We could have on the one hand the kind of requirement that the Belmont Report language suggests that Ruth read to us and on the other the recognition of the particular way the obligation plays out is going to be dependent upon what the research is, what stage it is in producing a useful product, et cetera, et cetera.

And so the actual implementation of what the reciprocal act is, -- is subject to the negotiation.

But what we would suggest would be that the U.S. researchers and their IRBs ought not to approve something which is on that very far end of that spectrum where you are going in knowing that you are just never going to do it there. Never ever within the life time of any of the people who would be subjects of the research are they ever going to see anything out of this and all you are going to do is bribe the Health Ministry by building them a new laboratory or something.

I mean, that notion of exploitation goes too

far.

But where you are in a circumstance where it does have relevance, it is a disease that is there, the treatment is being developed which could be used there, it may not be used next week or next month because it may not be approved, or it will take time to work out the licensing arrangements or, et cetera, et cetera, and in that interim there is going to be a process of negotiation which we do not dictate the terms of but we just recognize that there is an ethical issue there.

I, for myself, think that is about as far as we probably can go.

DR. CASSELL: Alex, what about the failed trial? We go in -- and do you think -- don't you think that even though the trial has failed, that you are owed something?

PROF. CAPRON: Yes. Yes, because you do not know in advance. I mean, this is -- this would be subject to an advance negotiation as something that will be coming out of this.

DR. CASSELL: Right.

PROF. CAPRON: And where the drug turns out not to be good but it still was valuable in telling the company or the U.S. sponsor, do not pursue this further, it does not work as it turns out, you know.

I think that is valuable information for which there should be some reciprocity.

DR. CASSELL: Absolutely.

PROF. CAPRON: And -- but I cannot -- but in that circumstance it would be impossible to say the reciprocity is the drug because the drug did not work. So I think we have this up as more of an absolute conflict than is really the case. There is a criterion of relevance and that relevance means some possibility of benefit, some realistic possibility of benefit, and it would be wrong as the Belmont Report says to involve persons or in this case a community or a country unlikely to be among the beneficiaries of subsequent applications.

And the farther you are on that end of the spectrum and the -- you know, you are really doing it for U.S. use and not for other -- it gets to the point where you say it cannot be approved but if you are back in the relevance range the exact pay out of the relevance ought to be subject to all sorts of negotiations.

And we should simply be saying that this is a point of ethical sensitivity, that the further it departs from being the treatment that was tested, the more justification is required and the justification

should be we do not have a product yet or it was good research, valuable research but it did not yield a product or whatever. And in the interim we are going to do something else for you.

And that trade off should be in the hands of the responsible persons in the host country and not dictated by us as being beyond the pale. That is my personal opinion.

Yes?

DR. COX: I would like to make an observation that this is not something that is worked out with respect to human subjects research in the United States. I would just like to point that out.

PROF. CAPRON: That is right and, as I said before, I think we should take this as an occasion to comment on some of the implications in terms of selection of subjects here. We do not have the same exact arrangement because if the U.S. government is sponsoring research that is done at a county hospital, the beneficiaries do not have a separate Ministry of Health that could be negotiating on their behalf as to what they are going to get out of it.

DR. COX: So I would like to make another comment which is not pointing out a fact but making an opinion, and that is that it is not -- I am

uncomfortable holding international standards to a higher level than what we can actually work out in our own country.

PROF. CAPRON: Okay. I have Bernie and then Steve.

DR. LO: I wanted to follow up on I think the line of thought you were pursuing, Alex. It seems to me we have just spent a good deal of time, about 15, 30, 45 minutes, you know, reasonably bright, thoughtful people unable to come up with a clear solution.

I think the lesson is that it is not as simple as some might think and that there are arguments that pull Alta one way, Ruth one way, Steve another way, and Eric another way, and I think we should try and lay those out and try and show the complexity of the situation.

What bothers me most about this international arena is that you get people sloganeering, saying this is, you know, as bad as the Nazis and someone else saying, no, this is, you know, terrific research. And it is very simplistic and it is very absolute and people are absolutely sure they are right and the other people are wrong.

It seems to me that kind of what we are getting at here is it is not so easy.

One of -- at one of our panels one of the people said, you know, "What is really difficult about this is people I ordinarily respect a great deal come down completely on the other side from me on this and I need to try and understand that."

So I would try and capture some of this discussion starting maybe with Ruth's, you know, pointing out that the Belmont Report as a starting point leads in a certain direction and yet in some circumstances we may be very uncomfortable, with Eric about sort of telling other people what they can and cannot do, with David being uncomfortable sort of holding international research to a higher standard, yet with Alta saying, "You know, I am still left with residual sort of discomfort even if there is not too much risk and the possibility of benefit that there is still some exploitation going on."

It seems to me the other things we need to throw into this because this is going to be very case based, is, are the individual subjects giving consent? What I found bothersome about that oophorectomy experiment is these people are in a culture where they are not told they have cancer so to what extent are they really making informed choices?

It is one thing if they say, "Look, you know,

I would rather have a few fractures because everybody in my country is bent over anyway, but if you think I have less chance of breast cancer in 20 years I will go for it." But, you know, that was not there.

And to go back to a point that I think Eric was making, also it seems to me it depends on the government of the country. There are governments and governments, and if it is really a deal where you, you know, can get in to do research by buying someone a nice lab and the government pretty clearly is really looking to kind of pursue its own agenda and not the best interest of the people, that is much more problematic. When a government says, "Look, we are in a tough situation. We wish we could do more but, you know, and a lot of bad deals, your offer is actually pretty good and you are going to actually help us -- Prof. Capron, you build us some infrastructure, whether or not it works and that is a pretty good deal. And we are willing to take that trade off because in the long run we think that is best and we are not hurting individual subjects too much."

I think if we can get all that in there it will give people a sense of how you need to think all this out.

I just think, you know, we are not going to

resolve this today or next week or by the end of the report, but what we can do is sort of show people how to think it through.

PROF. CAPRON: Steve?

MR. HOLTZMAN: Yes. I just want to endorse that line of thinking which I think follows on yours. To use the old phrase, it is the "richness of the texture" that we have to bring out.

And when people who are used to agreeing find themselves violently disagreeing, it is generally because they have a shared conception of justice in this particular argument but what they are -- or where they are falling apart is how do they -- how do you apply the shared conception? That is what is driving them. Right?

Just -- and I think maybe if we could get into richness of cases. And again I keep coming back and I am not sure how relevant it is to the issues of level of risk you are exposing people to because I think that also goes into the political rhetorical element about how much you are using them.

So to give you an example, you know, my company does a variety of kinds of research, some of which is very, very, very early. So, for example, we are collecting blood samples from people in Costa Rica

because we are studying the genetic basis of bipolar disease.

Why do we go there? I do not think we -- yes, there is bipolar disease there as there is in the United States. If a drug is developed from this work 7 to 10 to 15 years from now, all right, they probably will not get it as fast, if at all. All right. But it is so far away it is -- when people say, "Have you promised to give them the drug?" It would be disingenuous to promise to give them the drug. It would be totally irrelevant. All right. But it also plays in here all we are doing is taking the blood sample and we are protecting confidentiality and whatnot.

Now having isolated the gene and having isolated the protein, and we say, "Geez, it would be really interesting if we could get these people and we could do a PET Scan study with an MRI," all of a sudden the game feels to me like it has changed considerably in terms of what are our obligations to them if we are going to start to involve them in those kinds of studies.

So I just would like to get that kind of texture.

PROF. CAPRON: Alta, and then we are going to

move on.

PROF. CHARO: First, in reaction to David's comment that he is uncomfortable at applying standards abroad that we do not apply to ourselves, I do not yet agree fully with that. I think there are reasons why we ought to apply different standards abroad.

One of them is that when standards are developed, announced, adopted and applied domestically here, as a citizen, I have an opportunity, maybe not a phenomenally good one but an opportunity to participate in a political system that allows me to reform those rules indirectly or directly.

When we move abroad we are working with people who do not have access to the political system in the United States to effect those rules. And that is when, in fact, Bernie's comment about taking note of what kind of government they are living under becomes quite relevant.

So I do not find it difficult to imagine that I might want to be more protective of how we behave with people who do not have access to the political system here to protect themselves.

DR. COX: And can I comment?

PROF. CHARO: Sure.

DR. COX: So I balance that against the --

because what this is, is a balance between getting certain types of research done, too. And so then what is the benefit of that research, okay, that you are going to get done or not get done.

PROF. CHARO: Right.

DR. COX: And that is the hard one to weigh. So one thing for sure, okay, is that if you hold higher standards up, you will get less research done. I know that for a fact. Right? So then what are you losing by holding those higher standards? That is the only thing I am asking us to keep in mind because every time we put a tighter screw on one end, right, we lose something on the other end.

So we just have to -- and we do not have a good way of measuring what it is we are gaining and losing.

PROF. CHARO: That is --

DR. COX: And that makes me very uncomfortable because what we are doing is, is we are making recommendations not just for ourselves, not our own personal views, okay, but this is in the best interest of human subjects protection using American researchers and American money. That is what this report is about.

So unless we can measure those trade offs,

okay, I think we just have to be very careful about making these more stringent decisions without really being able to have a measure about what it is doing.

PROF. CHARO: The second thing -- I am sorry, Alex, but it is directly responsive to Bernie's suggestion.

It is something that may -- it is present in the text already but it may be that it has not been pulled out quite this way. And that is the connection between the notion of obligations after the trials and I am thinking now about the recommendations at the end of Chapter 4 quite specifically.

In fact, particularly Recommendation 4, which goes right to that.

The interplay between that, the previous discussion and Bernie's comments about truth telling and informed consent, in that case reaction to Vietnam. It strikes me that if we think about the provision of any successful intervention after the conclusion of the trial, not solely as a kind of independent virtuous thing that we take on, but as an integral part of how it is that we calculate the risks and benefits to make sure that this both is relevant to the health needs of a country and meets the risk/benefit equation. It allows us to see things in a kind of spectrum.

The more that the benefit is going to be something other than the provision of a successful research product, the more that the benefit is going to be one of the secondary things like capacity building and generalized health care and, you know, payments of cash or kind, the more essential it is that one can justify the trial scientifically and that one can be meticulous about the informed consent process, which may entail truth telling so that people can individually decide whether or not to participate in such an exercise.

And the more that one looks at whether or not there is an individualized benefit of some sort to those subjects which might be through other kinds of health care they are getting in the course of the trial, et cetera.

I mean, in a sense what you are doing is you are kind of putting much more -- much higher demands on every other aspect of the protocol when you do not, in fact, incorporate into the benefits something having to do with the provision of the research intervention.

And I fear that this creates a loophole that you could drive a truck through but at the same time I think in some ways focusing on the text and not on the recommendation language may actually draw some of these

threads together and even possibly bring along people like Harold so that there is some consensus at the end about what we want the recommendations to do.

PROF. CAPRON: I have been told by Eric that we ought to probably take a short break and let people get up and stretch. Please come right back. We have not discussed Chapter 5 and we have, in effect, discussed a couple of the recommendations in Chapter 4 but we have not fully discussed a couple of others.

(Whereupon, at 3:15 p.m., a break was taken.)

CHAPTER 5 - ENHANCING INTERNATIONAL COLLABORATIVE RESEARCH

PROF. CAPRON: If I may begin, the only comment we have from Chairman Shapiro, as I understand it, on this chapter specifically is that he believes the chapter needs restructuring since the recommendations do not follow from the concerns of the chapter. Moreover, the tentative conclusions seem to repeat other recommendations in the report about some of which I have some probably lonely reservations. So that is his comment.

Ruth, do you want to begin the discussion by focusing on --

DR. MACKLIN: Yes. We are supposed to focus now on the handout. This three page handout that is

called “Chapter 5 Recommendations.“

Chapter 5 was hastily slapped together from the discussion at the last meeting and from the responses from the Commissioners who responded to the exercise that we put out on e-mail.

These recommendations that you see here, 1 through 6, number 1, were just devised this morning but we have to look at these because in fleshing out the rest of the chapter we have to see what you think of these.

So Chapter -- we want to go one by one through these recommendations. Everything after the bold, all these recommendations in bold, 1 through 6, will be further supported or are supported by what is already in Chapter 5.

When you go to page 2 everything that is not in bold face type is the responses -- is what were sent on the exercise, suitably modified in response to what Commissioners said in response to that exercise. And the exercise, if you recall, were here are things that are in other national and international --

PROF. CAPRON: Documents.

DR. MACKLIN: -- documents, not in our own. Should these be added? And those who responded to the exercise responded to, yes, they should be added and

here were some of the suggested wording and modifications.

But I think we should just start at the top and go down one by one since this is the last chance we have to debate them.

PROF. CAPRON: Okay. Recommendation 1: "The successor to OPRR should abandon the use of Single Project Assurances in International Research. The Agencies should develop criteria for making a determination that regulations or guidelines in other countries afford protections equivalent to those provided in the U.S. Federal Regulations."

As you recall, the language about equivalent protections is part of the present 45 CFR.

Bernie?

DR. LO: I want to take a page from what David Cox did earlier and say let's try and clarify the problem and then we can sort of see if the recommendations address the problem.

I think one problem that, Ruth, you very nicely laid out in Chapter 5 was the cumbersome process -- the current cumbersome process of assurances for international projects and the need to kind of rectify that or address that.

So I take it Recommendation 1 is intended to

sort of make that process less cumbersome.

DR. MACKLIN: Yes.

DR. LO: So what I am not clear about is if we say we no longer have Single Project Assurances, what would replace that? Is it that we would give internationally based IRBs a Multiple Project Assurance? I am not quite sure what we are going to put in place.

DR. MACKLIN: I think since each of these recommendations will be inserted in the text -- in the supporting text or the text that shows what the problem is, maybe what we should do is read through all of these, Bernie, because the answer to number 1 is not given in number 1 but we provide it later.

So could we just read through all of the recommendations so you will see where they are going because your question is quite right. I mean, it is not answered there so I think we should just read through all of them.

PROF. CAPRON: All right.

Recommendation 2: "The heads of U.S. agencies that sponsor international collaborative research should harmonize their procedures for ethical review and oversight of research conducted in other countries."

Recommendation 3: "Researchers should include in the research protocol plans for facilitating communication between or among IRBs in the U.S. and collaborating countries."

Recommendation 4: "NIH, CDC and other agencies that sponsor international collaborative research should permit researchers to request indirect costs for research they conduct in resource poor countries. In addition, these agencies should permit researchers to request funds for the operational costs of IRB functions in resource poor countries."

Recommendation 5: "Researchers should include in the research protocol a description of the mechanisms of oversight and enforcement in the country where the research is to be conducted. U.S. IRBs should assess the adequacy of these mechanisms in the review and approval process."

Recommendation 6: "The U.S. research regulations should be amended to include a new section that addresses international collaborative research conducted or sponsored by the U.S. This section should include the following provisions:

"(1) U.S. sponsoring agencies should permit research ethics committees in other countries to adhere to their own research regulations, guidelines or

standards of practice. Where those do not exist, U.S. sponsoring agencies should permit research ethics committees to adhere to international guidelines such as the Declaration of Helsinki and the CIOMS internatinal ethics guidelines."

Do you want to continue from there, Ruth, or are these more --

DR. MESLIN: They are not bold.

PROF. CAPRON: No. She explained these are the responses to the questionnaire.

DR. MACKLIN: Yes. These are the responses modified but what 2 through 6 include -- what they consist of are additional elements that would be in this new section. So maybe we do not have to go through all of that right now.

PROF. CAPRON: Yes.

DR. MACKLIN: I mean, but they are --

PROF. CAPRON: Well, they are drawn from other parts of the report as well. I mean, number --

DR. MACKLIN: Some.

PROF. CAPRON: Some of them are at least.

DR. MACKLIN: Well, wait, wait.

PROF. CAPRON: Things like research is --

DR. MACKLIN: Let's make clear what this is. These are items that were found in the chart to be in

other countries -- in other countries' guidelines or regulations, not in the U.S. guidelines. We discussed some of these at the last meeting. Then we had the exercise asking people whether these should be in the U.S. regulations and among those who responded these were the items that they thought should be and moreover some of the wording that was chosen.

PROF. CAPRON: And did that in each case represent a majority of those responding or just somebody indicating?

DR. MACKLIN: Yes.

DR. EISEMAN: Absolutely.

DR. MACKLIN: Oh, absolutely.

PROF. CAPRON: Yes.

DR. MACKLIN: The only -- there is a majority. Every one who responded, responded that these items not in the current U.S. Federal Regulations should be in the regulations. That was point number one.

Point number two, there were suggested wordings that were added to the preferred. There was an A, a B and a C. A was the wording that we provided; B was another country's or another document's wording; and C was make your own wording.

So obviously if any -- there were disagreements, we had to choose and adjudicate. But in

some cases it was -- in most cases it was accept the wording that we provided and we have the chart. We can pass around the chart. We have the chart that Stu made.

MR. KIM: Another chart.

DR. MACKLIN: Another chart. The mini-chart. The Stu mini-chart that essentially collated the responses and summarized them briefly.

PROF. CAPRON: Well, to the extent, Ruth, that these points are points which were substantively discussed as we went through other chapters, it would seem to me that what we should take away from the exercise is that people think that these are points which deserve to be addressed. The substantive statement of how they are addressed would be more appropriately derived from our own deliberations than from people having checked them off because they were covered in some other set of guidelines, it would seem to me.

In other words, if you look at point number 6, for example, here. We have just had a discussion. We did not fully resolve that discussion because you understandably wanted us to move on to Chapter 5. About how -- what happens when research is conducted that is responsive to the health needs and relevant to

the health needs in a country because it could provide potential benefits but the terms of how those benefits are worked out are subject to negotiation among the relevant parties, and they may or may not decide to insist upon immediate provision to everyone in the country at an affordable rate of the results of the research for a variety of reasons like the research does not yet yield a product or whatever.

So it seems to me that whatever language we develop would be the relevant language to include in our suggestion under Recommendation 6 of what this new section on international collaborative research would contain.

What that means, I think, is that we not debate this light Roman type here and just stick with the bold face recommendations for the moment. Is that reasonable?

DR. MACKLIN: Sure.

PROF. CAPRON: Okay.

Now that you see the overall shape, Bernie --

DR. LO: Maybe I just need to be brought up to speed. So as a result of Recommendation 1, if I am an investigator doing an international clinical trial, how is that process of getting assurance from NIH, assuming they are sponsoring some of the research -- OPRR,

assuming NIH is sponsoring, how is that going to be more or less cumbersome than the current system? I am just not clear.

PROF. CAPRON: As I read Recommendation 1, its intent -- maybe I misunderstand what you mean, Ruth. It is not that they should abandon the use of Single Project Assurances. It is that they should abandon sole reliance on Single Project Assurances.

So what it could mean, Bernie, is if some place in Uganda has set up a clinical research center and has an IRB functioning, and a number of international agencies or U.S. companies or CDC are coming up with projects to be done in Uganda, and they are all going through that committee, that once the committee meets the criteria that we are asking the new Office for Human Research Protections to develop, they would have a Multiple Project Assurance with them and it would lessen the burden because you as an individual researcher coming up with a new project would not have to gear them up and get a Single Project Assurance.

DR. LO: Well, I would prefer what you just said that the OPRR -- new OPRR should set up procedures by which international IRBs based in other countries can obtain a Multiple Project Assurance so that all clinical research being under their purview can be

approved on the basis of the MPA rather than --

PROF. CAPRON: Than an SPA.

DR. LO: -- an SPA.

PROF. CAPRON: That is what you meant.

DR. LO: Is that what you meant?

DR. MACKLIN: Not necessarily.

PROF. CAPRON: Not what you meant.

DR. MACKLIN: Not necessarily.

PROF. CAPRON: Okay.

DR. MACKLIN: We certainly did mean they should abandon the use of Single Project Assurances all together. We certainly meant that. So when you asked is that what we meant, yes, that is what we meant. They should abandon that.

But rather than relying on the assurance mechanisms, including possibly the Multiple Project Assurance, they should -- the agency should develop criteria for making determinations that regulations or guidelines in other countries afford protections equivalent to those provided in the U.S. regulations.

One way of doing that is to look at the guidelines or the regulations or the laws in those countries and see what those laws are. Now that is different from looking at the IRB and looking at the composition and providing for each single project,

according to the funding mechanism -- remember this is inserted -- this recommendation is inserted in the text after the description of all the faults and flaws and difficulties, including funding funder by funder so that the very same research project has different assurances based on who it is that is funding it.

That is what the Multiple Project Assurances do.

What we heard from -- what we got in the response from OPRR in the Puglisi memorandum was a detailed set of answers to just how they go about making these assurances but what we did find from them is that there are no criteria for determining that another country's protections are equivalent.

PROF. CAPRON: Right. They frankly stated that. What I do not understand, Ruth, is I gather even in this country there are any number of SPAs extant. There must be some reasons why sometimes a sponsor and an IRB or an institution determines that an SPA is all they want. They do not want to go through the process of an MPA.

And so I do not see why we need flatly to say that they should abandon all SPAs. They should abandon sole reliance on SPAs. In order to do that they also need to develop the criteria for approving an MPA.

That the country and the institution have guidelines and regulations equivalent to those in 45 CFR.

But having done that, I can imagine maybe somebody will say, "Well, actually all we want to do is get an SPA. We do not want to go through the process." I do not know why they would. I do not know -- but I do know that in this country we have SPAs as well so I do not understand why we should outlaw SPAs.

Do you? Isn't it just that we do not want them only -- now they have no criteria and they only use SPAs and all the problems that are in the chapter and that we have heard about say why that is -- that is a problem worth addressing.

Yes, Alice, please.

MS. PAGE: If you look at the chapter on page 9 where there is a description of the circumstances under which SPAs are used, admittedly there might be limited circumstances in which you could still use those but the problems that -- the problems come in the example for -- that Professor Tielsch at Hopkins -- he provided the case study in Nepal and there was a situation where studies were funded initially by USAID and they received the approval based on the Hopkins' MPA as the collaborating institution in the United States but when the funding source changed to NIH, then

they had to go back to OPRR and get the SPA, and those are the situations that you want to get rid of the SPA.

PROF. CAPRON: No one disagrees with that. No one disagrees with that. Any smart research administrator would say once we gear up to get an SPA, why don't we apply for the MPA so that we do not face that dilemma in the future.

MS. PAGE: I think then what we need to do is lay out the situations in which we might want the SPA to remain in international collaborative research.

PROF. CAPRON: You are in charge now.

PROF. CHARO: I guess I am in charge now. Bernie?

DR. LO: I guess it is late in the day and I guess I am still feeling very literal so it seems what we want to be able to say is that DHHS should make available MPAs for international research. Right? I mean, do we need to say that? In order to do that they need to set forth clear criteria for when they are going to consider regulations or guidelines in other countries as giving at least equal protection.

And it seems to me we also want to say -- I mean, is it clear that once you have an MPA and you change the funding source you do not have to go back for more? So it is really you want this -- I mean, it

seems to me what you are really telling them to do is use the MPA to approve international research to the extent that is feasible and the investigators and sponsors want it and to set up the --

DR. MACKLIN: Well, but there is just one other point. Sorry. And that is in the USAID section there are other ways -- ways other than the MPA. If you take a look at that section -- I mean, this is to go away from solely a reliance on assurances so the USAID specifies other ways in which it can find that there are equivalent protections.

So we want to put the emphasis on a finding of equivalent protections and a development of criteria -- of good solid criteria for making those determinations and there might be more than one way but it is not only the MPA.

PROF. CHARO: Bernie, would it be fair to say then that what we want to do here is the following: We would like the U.S. sponsored research to be facilitated by an emphasis on criteria being -- to be facilitated by being able to determine that regs and guidelines of other countries afford equivalent protections.

And where that cannot be done because, in fact, they do afford equivalent protections, that we

would next like to urge emphasis on more flexible instruments like MPAs and that the goal is to deemphasize high -- you know, kind of high transaction costs, low value tools like the SPAs.

Right? So it is just a matter of kind of a hierarchy of what you start with because there will be -- there will probably be as Alex thinks some occasions where you will still want to use these old nasty tools but the goal is to minimize those circumstances.

DR. MESLIN: Just as a discussion point and information, we have heard now from Australia, we heard from Dickens from Canada, and it is likely that in a place like Canada the second sentence of this first recommendation would be very relevant if HHS determined in cooperation with the -- with Health Canada that the Tri-Council policy and 45CFR46 were equivalent. Then you would not have to -- as a matter of international experimental policy -- you would not have to avail yourself of an MPA at McGill and the University of Toronto. You would be able to establish those criteria.

So in most cases the negotiation of the MPA has been stalled by a failure to identify the criteria that the U.S. Government would use when negotiating with the McGills or the Simon Frasers or the

Dalhousies. So the suggestion that they are linked is quite right. Your hierarchy is quite right but they are not jointly necessary. They can be separated.

PROF. CHARO: Bernie?

DR. LO: On page 11 it appears to my reading that under USAID approval you do not necessarily need a foreign IRB to approve the protocol. You can use the U.S. based MPA, is that correct? And are we willing to sign off on no IRB approval from the host country?

I mean, it just seems to me there is a lot of alternatives here all under the general rubric of making approval less cumbersome and it would help me if we could just sort of spell them out in the recommendations. Among the following, which we would like to encourage, are da, da, da, da.

But I am not sure one of the USAID ones, which -- it seems to me it says that you can use the Hopkins IRB and ignore -- and not go through another one -- is something we would want to support.

PROF. CHARO: Alice?

MS. PAGE: Technically that is true. I talked to Jim Sheldon about that and they do not require the local IRB review but they encourage it and institutions -- for example, I know Hopkins requires local IRB review as part of the collaboration. So in that

particular situation the case study that we presented to you, there was IRB review at Hopkins but then there was IRB review in Nepal as well.

DR. LO: Yes. I would feel uncomfortable not making that a requirement rather than just a --

DR. MACKLIN: But, Bernie, we have -- we make it a requirement. I mean, to say that USAID has other mechanisms does not mean that in our report we are going to accept all of the details that they might accept. We can impose any other requirements we want.

The value of at least part of what USAID does is that it seeks to make some determination of equivalent protections beyond or different from the multiple -- the assurance mechanism and that seems to be a positive thing. If, in fact, they will allow only a U.S. IRB and we do not want to allow that so we can say that. We are not saying we want to buy into the details.

DR. LO: And where do we say that, that we require a host country IRB to approve it as a recommendation? It seems to me that should be a recommendation.

PROF. CHARO: We could make that a recommendation. If I understand correctly, Ruth, when we write -- let's look at Recommendation 1 with the

first sentence omitted and just focus on the second sentence. That the successor to OPRR -- I guess it is OH --

DR. MESLIN: OHRP.

PROF. CHARO: OHRP. OHRP should develop criteria for making a determination that such and such is equivalent. We could choose to further recommend that when OHRP makes those criteria that it insists on local review as one of the criteria. We could do that if we wanted to.

It still leaves OHRP with the recommendation that it continue to flesh out the details of what constitutes equivalence, right?

DR. LO: I may just be having trouble with the hour here. I mean, why can't we have a recommendation to say OHRP, whatever their alphabet soup name is, should develop procedures to approve research sponsored by the U.S. conducted in international settings that is less cumbersome. Among the ways they may do this are bullet one, bullet two, bullet three. I mean, somehow the recommendation does not -- I mean, it sort of does not give me the gist of why we are doing this. To just say that we should develop criteria, you have to know an awful lot about sort of, you know, the ins and outs of international research approval to know that that is

going to make stuff less cumbersome. I would just rather be very clear and --

PROF. CHARO: Alice and Ruth, is that a realistic --

DR. LO: -- straight forward.

PROF. CHARO: -- is that a realistic edit? Because I know when it goes back into the body of the text, some of what you are saying is not obvious, and the recommendation will have just appeared in the paragraphs immediately preceding but nonetheless is it a realistic edit or reasonable edit to just say what Bernie was suggesting? OHRP should develop a less cumbersome mechanism for approving research, approving U.S. sponsored research in other countries. Among the less cumbersome mechanisms that are recommended are recognition of substantially equivalent protections according to criteria to be developed by OHRP.

DR. LO: To using granting MPAs to internationally based IRBs. I mean, I do not know what the other -- I mean --

PROF. CHARO: Right. And you should use your microphone. I am sorry.

DR. LO: Sorry.

PROF. CHARO: Eric?

DR. MESLIN: Well, I was just going to say we

have already provided to Commissioners copies of the draft revised assurances that OPRR has been circulating and discussing for some time in collaboration with the Fogarty Center.

So, Bernie, your suggestion make some sense so long as the text that acknowledges that the assurance system that we know now with SPAs, MPAs, is going to be changing. So that is kind of a given.

So if you want to add your list there is nothing -- I do not think that would preclude the -- but it changes the nature of the recommendation from this is what this group should do now to this is the things that the group should consider doing to make it a lot easier for everyone else to do research.

I think the easiest thing, though, is to make -- the most noncontroversial is to suggest that they establish criteria for this. That is completely absent and we have heard testimony for three years. Unless you folks have read those new assurance documents and have said these are very nice documents and we are delighted to see them and encourage more of that kind of simplification, you probably will not feel comfortable making the recommendation you made.

PROF. CHARO: Because of the hour and the fatigue factor that I suspect is dogging us, may I

suggest that we try folding this into the next and last go round because I think that we all intend very similar things, if not perfectly identical things.

DR. MACKLIN: I am not sure what you are saying.

PROF. CHARO: Move on to Recommendation 2.

DR. MACKLIN: Oh, yes.

(Laughter.)

DR. MACKLIN: It could not have been said more clearly.

PROF. CHARO: Let's move on to Recommendation 2. Comments on Recommendation 2.

Does anybody think that we should not harmonize?

Bernie?

DR. LO: No, I am just --

PROF. CHARO: You are just flipping the computer down.

(Laughter.)

PROF. CHARO: Going once. Going twice. Going to Recommendation 3. Oops, David, you just got in before the gavel fell.

DR. COX: Yes, I mean, sure, this is great but the -- I do not -- if I was reading it and I was one of these heads of a U.S. agency, I do not know how I would

do it because right now, you know -- so our job is not necessarily to tell them, you know, how to do it, I guess, certainly in the recommendation.

But unless we lay out, you know, possible ways that would facilitate them doing this, the -- we say we want it to happen but just by saying it, will not make it happen.

PROF. CHARO: Suggestions for ways we might get some concrete examples of how one can operationalize this that might be added to the text?

DR. MACKLIN: I want to just understand what David is saying. I mean, this recommendation will come immediately after a description in the text of what OPRR does.

DR. COX: Yes.

DR. MACKLIN: And what USAID does.

DR. COX: Yes.

DR. MACKLIN: And a quotation from a researcher that says NIH, FDA and USAID should get their act together and have one set of regulations. Now we cannot -- I mean, I am not sure what you are asking --

DR. COX: But then what I would say is if that is what we want is one set of regulations, we would say we recommend that all U.S. agencies that sponsor

international collaborative research have one set of recommendations.

DR. MACKLIN: Well, mechanisms.

DR. COX: Yes.

DR. MACKLIN: Yes. One set of mechanisms.

DR. COX: Say it. So we do not want them to sort of harmonize. We want them to get one set of recommendations.

PROF. CHARO: Any interest in responding? I think there is obviously a cross fertilization here with the oversight report and I think it is probably worth making a note here that there is cross fertilization with the oversight report, that the rule making process is cumbersome, any formal adoption of a new set of common rules is a cumbersome deal so that as an interim measure people can simply harmonize.

DR. MACKLIN: These are not in the rules.

DR. EISEMAN: These are procedures.

DR. MACKLIN: These are what OPRR has done and has decided to do. This is what USAID has done and decided to do.

PROF. CHARO: Oh, so these are amenable to --

DR. EISEMAN: These are not the regs.

PROF. CHARO: Okay.

DR. MACKLIN: Not regs. It is just how they

see -- what the reg says only is equivalent protections.

PROF. CHARO: Got it.

DR. MACKLIN: It does not mention SPAs, MPAs, et cetera.

PROF. CHARO: Got it.

DR. MACKLIN: All it says is equivalent protections so it does not require anything other than some guys getting together. That may be hard, David, I admit.

DR. COX: But, you know what, what my problem is, is that I read that the recommendation says to get together but I do not understand, okay, to do what. Sort of to what end. What you want them to harmonize in this but what is -- to be really specific, okay, about what the purpose of the meeting is.

PROF. CHARO: Recommendation 3. "Researchers should include in the research protocol plans for facilitating communication between or among IRBs in the U.S. and collaborating countries." Reactions?

DR. CASSELL: Well, then what else?

PROF. CHARO: Recommendation 4.

DR. MACKLIN: Well --

PROF. CHARO: I just did not understand what you --

DR. MACKLIN: -- that does not exist at all now.

DR. CASSELL: Well, I mean it should be there.

DR. MACKLIN: Oh, all right.

DR. CASSELL: I mean if you do not get an argument, Ruth, do not bite.

(Laughter.)

PROF. CHARO: Recommendation 4.

DR. COX: I would just like to make a practical comment on this.

PROF. CHARO: Yes.

DR. COX: This is dangerous because it is anecdotal. It is personal experience.

PROF. CHARO: This being 3 or 4?

DR. COX: This being 3.

PROF. CHARO: Okay.

DR. COX: Is that in efforts to do that in my own personal experience, I was told that I had no business even knowing who was on, okay, the institutional review boards of the other countries, and that they specifically did not want me to have any contact with them.

DR. MACKLIN: Your own institution told you that or the other country's?

DR. COX: No, the other country's.

PROF. CHARO: Okay.

DR. CASSELL: Undue influence.

DR. COX: That was part of it. They had their way of doing it. They were not interested in my way of doing it and that they did not want me to have any contact or any knowledge of who the people on the board was.

DR. MACKLIN: You know, that is very interesting because there are some -- in the international guidelines, and specifically in the one that is most detailed that does not apply and does not bind a lot of countries, the ICH Good Clinical Practice Guidelines, there is a wealth of specific details about IRBs and what must be presented, what must be the names of the members of the IRBs, their service, their areas of -- I mean, a whole lot of information.

So this sounds like an idiosyncrasy rather than something that one would expect to be common and --

DR. COX: Well, these were four of the major hospitals in a not very -- I will say the country. Taiwan. All right. Not an unsophisticated country with respect to research.

PROF. CHARO: Are you sure it was not just personal and they did not like you, David?

DR. COX: Well, that is a separate issue, Alta.

(Laughter.)

PROF. CHARO: Do you think that that anecdote actually indicates some reason to actually change this recommendation? Do you think it is --

DR. COX: Well, all I would point out --

PROF. CHARO: -- more general point there?

DR. COX: -- is that under this recommendation if that was something where I had to basically do it in order to have the international research done, I would have been absolutely unable to meet that requirement.

PROF. CHARO: All it says is that you have to include in the research protocol a plan. It does not mean that you have to be successful. If you are rebuffed, you are rebuffed as far as I read it.

DR. MACKLIN: Right, exactly. And, in fact, then you bring it back to your IRB and your IRB says -- and your IRB approves it based on the plan and then you come back and you amend your protocol by saying here is what happened. When I communicated with them, they said "no dice."

PROF. CHARO: Are you still worried, David?

DR. COX: If I can do that, it is fine. But it also does not allow -- okay -- the purpose of the

recommendation is so that there be communication. All right.

DR. MACKLIN: Well, you cannot make there be communication but if there is a plan and their people are of good will -- and what we heard from the people who testified -- I mean, at the -- two meetings ago was an urging of greater collaboration, that the chair of the IRB in the industrialized country visit the IRB in the other country and that they exchange regular communications and visit one another, I mean. And that was one of the suggestions and it is in the text.

PROF. CHARO: So either in the text or rewritten in the recommendation that the plan is to facilitate all mutually desirable communication.

DR. COX: Or, I mean, I think it is fine the way it is written. I am just trying to give a bit of reality to what is going to happen when the rubber hits the road.

PROF. CHARO: The rubber hits the ground. Bernie?

DR. LO: I mean, this is all -- this recommendation, as stated, has the responsibility of relying on the research. Does the IRB have any obligation to sort of -- to make some attempt to see what the other IRB has to say about the protocol?

PROF. CHARO: Reactions?

MR. HOLTZMAN: Just something to think about it. I think he has -- it is just late in the hour.

PROF. CHARO: I do not think anybody can say it is a bad idea for the IRBs themselves to take advantage of these but it is usually the investigators that are actually communicating because they are actually collaborating, right?

DR. MACKLIN: Yes, I mean, I think --

DR. COX: That is exactly right.

DR. MACKLIN: David's example, I think, goes more to this recommendation -- I mean, to this point, that point, that the IRBs -- I mean, if the chair of your IRB tried to contact the other person, I mean, they would throw up, you know, a barrier.

DR. COX: Exactly.

DR. MACKLIN: So the researcher is the one who is supposed to facilitate it and then there has to be some cooperation.

DR. COX: Yes. And if there is not cooperation then you have done the best you can but I am just -- the -- and what this is -- the reason is insecurity across international boundaries about the people will be told that what they are doing is not adequate. I mean, that is -- or -- okay -- other internal politics

that they do not want any Americans dealing with.

So -- but either one of those is a fine reason not to let -- you know, you see it but that the -- I think that is going to be -- I do not know -- actually I do not have a -- since it is personal experience, I cannot generalize it. But I know it happened once. So then if that is the only time in the world it ever happens then my statement is irrelevant.

PROF. CHARO: Okay. I gather we have probably mined this --

DR. MACKLIN: Yes.

PROF. CHARO: Any further comments on this? Recommendation 5.

DR. MACKLIN: No, 4.

PROF. CHARO: Excuse me. Recommendation 4.

DR. CASSELL: Well, just as a matter of fact, at the present time they do not get indirect costs?

DR. MACKLIN: They are not allowed to.

DR. CASSELL: So I am at Cornell and I want to do a piece of research that is going to take place in Thailand, my institution gets no indirect costs?

DR. MACKLIN: Cornell does.

DR. CASSELL: Cornell does.

DR. MACKLIN: The Taiwan institution does not.

DR. CASSELL: I see. So that is indirect

costs for the host. I see.

MR. HOLTZMAN: That should be clear.

DR. CASSELL: That is not clear so it should be for the host in the resource.

DR. LO: I am sorry. A question --

PROF. CHARO: Bernie?

DR. LO: That is true even if it is not a contractual arrangement but that it is a co-investigator site, you cannot get -- what is the rationale for that? I mean, is there a rationale?

DR. CASSELL: Save money.

DR. MACKLIN: No.

DR. LO: They do not like our tax dollars going --

DR. MACKLIN: I do not -- it might be that. I do not know. I mean, I actually know since we are telling anecdotes from my own personal experience where I just put in a grant to the Fogarty Center that my collaborator and the co-director of the program in a developing country was not allowed -- not only not allowed to have any indirect costs so the institution through which this program would take place said, "We have to get indirect costs so we are going to take it out of your salary or we are going to take it out of some other. We are going to take it out of stipends

because we need the money."

So, I mean, without doing anything dishonest, and we did not, or anything illegal, I mean we had to figure out how some benefit could go to that institution which said “we need it, we cannot let you do a project here.” But it was prohibited by the NIH because there were no indirect costs permitted.

PROF. CHARO: Bernie?

DR. LO: Well, then I think the recommendation is not just that you can request it, you can request anything you want, they need to cough up the money.

(Laughter.)

DR. LO: Right. I mean, the NIH has to pay for indirect costs for research conducted in developing countries just as they would for research conducted in the U.S.

DR. CASSELL: Okay. Well --

PROF. CHARO: Eric, what are you muttering about up here?

DR. MESLIN: Never mind. He was just --

PROF. CHARO: Rachel?

DR. LEVINSON: I would not tie it necessarily to indirect costs. The point is that you want supporting costs, however they come out, and because we have a cap on the administrative expenses and indirect

costs here that limits the amount of money that can go to it here, there is going to be something coming out that might give you clarification of what you can direct costs.

So I would not even refer to indirect costs. It is the support, however it is most appropriate and easy to get, and if you want it to come out of your sponsor then so be it if it is necessary in order to get it done in the other country.

But I would not be so prescriptive right now as to say indirect costs. Some other way might be better.

PROF. CHARO: Bernie?

DR. LO: That is a good point. I mean, the problem is that as we all know from our own universities there are indirect costs and direct costs. I mean, it seems you have got to pay for the telephone and the fax machine and the secretary. And when the NIH says, "Oh, that comes out of your indirects," you cannot do that.

But in addition your university says, "Well, there is the library, there is the janitorial service, there is this and there is that," and, you know -- I mean -- so it seems to me they are both above the line costs which I think Ruth might be able to sort of get

some of those expenses. But the university board is going to come back and say, well, you know, there are all these other things as well that you pay for in the U.S. and you are not paying for here and you cannot write it as a line item because you cannot write, you know, $400 for use of the library or something.

DR. MACKLIN: Well, there is also -- the second part of this says, "In addition, these agencies should permit researchers to request funds for the operational costs of IRB functions."

PROF. CHARO: Right.

DR. MACKLIN: I mean, that was another thing that we heard here, that is they have no money at all to support the IRB, much less the photocopying and the personnel because there are no costs that the institution will provide for that.

PROF. CHARO: David?

DR. COX: So I really like Rachel's suggestion on this because when we start prescribing under the context of whether it is direct or indirect costs, okay, whether it is public agencies or even private agencies, many private agencies limit the amount of indirect costs that they will do. The universities say, well, you know, then we will not take your money.

Guess what? Even though I get that grant, I

cannot get the grant because the university will not let me accept it. So that is the reality of research even in this country.

So what do you do for colleagues in other countries? You put them above the line in terms of the direct costs and you send them that money.

Now it still is not fair because it does not support the infrastructure of the country, which is what this recommendation is all about.

So that I think what you are really saying is it is a fundamental change in terms of the policy of the funding agencies and you will have to deal -- it will be a separate deal with each funding agency.

So even accepting that, that you are going to do that, then there is another component to this. What defines a resource poor country? How poor do you have to be before you actually deserve to get those kinds of funds?

So I think that although the spirit here is one that any of us that do international research support, implementing this, I think, is really difficult.

And that there needs to be a mechanism if you are going to be doing international research to support the functions of the research. I mean, that has to be

the case in the broadest way but that if you -- if the governments will not let you do it unless you support the governments, that is what this is about. Right?

I know that the NIH view -- the reason why they will not do this is because they feel like they get bled dry. And that the governments have plenty of money and this is just a way for the governments to recoup more money and they do not want to have their research funds spent that way.

PROF. CHARO: If I may put myself on the list now. Suggestion 1, with regard to deciding which countries we want to be covered in this recommendation, USAID has terminology -- and I do not know what word they use but it conveys the meaning of which countries are on the list that are eligible for USAID assistance.

And that would roughly correlate with resource-poor and might be a good working definition and it is amended from time-to-time.

DR. COX: Perfect.

DR. MACKLIN: There is an index.

PROF. CHARO: There is some kind of --

DR. MACKLIN: There is an index, yes.

PROF. CHARO: But whatever they use might be a good proxy to adopt so that we get rid of that one area of --

DR. COX: Perfect. Done. That is the easy one.

PROF. CHARO: The second is that it may be that what we want to say is that we want NIH and CDC and other federal agencies to remove existing obstacles to providing --

DR. MACKLIN: That is --

PROF. CHARO: That is step one but that is step one. We want them to remove the existing obstacles to providing funds that would cover indirect costs.

And then step two is that there is a more proactive thing that says we want the Federal Government when it is supporting research to provide adequate funds to cover the necessary infrastructure IRB creation and maintenance and other research related -- no, or compliance related costs. You know, interpreted broadly. And then try to get away from things that might indirectly, no pun intended, get us caught up in the details of U.S. technical rules.

DR. MACKLIN: Yes. But let me go back to what David said about the governments bleeding people dry. I mean, this is really intended to be at the institutional level. You have a collaborating institution. It is going to be a hospital or a clinic

or a research unit within a university. So it is not going to be one of these government situations or it should not be. So maybe more specifically we are really talking about supporting the IRB. It is the researcher and what the researcher needs to conduct the research and deal with the administrative mechanisms.

We did not want to limit it to the IRB but if it is at the institutional level, would that --

DR. COX: If you say that, okay, that is very different from indirect costs supporting the whole other institution.

DR. MACKLIN: Yes. We are going to drop the words "indirect costs."

PROF. CHARO: Okay.

DR. MACKLIN: So we are going to drop that. We are going to say "financial support." I mean, use the term "support." You say "financial support for administrative and other operational matters at the institutional level" because that is where these researchers --

PROF. CHARO: Right.

DR. MACKLIN: -- the institutions are poor. We know the governments have a lot of money. They are fighting wars. They are, you know, paying billions for their wards but it is at the institutional level where

they do not have the funds. So maybe that is how we have to specify it.

PROF. CHARO: Okay.

Steve, then Rachel.

MR. HOLTZMAN: Well, Rachel seemed to have a question.

PROF. CHARO: Rachel?

DR. LEVINSON: No, it was just that if you say "administrative," it is a buzz word for indirect costs. So I would suggest instead to use the cost of compliance. It is going to be the new buzz word.

DR. COX: Perfect.

DR. LEVINSON: It is not prejudicing it, whether it is direct or indirect or administrative or anything else.

DR. COX: Perfect.

MR. HOLTZMAN: Yes, but we have two different issues there. So let me introduce an industry term.

PROF. CHARO: Steve, then Bernie.

MR. HOLTZMAN: Fully burdened costs. That is what we call it. That is what we call it in industry.

PROF. CHARO: Fully burdened?

MR. HOLTZMAN: Fully burdened costs.

PROF. CHARO: What does that mean?

DR. CASSELL: That is wonderful.

(Laughter.)

MR. HOLTZMAN: No, but -- what does it mean?

PROF. CHARO: Yes.

MR. HOLTZMAN: It means the fact that when I pay -- in your terminology I pay your salary, your direct costs, right, but I also have to pay for the air conditioning. The full burden of having you on my payroll is X. That is the concept. All right.

Okay. But what are we focusing on here? Are we focusing on the fact that it seems an oddity that the government will not pay the fully burdened costs of researchers outside the U.S. or do we want to say -- and, therefore, we want to say they should? Or do we want to be making the point that there is a cost associated with research, namely the operation of ethically related functions, which is not normally paid for but should be.

Those are two different points. Which one is our focus here?

PROF. CHARO: Bernie?

DR. LO: I think that is a very helpful clarification. I would say you need to do both because, you know, the battle we all fight with indirect costs is that a lot of things like secretarial support, telephones, stuff like that, which is an

ongoing battle. They say that is including your indirects, you cannot charge above the line, and they cross it out of your budget so that --

MR. HOLTZMAN: So I will play devil's advocate here for a moment since I do not have to live with this problem. This is about the ethics of international research. Why are we tackling a recommendation about what should be allowable costs that the government funds that have nothing to do with the ethics of research in this report?

DR. MACKLIN: Because they cannot do what they have to do to comply with our ethical requirements without any money.

MR. HOLTZMAN: But, Ruth, then we could say that focusing in on the ethical -- the funding for that which is necessary for the ethical compliance as opposed to all "indirects."

DR. LO: Steve, I think --

DR. MACKLIN: That was the intent.

MR. HOLTZMAN: Okay. That was my question.

PROF. CHARO: Bernie?

DR. LO: But there is another ethical argument. That is we make a big deal of infrastructure building and you cannot build infrastructure if you do not have the money to pay for the personnel, the

equipment, and things like that.

So, I mean, to the extent that we say that part of what you need to do is, you know, help train people and, you know, provide the infrastructure, if that is not in your budget then that is -- then we are making an empty gesture, and that is the fully burdened costs.

DR. MACKLIN: It can be, though. I mean, for example, you can -- equipment. Part of the infrastructure is equipment and you can -- the NIH has no prohibition on equipment that you need to carry out the research. I mean, including computers, et cetera, in those places. So, I mean --

DR. LO: But secretarial support, telephones is often, you know, in this country said that you cannot put that into a grant, that should be part of the indirects.

PROF. CHARO: I think that --

DR. LO: And that is the infrastructure.

PROF. CHARO: I think that it would be lovely if we could try to capture both kinds of costs. And I understand Steve's point that the generic support of research abroad is separate from the issue of the ethical conduct of research abroad. But I do think it is disingenuous to say we are going to write an entire

report about promoting ethical conduct of research when we have no interest also in simply promoting research per se.

I mean, this is --

DR. COX: Well, I am not sure about that.

PROF. CHARO: I would put it out then as a proposal that it is appropriate that we want to, in fact, foster healthy collaborations and healthy collaborations mean that you have to make it possible for the institutions to say, yes, we would like the research done.

DR. COX: Okay.

PROF. CHARO: Something they are not currently able to do because it leads them to say yes. And that, second, having said yes, that they now are given the means to do it the way that we all ideally wish it would be done.

MR. HOLTZMAN: Right. So, Alta, what I have no information about, what we as a Commission, I would submit to you, have no information about, which we have had no discussion about, okay, are federal policies pertaining to what a reimbursable expense is, in general, per se, excluded and not excluded, for what kinds of research, et cetera, et cetera, and we are making -- you were making a bunch of assumptions there

that there is not good reasons why different rules are applied.

Now so I am just uncomfortable with that because we have not looked at that issue at all.

I am very comfortable with the fact that we spent a lot of time saying that putting in place the necessary -- putting in place the necessary institutional apparatuses, apparati, to ensure ethical conduct of research is something we have a stake in and we should put our money where our mouth is.

PROF. CHARO: Eric?

MR. HOLTZMAN: Thank you.

PROF. CAPRON: I am sorry.

DR. MESLIN: I would just like to remind Commissioners that in two reports, the Capacity Report and the HBM Report, we did address issues of ensuring that there were adequate resources available to ensure that the protections we were proposing in those reports could be carried out by the institutions.

The wording was general. It was wording that institutions should seek ways to find appropriate resources. So as a matter of historical record the Commission is on record in speaking about resources but in the narrow description maybe that Rachel used. I forget the phrase.

PROF. CHARO: Cost of compliance.

DR. MESLIN: The oversight report will address this issue as well. So since Ruth has already admitted that the intention of the phrase was to cover those types of issues rather than everything else, I will just submit that we already have had a bit of a discussion over the last three years, and this is not going beyond the pale so long as it is within Steve's interpretation.

DR. MACKLIN: We have a recommendation about capacity building in another chapter. Okay. This is specifically with regard to enhancing collaboration and the operation of IRBs and all of that stuff. So this is not the only place where we are talking about enhancing -- about capacity building and that really is a whole section of another chapter.

PROF. CHARO: Okay. Then in that case would it make sense to move on to Recommendation 5?

Recommendation 5. Reactions?

DR. COX: So I come back to my example again because if I had to do this, okay, and that they will not even tell me who is on the IRB or how it works, it is impossible for me to provide any of that information as a researcher.

PROF. CHARO: Also, a question to Ruth and

Alice. In light of Recommendation 1, which as eventually written is emphasizing the kind of finding of substantial equivalents in lieu of the kind of site by site system we have now had, what is it that in Recommendation 5 you would like the IRBs to add that will go beyond what would have been accomplished already by virtue of this kind of certification of substantial equivalency?

DR. MACKLIN: Well, I guess the one thing we heard without getting a very clear resolution of and the one thing that came out from Puglisi's memorandum for why they do what they do or why OPRR did what it did, was that other countries do not have the enforcement mechanism that OPRR -- that OPRR has essentially been in this country.

And at least -- well, it was Sana Loue. I am not sure if there was anyone else. When asked what is the assurance in those other countries that the regulations that they have will be complied with, there was no -- there was little or no answer to that and a lot of people said, "Yes, we have all these rules but there is no enforcement of the rules."

PROF. CHARO: Well, in that case it seems like in some ways what we may really want to be saying in 5 is that the researcher has to work with the IRB to

figure out how the American IRB is going to be able to know that the protocol is being carried out as expected when it was approved.

Now that may entail -- that may involve telling them all about the local or host country IRB but it may be that there is going to be another mechanism because they are dealing with an IRB that is not cooperative like David's or something.

But it seems like the goal here really is that the American IRB has some way of assuring itself that things are going according to plan and that it does not really matter what the mechanism is, and it does not rely necessarily on knowing how the host country IRB operates. Just something that will give them some way of pulling that off.

Is that reasonable?

DR. MACKLIN: Yes, it is. I am just going back to your first comment that what does this accomplish that is not already accomplished.

PROF. CHARO: Well, I am actually -- I am glad that it is here, though, because Recommendation 1 when it focused on national level regulations and guidelines did leave me uncomfortable about how that translates into site specific enforcement. So without 5 I find myself uncomfortable with one standing alone as a

sufficient guarantee.

So I am -- personally I am pleased to see something in 5 that to me does go beyond. The first is kind of is there something in place that in theory can help all this happen properly and then 5 is now how can we be sure.

Diane, and Steve.

DR. SCOTT-JONES: Alta, I have a question. If you are recommending that there be some mechanism for making sure that as the research is conducted, it is done according to the plans and agreements?

PROF. CHARO: No, it is not -- the usual kinds of things we do here. We have got periodic continuing reviews. There is a means of auditing.

DR. SCOTT-JONES: Okay. That is not really done here. One of the anthropologists who spoke to us in a previous meeting made that point. He said that there should be more done to make sure that researchers really do follow through and do what they are supposed to do. That really is not done to any significant degree here for U.S. researchers. It is not done.

PROF. CHARO: Steve?

DR. MACKLIN: Well, we are not asking --

PROF. CHARO: Wait, wait.

DR. MACKLIN: I am sorry.

PROF. CHARO: Steve, Rachel, Ruth. Steve, weren't you going --

MR. HOLTZMAN: Yes. But was Ruth going to provide an answer?

PROF. CHARO: Okay. Sorry. Ruth?

DR. MACKLIN: Well, I mean, there are two kinds of monitoring. You are certainly correct that there is no monitoring of the research activities or of the informed consent process in order to ascertain that they are doing what they say they are doing. I mean, that would have to be an on site monitoring.

This is really talking about --

DR. SCOTT-JONES: That is not what she said.

DR. MACKLIN: I did not -- I do not think you were talking about on site monitoring but --

DR. SCOTT-JONES: She just said site.

PROF. CHARO: No, I did not or if I did, I misspoke.

DR. SCOTT-JONES: Okay.

PROF. CHARO: Eat one or the other. All I meant was that in lieu of the research in the United States having to explain how the Taiwanese IRB is going to operate and enforce, I was saying that what is really at issue here is how the American IRB is going to be comfortable at the end of the day that its

protocol is the one that is in operation, that it will be getting adverse event reports, that it will be getting an opportunity to conduct continuing reviews, et cetera, et cetera.

I mean, all the stuff that it would usually do for itself here where the local is what it can accomplish and I do not care how -- it can be done by many mechanisms. That is not on site continuous monitoring.

MR. HOLTZMAN: So two points. The first is that if we consider Recommendation 1 as, so to speak, let's look at a country and see how they regulate, and if we feel good about it or not, it seems to me 5 is more about with whom you are working, are they implementing. Not in the sense of monitoring.

And so that maybe what you should be convincing yourself is not that the country's mechanisms of an oversight and enforcement but it is rather for this study, are they doing it? Are they going to do it? What is their plan? So I think if you read it that way it is sort of the drill down to the next level.

Then the second question which we seem to be dancing around a little bit is whose responsibility is this, where do we wish to identify, locate the

responsibility for the ethical conduct of the research or that institutional ethical conduct?

Are we saying that Dave Cox, researcher, has to go out and make sure and bring to his IRB -- because we want researchers to be thinking that way -- that that institution does things right before he says I want to collaborate with so and so.

Or do we want to locate the nexus of that responsibility with the IRB, the local IRB, which is where some of your comment was going.

And so -- I mean, that is a very interesting question because there is policy implications on how we are thinking about what we are trying to say about whose job it is.

DR. MACKLIN: Well, there is not -- I am sorry.

PROF. CHARO: No, no, you want to answer that and then Rachel had a comment.

DR. MACKLIN: Yes. There is not just one right way or only one way and it may depend on the circumstances. For example, we heard two different -- two researchers who provided testimony in the same meeting. One of whom conducts research in Haiti under the sponsorship -- with an IRB from Haiti as well as the Cornell University Medical School IRB.

He had to satisfy the Cornell University Medical School IRB. There is a Haitian IRB and he was uniquely placed because he happens to be on the faculty of both places. That is going to be rare but that is why when you ask whose responsibility he was able both to facilitate and communicate and be present at both IRBs, and he was the one who made the recommendation that the chairs of the IRB should visit each other.

Then we heard from a researcher, who used the expression that he felt -- that the host country's IRB was inscrutable and when asked what he meant by that, he said, "Well, in the first place I do not know how they operate. I do not know exactly what they do. I have to place my trust in my collaborator in Mali." Why did he have to do that? Because, among other things, he did not speak the Malian language and so part of what was described in that testimony was the need for trust, placing trust.

So in his case because he could not even visit -- I mean, he might have visited the IRB, I do not think he was prevented from doing so, but he would not have understood a word.

On the other hand, if you do research in a country where the IRB may be an English speaking country, a resource-poor developing country, then you

can visit the IRB. So there may be many models and I think we cannot shoe horn it. I just want to know whether we -- the recommendation should be in some form or another and it may be too hard to make it specific.

PROF. CHARO: Rachel, did you want to add something?

DR. LEVINSON: Yes, I guess I do. I think everybody is right. Diane, you raised an interesting point about what is or is not done here, and it brings to mind the fact that there is going to be increased emphasis here in the U.S. on continuing review.

And so it is appropriate for the IRB here, and they may be more demanding in the future of that, to know what kind of continuing review will be done in the host country on site, whether or not there is any visiting or understanding of language or not, they still ought to be in the position to be able to ask and receive information about how that is going to be done.

So that is on one point.

Steve's point about level, what is done at the country, the institutional, the researcher, the IRB level is important, also, and I do not see that 1 and 5 lead to problems in that respect, that there will be responsibilities at all levels.

And Ruth brought up something that is relevant

there having to do with the fact that the compliance will be different project by project so that the agencies should look at the national regulations as we have them that still leave flexibility for different options for ensuring compliance, and that the actual options that are selected for a specific protocol should be known to the researcher here, including those that will be put in place by the IRB in the host country, and they ought to be able to relay that to the IRB here.

So it is just information flow at different levels that ought to be facilitated by these recommendations.

PROF. CHARO: Further comments? Diane?

DR. SCOTT-JONES: As I read the text, it seems that there is a lot of emphasis on trust, which Ruth just mentioned a few minutes ago, and it seems that there is not much of a way to get around the need for trusting that some of these standards are going to be put in place.

It seems to me that what there is a lot of discussion of is the need for trust. And so I am not sure how that plays a role in what you are recommending here.

DR. MACKLIN: Well, there is a section in the

chapter that deals with trust.

DR. SCOTT-JONES: No, that is what I just said.

DR. MACKLIN: Yes, I know. I know. But you cannot put trust in the recommendations. You cannot say "trust me, I am an honest researcher." I mean, but it is --

DR. SCOTT-JONES: Basically that is what you have got in the text. That is my point.

PROF. CHARO: David?

DR. COX: Can I just say from a researcher's perspective, this issue about language is really good.

From my perspective, what I absolutely have to do is trust my collaborators to do it because, okay -- is that -- and let me tell you what I have done in the past is that I have people who work for me who speak the language who have gone and sat in on the interviews to see what is going on, and that it was not what people told me what was going on.

Now -- and then when we talk to them about that they said, "Well, but we did not know that you really meant that."

So for me to even know what is going on as a researcher is extremely difficult. Now I know generally what is going on but not sort of specifically

what is going on and when the rubber hits the road on the important stuff that is where you need to know what is going on and you simply do not.

So what this is doing in my view is implying more knowledge on the part of the researcher of what the situation is that it is, in fact, the case, and that builds a series of Emperor's New Clothes things.

Now I know that is not the intention but looking at it from the point of view of the researcher who is trying to do this stuff, he or she knows that some of the stuff they will actually know about and some of the stuff they will not know about, okay, and they have to trust.

So the more things we put in there that really implies that you know more than you know, I think is going exactly the opposite direction of where we are trying to go.

DR. MACKLIN: Should we eliminate Recommendation 5?

PROF. CHARO: Well, but then we are left with nothing that has to do with site specific confidence.

I mean, I am finding myself wondering if what we would like to achieve are a set of criteria first for determining whether regs and guidelines in other countries are substantially equivalent and, second,

criteria for when the protections -- the operationalized protections at other institutions are substantially equivalent.

DR. COX: Yes. And could I --

PROF. CHARO: And with that latter, the risk, of course, is that it is going to get bureaucratized the same way because that is the SPA/MPA process. And what one would love to be able to communicate is something that is more flexible than that.

DR. COX: Yes.

PROF. CHARO: Or instead of demanding that they have seven people with these particular areas of expertise, that the criteria actually go to the guts, the substantial equivalents at the institutional level is something that ensures that the people being recruited have been screened to make sure that it is really voluntary, that they are really being given enough information to make a reasoned decision that they really understand that they are able to drop out whenever they want to.

And it does not really matter how this is being accomplished, whether it is by a committee of seven or 17, so long as it is being accomplished. I am not sure if that is a realistic kind of recommendation.

DR. COX: Well, it is, Alta, and it comes back

to Steve's point, which he put sort of very -- he put it up, you know, sort of for grabs but I would like to be more specific about it.

I think that it relies completely on hearing how the foreign IRB does its job and that -- and put the onus -- okay -- on that local institutional part on how the IRB does business. This is why I wanted to know about the IRB of my collaborators so I could actually judge how they were going to do it --

PROF. CHARO: Right. But --

DR. COX: -- and that is exactly why they did not let me talk to the IRB.

PROF. CHARO: But my point is that if you could not know about that IRB that you could similarly accomplish that goal by telling your IRB, you know, you, the American researcher, David Cox says to his IRB at Stanford, "I cannot find out about the Taiwanese. But I can, in fact, make you confident that there are going to be substantially equivalent protections there because I am going to send three of my own students who speak the language to be part of the trial, and that is in lieu of relying on their IRB because I have no way of doing that because they are not giving me the information I need." So I am giving you an alternative way of getting to the same place and that is the kind

of flexibility I would love to be able to offer up rather than making it -- rather than tying it to the other IRB's enforcement.

Bernie?

DR. LO: Well, Alta, I think we are talking about two very different kinds of things that is really going on. On one level I think David is talking about are they really saying in the informed consent process what we said they were going to say. Are they really enrolling people who we thought were going to enroll?

From the IRB's perspective, I think it is a lot different. It is, you know, are you doing something totally different? Have you turned this into a clinical trial rather than an observational study? Have you reported side effects, complications?

And so I think there are things that really have to deal with what is actually going on when you close the door and the researcher and the potential subject go into an office together.

And there are things that have to do with kind of aggregate data about what did you do during the past year in your study that an IRB here is supposed to look at.

I think the first is very, very hard to do because it really does require on site direct

observation, which as Diane pointed out, we do not really do in this country.

We are supposed to at least keep -- I mean, at least my IRB keeps track of am I, you know, just continuing the study indefinitely when it is supposed to wind down. Am I enrolling, you know, ten times the number of people or something?

I think that is something that we should hold people to the first --

DR. MACKLIN: That is the compliance really.

PROF. CHARO: Do you have enough ideas about ways to try to redraft this yet?

DR. MACKLIN: No.

PROF. CHARO: No.

DR. MACKLIN: I mean --

PROF. CHARO: Because I mean this was the first take on these so it is --

DR. MACKLIN: Well, but the -- I mean, no one seems, in principle, to object to the recommendation but what people are doing, quite appropriately, is saying here are some problems and I do not know how a redrafting can meet the problems. I mean, that is, either we do not have any such recommendation or we have it and acknowledge somewhere in the text that, you know, this is -- it is not going to be easy to

implement.

DR. COX: But, Ruth, what I have heard -- at least what I heard Alta say -- is that she -- more than the general things, she wants some site specific stuff but then in the context that it has to be a requirement if there is a local IRB, which has to be a requirement, we have said that, then we just want to know how are they at a local IRB dealing with this issue. Okay. Dealing with this, period.

PROF. CHARO: That is actually -- that is exactly what Recommendation 5 now says.

DR. COX: No, that is not what it says. It says the researcher supplies that, right. So that in this situation -- I mean, if we are going to do the stuff, just not have the onus on the researcher per se but say that the IRB has to say how they are doing this.

DR. MACKLIN: Right, but I guess the question is what is -- the researcher is the conduit because IRBs do not communicate with one another. Now somewhere else we are saying, yes, they should communicate with one another but, in fact, IRBs do not communicate with each other and --

DR. COX: Well, they do not communicate with researchers either.

PROF. CHARO: Well, then where is this information supposed to come from, David?

DR. MACKLIN: There are two parts to this. The first part says, "Researchers should include in the protocol a description of the mechanism," which means that the U.S. researcher should have some knowledge from his or her collaborator in the developing country what goes on at that site. And I think we should make it site specific.

The second part says, "U.S. IRB should assess the adequacy of these mechanisms in the review and approval process." So that puts the onus on the U.S. IRB to look at the site specific information that it gets from the other country.

Now maybe we do not need the second part if we have the general approval. I mean, the mechanisms in Recommendation 1. But I do not see how -- even though the IRB has to provide the information, it has to go through the researchers in order to get back to the United States.

DR. COX: I hear you, Ruth, but I just -- this is a -- I mean, I am having a hard time operationalizing this.

PROF. CHARO: We can -- Diane?

DR. MACKLIN: Let's go on. Let's go on.

PROF. CHARO: Diane?

DR. SCOTT-JONES: I just wanted to point out that I thought the discussion of this was very interesting and a lot more -- incorporated a lot more of the problems that would occur than the Recommendation 5 itself because there is mention of the problems that would occur in getting information. There is an acknowledgment that you cannot write policy and regulations around this problem. It seems to me that there is something that could be done to take some of this language and incorporate into Recommendation 5 so it will not read as if this is something that is a fairly easy and routine kind of thing to do because it is not.

PROF. CHARO: I know Ruth just asked us to go on but let me just ask Eric a procedural question. Is it possible as we send this out for public draft to have, in a sense, an asterisks that flags this and say, "Look, we have already anticipated some difficulties in implementation and we would particularly appreciate feedback from IRBs about how one might best go about it?" I mean, some -- or something that would get us more information from people that actually have to try it out and see if we get any good ideas from them.

DR. MESLIN: Yes.

PROF. CHARO: So that would allow us --

(Laughter.)

PROF. CHARO: -- to do what you asked for, Diane.

DR. MESLIN: I could give you the long answer but the answer is yes.

PROF. CHARO: Steve?

MR. HOLTZMAN: Putting aside the fact that, in general, as Rachel pointed out, hopefully in the future we will have better mechanisms for monitoring compliance as studies go on. The SPA as it currently works effectively is a blend of two things. What we are doing in 1 and 5. It is the removal of the SPA in 1 that then raises the question about what about this site.

In some ways I find myself saying think of the site as, so to speak, that foreign site as a subcontractor. So if you get a government grant or contract and you propose to subcontract, all right, what liabilities and responsibilities do you as the contractor have for the conduct of the subcontractor, okay, in terms of their compliance with whatever are the rules of the game that you signed up for.

I think that is what we are driving at here. And the question here is who is responsible for that.

Is it the researcher or is it the IRB or a combination of the two? And I think what we want to do is get at it is a responsibility -- it is both. The researcher is saying I think here is a good, this research should be conducted, I should take some ethical responsibility. The IRB in its role of approving the study and allowing the subcontract, if you will, also has a responsibility in its function of the IRB.

So that is how I conceptualize it.

Now how that plays itself out could be more or less easy but if you say you have that responsibility, you the researcher, you the IRB, effectively you are saying if you are not comfortable do not do it.

PROF. CHARO: It is the Kathy Lee Gifford rule, huh?

MR. HOLTZMAN: That is exactly what I was thinking. I had her in mind the whole time I was talking, yes.

(Laughter.)

PROF. CHARO: Recommendation 6. Now most of 6 reflects what was already discussed at the last meeting and then signed off on by discussion through e-mail but there is a bold preface that is new.

DR. MACKLIN: A preface and a number 1.

PROF. CHARO: And a number 1.

DR. MACKLIN: The preface is the preface to all of them and the number 1 is the first of the recommendations.

PROF. CHARO: Thank you.

Reactions? Oh, sorry, Bernie.

DR. LO: A clarification. On number 1 under Recommendation 6, do we mean to say that these regulations, guidelines or standards have been judged to be equivalent in protection to the U.S. Federal Regulations? They cannot just do whatever they want, right?

PROF. CHARO: For the record --

DR. MACKLIN: Yes.

PROF. CHARO: -- Alice is shaking her head.

DR. MACKLIN: Yes. The reason for this -- this is an amendment in the recommendation -- this is -- I am sorry, to amend the Federal Regulations. It, in fact, overlaps with what we say in Recommendation 1 but Recommendation -- that the items in there appear no where in the Federal Regulations. So this as a suggested amendment to the U.S. Federal Regulations, it actually says something specific about what could -- should be allowed to take place.

Now maybe we have to add here also the equivalent protections language and that is somehow,

you know, missing and it should be there.

PROF. CHARO: Other comments?

Ruth, I had -- by the way, we have just been informed that we only have the room until 5:00 and I know you wanted to go until 6:00 but we are not allowed to. So we only have about 8 minutes left max.

Ruth, just in terms of tone, there was a -- I had a question about 1 where it talks about sponsoring agencies should permit the research ethics committees in other countries to adhere to their own research regs.

I was going to assume that what we really wanted to say was that U.S. sponsored researchers should be permitted to work with research ethics committees in other countries that are adhering to their own research guidelines.

I mean, we are in no way trying to govern the other committees.

DR. MACKLIN: Right.

PROF. CHARO: Only what our sponsored researchers can do.

DR. MACKLIN: We tried and we kept slipping on that.

PROF. CHARO: Right. I just wanted to catch that.

Other comments?

We have seven minutes, guys. Steve?

MR. HOLTZMAN: We made a lot of progress this afternoon and I think it was great work.

Thank you.

DR. LO: It is all off the record.

(Simultaneous discussion.)

DR. MACKLIN: We have to thank our chair.

PROF. CHARO: Yes, well, he left already.

Eric has concluding comments before the meeting is officially adjourned.

DR. CASSELL: If you want to have a lot of progress, cut the group down to five.

(Laughter.)

PROF. CHARO: Feed them a lot of cake.

Eric?

DR. MESLIN: I have two remarks. One is I very much appreciate all of the Commissioners staying for a full two day meeting. I especially want to thank the staff who have worked extremely hard in between these meetings to get the work done.

Lastly, I think it would be very appropriate to finish on a high note, and I hope everyone will join me in wishing both Margaret Quinlan and Alta Charo a happy birthday because both yesterday and today are

their birthdays.

(Applause.)

DR. MESLIN: The next meeting is in Washington, D.C., July 11th and 12th.

PROF. CHARO: See you then.

(Whereupon, at 4:55 p.m., the proceedings were adjourned.)

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