41st MEETING

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Volume I

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I N D E X

P R O C E E D I N G S

OPENING REMARKS

PROFESSOR CAPRON: Good morning, everyone.

We are gathered here in this lovely sybaritic city to throw ourselves into 48 hours of work. We begin with some marching orders from our Executive Director.

DR. MESLIN: Let me also extend my greetings and to thank Bernie Lo, although he is not here yet, for helping to arrange the San Francisco meeting.

First, I want to apologize on Dr. Harold Shapiro's behalf for not being able to be here today and tomorrow to chair the commission meeting. He has been obviously following discussions over e-mail and elsewhere but he is grateful to Alex and to Alta for agreeing to chair the meeting in his absence.

Secondly, let me both extend my apologies yet again for experimenting with you with the briefing book being sent electronically rather than its customary three-ring binder version. I know that it was difficult for some to download materials, et cetera, but I hope this has not proven too difficult.

Our staff will be able to assist you in putting together a virtual book during the course of the meeting, both with tabs and three-hole punches and

the like, if you need that assistance.

The briefing book is large enough that you should be able to set parts of it aside. Today we will be -- this morning focusing on the International Report and switching over the Oversight Report in the afternoon, and then reversing that order for tomorrow.

Some of the things that did not come electronically in your e-mail briefing book included my Executive Director's report.

The only item of which I want to bring to the Commission's attention and the public who are here, and those who will be reading transcripts, is that it is our intention following the July meeting that the International Report be of sufficient quality and consensus by the Commissioners that it will go out for a public comment period, a formal public comment period.

That public comment period would begin on or about the 18th of July and would extend until the end of August, approximately 45 days.

It will be widely circulated and disseminated. It will be on our web site. We will post a notice of this report in the Federal Register.

We will make copies available to the public in hard version from our office and any Commissioners or

members of the public here who wish to make their interests known in getting copies of that report should let our staff know.

It is the intention of the staff and Commission that the International Report be as widely disseminated as possible so that we can take advantage of the public's views on the recommendations and the body of the report.

The time line that we have worked out would allow for the Commission to discuss some of those comments at its September meeting and then to, hopefully, sign off on the final recommendations at the October meeting.

The only other thing, Mr. Chair, is to mention, as I often do, that we have changes in staff that are, I think, important for Commissioners to know.

Dr. Anne Lyerly, as you know from communications, has joined the staff as a Greenwald Fellow and Dr. Lyerly is sitting there, and I hope you will all have a chance to meet with her.

Those are the only major items in the report. I can read other items but you can see them yourself. The Stem Cell Volume 3 report -- volume rather -- will be available in July. It is going to the printers within the next couple of weeks.

For the public who are here, that is the volume devoted to testimony and papers from religious scholars who appeared before the Commission at their May 7th meeting.

Those are my comments. If you have any questions about my report or any other items that we will not be discussing, including, for example, Ellen Gadbois' Comprehensive Legislative Update, also made available to you, please let us know now or later on in the meeting.

And that is my report.

PROFESSOR CAPRON: Thank you, Eric.

David?

DR. COX: I just had a comment. My back thanks you because instead of carrying around the report, I can carry around this. So although I realize it may be difficult for some, I really appreciate getting an electronic version.

DR. MESLIN: You are welcome.

PROFESSOR CAPRON: Is Trish with us on the telephone?

PROFESSOR BACKLAR: Hello.

PROFESSOR CAPRON: Hello, Trish. I want to welcome --

PROFESSOR BACKLAR: It is actually very

difficult to hear and it sounds as though -- it sounds again as though you are under water. You keep going in and out and I do not know if it is the phone line or if it is the system at the hotel.

PROFESSOR CAPRON: It may be both but I will see whether anyone can improve it. Is that any better for you? Not really?

PROFESSOR BACKLAR: Yes. Yes, it is for some reason but before when Eric was speaking and when you were speaking until just now, it is as though there were sort of blips where one heard absolutely nothing and then it came back on.

PROFESSOR CAPRON: Well, we will see whether if we all speak directly into our microphones you are able to pick us up. I am glad you are with us because you are actually our quorum. We have eight members --

DR. DUMAS: Rhetaugh Dumas is on, too.

PROFESSOR CAPRON: Oh, Rhetaugh. Very good.

PROFESSOR BACKLAR: So you have got an extra.

PROFESSOR CAPRON: We expect, I know, Tom Murray and Steve Holtzman arriving this morning. And I assume our local host is somewhere on the BART on his way in, and Diane is in the building somewhere, and Laurie, also, I hope.

In any case, welcome to Rhetaugh and to Trish

on the telephone.

We turn now to Ruth Macklin and Alice Page to provide an overview, an introduction, to our discussion of the chapters that we will be looking at today and tomorrow of the International Report.

Ruth?

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

OVERVIEW OF WORK TO DATE

DR. MACKLIN: Thank you, Alex.

There is not much of an overview because you have all the chapters.

The chapter that still needs to be polished and revised is Chapter 5. Needless to say, you must recognize there was a lot of work between the last meeting and this meeting so we consider that the first four chapters are in good enough shape pending discussions and revisions that come out of this meeting.

Chapter 5 will need a little bit more work.

Let me just point out what you have seen before, and what you have never seen, and what you have seen part of.

Chapter 1, which is the first item for discussion this morning, is -- it really is Chapter 1. It is called "Introduction to Report," but it is a

full chapter. I apologize to the Commissioners that the introductory chapter came so late because throughout discussions it would have been useful to know where we were going, what the scope was, and what the justification for that scope was.

However, as anyone knows who has ever written a book or a doctoral dissertation, you always write the first chapter last so that is why this was so late in coming.

However, as currently written, it should stand to define the scope, provide a justification for doing the report, and lay out some of the basics, some of the terms and some of the distinctions that we make. So that will be the first item of business.

There are no recommendations that flow from the discussion in Chapter 1.

Chapter 2 on "Informed Consent," if you jog your memories, you will recall that it was the very first subject matter in this report that we discussed in very truncated form.

What we presented you with back in September -- September? September, yes. September. No, I was not here in October. Oh, the meeting was in October. Exactly.

But we -- there were a series of findings and

recommendations, very truncated, and those exist in almost the same form but have been revised in light of discussions at subsequent meetings and especially in light of some of the comments that Commissioners made along the way.

So you now have a full Chapter 2 on "Informed Consent."

Chapter 5, which I just referred to, you also obviously have not seen before. And we will try to point out when we discuss the chapter what more we are going to do with it. I will not do that now but when we come to Chapter 5, I will mention some things that we know are revisions and changes and additions that have to be made.

The two remaining chapters, Chapters 3 and 4, are scheduled for discussion tomorrow. And maybe someone can explain why there were no copies of Chapter 3 out there in case anyone did not pick them up. All chapters were out there. Maybe they are there now. Eric is going to see.

PROFESSOR CAPRON: I believe they are.

DR. MACKLIN: Okay. All right. They are there now. Okay. It is just in case anyone did not get them or did not have them before.

Chapters 3 and 4 you have seen versions of

before. The current version of Chapter 3 is virtually unchanged.

Chapter 4 we discussed at the very last meeting in May. You were sent a revision at the end of the weekend following that meeting and it has all been substantially revised again.

So both of them bear some looking at lest you think that the Chapter 4 that is up for discussion today is the one that was sent to you, the revised one, after the meeting.

It is also likely that there will be some additional revisions of Chapter 3. Let me just mention what that process has been.

We sent -- that is a key chapter, both because of the recommendations and also the descriptive material, the technical material concerning different study designs, research designs.

We thought it important before the time that the report is sent out for public comment to send it to a few key people to ensure that what we say there is both accurate and credible. Accurate in the sense of the description of the various research designs.

Remember we had those two panels at the meeting where that was discussed.

And, also, credible because we got a little

informal feedback that the recommendations or some of the material in that chapter does not accurately describe what scientists who do international collaborative research actually do.

So we have sent it out to a few key individuals, a couple of whom were people who testified at our meeting, at the meeting in which the research design was discussed, and also at another meeting just to ensure that what we have there is, as I said, accurate and credible.

We have begun to get some responses. As those responses come in, it may call for additional revision of the chapter.

So the only other thing to point out is when we formulated the agenda for this meeting, we really had no idea how long the discussion would be for each chapter. So I think we should consider the times flexible.

If everything seems perfectly fine, and I do not mean the wordsmithing but the principles and the justifications, then we can probably move on to another chapter. So there should be some flexibility in the time.

PROFESSOR CAPRON: Thank you, Ruth.

Anything from Alice? Nothing additional.

Let's turn then to Chapter 1. As Ruth has suggested, our major concern is with the substance of each of the chapters we will be looking at, but sometimes I know it is difficult to separate the substance from the presentation, and comments that you have in that regard will be also in order.

As Ruth also suggests, if the time arrives when we are going too slowly, we may need to just focus in on a few of the main points. If we have more time, we will be able to get more deeply into the process since we do hope by the time of the July meeting to have a draft with which we are all comfortable for its distribution for comment over the summer.

So I turn then to open the floor for the discussion of Chapter 1 and I think it is sensible to go sort of section by section. So the opening couple of pages before the first break, we will go through any comments that people have there.

Alta?

Please wave your hand so I can see.

CHAPTER 1 - INTRODUCTION TO REPORT

PROFESSOR CHARO: First, I want to say how much I really enjoyed reading this. As I had mentioned before the meeting began, it actually feels like a complete report now and it is a pleasure.

I found as I read the beginning of the introduction that I still wished to see incorporation of a background phenomenon that drives part of the problem here and would even offer to write some text to that if there was consensus that it is pertinent.

And that is that, in part, the problems that are faced by developing countries are created by the developed country governments and the pharmaceutical industry's preference for maintaining intellectual property rights on a global scale to the point of imposing trade sanctions on countries that violate those intellectual property rights even when those violations are done in order to manufacture or sell pharmaceuticals that are needed at a reduced price.

I would like to see that incorporated specifically because there is a bootstrapping issue in the ethical analysis here. If one argues that certain kinds of research is permissible and certain kinds of treatment interventions are permissible specifically because gold standard therapies are unavailable due to expense, then I think that one has to acknowledge that the expense is simply not an artifact of nature. It is an artifact of an international trade system that preferences maintenance of intellectual property rights over affordability of drugs. It may do that for very

sensible reasons and I am not suggesting that this report has to be a critique of the international capitalist system, only that we acknowledge that there is a relationship between the way in which these problems come about and the analysis that then results in determining that what we would consider here in the United States to be substandard therapies may nonetheless be tested.

I think that begins to strengthen the intuitive understanding of the dilemmas here of why some people might be outraged here of the avenues for compromise, including the ones now being pursued by the U.S. Government, WHO and the pharmaceutical industry with regard to affordable access to AZT and other AIDS and HIV-related drugs. And opens up for the rest of the report the wider range of the solutions that, in fact, are being suggested with regard to provision following research at affordable prices of research interventions that have been developed.

PROFESSOR CAPRON: I want to note for the record our pleasure in having a real, as well as a virtual, quorum now with the arrival of Diane Scott-Jones and Bernie Lo.

Welcome to you both.

DR. MACKLIN: Just a question of clarification

to Alta.

Chapter 4 goes into those matters in considerable detail. Would your suggestion be accomplished by adding the points you make here early on or at some point, and referring then the more detailed discussion to Chapter 4? Would that do it?

PROFESSOR CHARO: Yes. I recognize that Chapter 4 discusses it but I do not think it is ever put all that boldly. And I would be the one person here in the group perhaps that might urge for an even more dramatic presentation of the way this dilemma comes about.

The place where it struck me, as I was reading through the chapter specifically, was on page 4. I hope the page numbers turn out to be the same for everybody. This was a straight printout from the attachment.

For me it was page 4, towards the top of the page, just before a paragraph that begins "However, several factors made it impossible to use this treatment in resource poor countries," and then proceeds to talk about the 076 AZT regime.

Now that is a trial that was marked by problems both of affordability of the gold standard therapy as well as logistical problems in the gold

standard therapy. So I would not suggest that we use that trial as an example of one where legally created financial barriers to access had, in turn, been the entire justification for the short-course therapy being tried there. But it did seem to be the natural place to introduce this phenomenon and the degree to which there is, I really do believe, a bootstrapping issue here in the justification of these trials.

DR. CASSELL: (Not at microphone.) I did not understand what you just said.

PROFESSOR CAPRON: Could I try another -- as I understand it, the argument in favor of the short-course AZT trial was that it was impossible in these countries to contemplate the 076 regimen, the regimen that was standard. And, therefore, it was necessary to seek some different method, some different and cheaper method.

Now, as Alta points out, there was an additional argument that logistically, and I think in terms of local practice -- postpartum practice, that is to say --

PROFESSOR CHARO: Right.

PROFESSOR CAPRON: -- whether it was feasible, as with the 076, that the mothers would not breast feed their children. That was also probably not possible.

But let's just limit it for the financial side. If it were possible for the country to obtain through its own manufacture but not subject to the restrictions that require license -- heavy licensing fees or whatever, or importation of the AZT and anything else that is in that drug cocktail, then it might have been possible for them to have used the "Western" standard at a rate which was affordable to them if that were the only problem.

That would then raise a question, (a) do you need to do -- to look for a less expensive method; and (b) if you do, can you now say that the research can be done using a placebo control instead of the 076's control where the grounds for using the placebo rather than the O76 is that the 076 is unavailable?

If it is a financial unavailability -- and that is what I understood Alta to have said.

Is that correct?

PROFESSOR CHARO: Yes.

PROFESSOR CAPRON: Okay. So that this is not to be a report on this contentious trade issue. We have no basis -- this is a report about the research.

And what Alta has said is that the research issue is embedded in a set of factors, one of which derives from the way in which American companies and

maybe European companies --

PROFESSOR CHARO: International companies.

PROFESSOR CAPRON: International companies -- restrict the marketing at something much closer to cost of the drugs or the restriction on other companies -- countries setting up manufacturing plants to manufacture them at a cost that they can afford.

Now that is what I understand to be the framework as to how you want to introduce this. Is that right, Alta? Is that basically --

PROFESSOR CHARO: Yes. What I would like to get at is the degree to which this can strike people as being very unfair. It is as if, Eric, I were to tell you that you may not purchase -- you may not get antibiotics from me for less than $100 a pill. You cannot afford it at $100 a pill. You could, in fact, make it or bring it in from some other place for $2 a pill but I will not let you do that and if you do that I am going to impose trade sanctions on you. This is just what happened to South Africa.

But now since you cannot afford antibiotics because they are $100 a pill, on that basis it is now ethical for us to try garlic for the control of infections because you cannot afford the gold standard so we will try a second best.

This is the dilemma that these countries have found themselves in. This is why they have been going to the international arena to debate the TRIPS Intellectual Property Agreement and why WHO has been so active trying to carve out exceptions for necessary pharmaceuticals.

PROFESSOR CAPRON: I have Eric and then Bernie.

DR. CASSELL: Well, there is no argument about the fact that it is unfair. I do not -- there is no argument about its being unfair or that it is not unfair just because of the United States or because of international corporations.

The question, it seems to me, is not is it unfair and because it is unfair that does not count, which is -- actually what I am sort of hearing is because of this particular peculiar unfairness, we cannot talk about that aspect as we discuss the research. That is the environment in which the research is done.

If you say, and you might very well say, the whole project, like Bernard, the whole project is unethical because that country stands no chance of benefitting from the research, never mind they do not have the drug. They simply cannot benefit at all.

There is no health benefit that will come to them from this research done in their country. That is an argument because that is the environment.

But I am having trouble understanding. What I hear you doing is separating that element out as though, in fact, it could be separated out, and I do not see how it can.

PROFESSOR CAPRON: Bernie, would you yield to a response by Alta?

Alta?

PROFESSOR CHARO: Two things. I do think actually it can be separated out somewhat because, in fact, there are international responses that are available to this very point.

An example of that is the negotiation that has gone on between South Africa, the United States, the pharmaceutical industry, specific companies in the pharmaceutical industry that has recently yielded a change in the rigidity with which intellectual property rights were going to be protected with regard to AZT.

So in the area of AIDS, due in part to WHO intervention, political action, et cetera, there was, in fact, a change in international policy to make those drugs affordable, which, in turn, will, in some cases and in some countries, change the equation of what

kinds of research is appropriate now that the drugs are somewhat more affordable than they had been.

But even more centrally, I think that later as we get into the report and into places like Chapter 4 where we have debated the degree to which conceptions of distributive justice affect our understanding of what should be made available following a trial, I think an awareness of the acknowledged unfairness behind the lack of access to first -- kind of first order therapies is important, because when we debate whether we think that continued access to the second order therapies is an essential element of an approve-able protocol, whether it is because it means that the risk/benefit analysis is now adequate, or because it is simply an independent obligation.

I think that our discussion is likely to get more pointed as we realize that failing to make even the second order therapy accessible after the research is done just kind of compounds the unfairness.

First, they cannot afford the first order therapies because we are more concerned about intellectual property rights than we are about accessibility to important drugs.

And now we are going to go ahead and justify research on second order therapies because they cannot

afford the good stuff.

And now we are going to say, on top of that, that having done the research on the second order therapies, we are not going to insure that there is access to it at affordable prices for the long-term.

At a certain point I think people will simply find that there is revulsion at the notion that this is all acceptable in the name of ethics.

So I want to get us started off with a notion of outrage. I guess I want us to be outraged to begin with.

DR. CASSELL: Okay. Then I -- just one quick thing. Then let it be outrage. I think that is where it should stay. It should stay as a statement of outrage.

PROFESSOR CAPRON: Bernie, and then Bette.

DR. LO: I also think there are important, sort of, scientific and research issues which we need to try and keep clear.

I agree with Alta and Eric that there are real, sort of, issues of ethical outrage against -- with regard to the unaffordability of drugs in developing countries.

But I think we need to point out that we are citing things with the hindsight of having had

randomized placebo-controlled clinical trials in a Third World. And at the time that the Thai study, the short-course Thai study was done, there were real scientific issues in addition to economic and financial issues.

I think we cannot oversimplify by losing sight of the fact that there are real issues with regard to whether intravenous or whether oral AZT was equivalent to intravenous AZT peripartum.

In retrospect, we say, "Oh, it should have been obvious." At the time I do not think it was scientifically obvious at all and I think to sort of overlook that over simplifies things.

There are real concerns about -- in many parts of the world in addition to breast feeding being standard care, women do not present for prenatal care as early as they do in the United States. So the ability to use the 076 regimen is compromised if women do not come for prenatal care early in pregnancy.

Again, in retrospect, we go back and say, "Well, you know, there is evidence even from the original 076 trial that a little AZT is better than none."

Those kind of post-hoc analyses simply are not acceptable as a matter of scientific validity. It is

suggestive but the thing that is standard of, sort of, evidence-based medicine in this country is you then do a second study to say whether the insight you gain from the post-hoc analysis holds up in a prospectively designed study.

I think obviously passions run high here but I think that where there is sort of legitimate scientific uncertainty we cannot sort of just sweep that aside and say it is so outrageous that people cannot afford this that we lose sight of the fact that it was not clear before some of these studies were done what was effective in those circumstances and what was not.

I think another related point is that a lot of the argument in this paper suggests -- in this report suggests that everything needs to be worked out in advance.

I would argue that a lot of the reason that there is so much pressure for using AZT is the fact that a convincing study was done and without that study I think it is not at all clear that there would have been so much pressure.

So to say that everything has got to be worked out in advance overlooks the fact that sometimes a pivotal study creates both scientific but also sort of political momentum to change a policy that otherwise

would have been accepted without question.

So I think that outrage is fine but we should not let our outrage override sort of what would be considered to be rigorous scientific evidence.

PROFESSOR CAPRON: Bette?

MS. KRAMER: The problem I have with it is that the outrage -- from my perspective, the outrage is not just in this particular area. The outrage is really the whole set of circumstances in which these countries and the people who live there find themselves.

And I do not say that this should not be mentioned but to single this out as a focus of the outrage, I think, is going to give the report -- it is going to look as though it is set out to oppose this particular area as opposed to stating what the situation is and that these are the circumstances in which we find ourselves.

Throughout the report I had a problem with the fact that we are trying -- we are working so hard to better the condition of these populations. Not that I do not think it should be done. Of course, I do. But I kept thinking to myself but, you know, we have such terrible situations here around these same issues in the United States.

It seems as though there is an inequity in the focus that we are putting on this. It is not that we do not mention that there are those problems in the United States, but this seems to be the target of our concern, as is appropriate in this particular paper, but it is just that we pay lip service to what is here.

I had a problem throughout the report whenever there was a reference to the fact that in the United States most people were able to get the drugs and prescriptions, whatever, that they need, the care, the medical care that they need because that just is not true. And to say that through Medicare or Medicaid they are available, that just is not true.

So I think that the report could benefit very well in the introduction from a description of a fuller description of all of the circumstances in these countries that create problems and I think that that is really just one of them.

I think the people who are picking the report up, who do not have the background, that will be very helpful.

PROFESSOR CAPRON: Arturo?

DR. BRITO: First, I want to say thanks to Ruth and Alice for the incredible amount of work they have done, and I really think it is coming together.

I was telling them this morning, I thought, you know, we are almost there but then, of course, different issues were going to be raised this morning. As we all know, there always are.

I am in favor of Alta writing a piece in here because I would like to see it in writing a little bit more clearly.

The only request I have, Alta, is that when you do it, if you can minimize the 076 trials within that writing. That is one side note I had written about this.

In here it is not real obvious that this is -- even though I understand the reason that this particular study is cited so often in this report, in this chapter, in the introductory chapter, it almost gives you the sense that this is what this whole report is about.

So I would suggest to Ruth if you could somehow make it a little more obvious to the new reader that this is just one example that provides all these different caveats.

Bernie, the one thing I did not agree with what you said, even though I agree with most of what you said, is the 076 trials, it was not -- it was -- one thing was real clear, is that a placebo trial was

not going to work.

I want to make that distinction clear because I had a hard time with the justifications and rationalizations to use placebo arms of 076 in under developed countries when it was already known that those were not going to work, so that is one thing I want to make a little clearer.

And that, also, makes me think about why I think we need to try to minimize as much as possible this 076 trial because there is a lot of controversy surrounding it and we do not want them to get the flavor of this report is about that trial.

PROFESSOR CAPRON: Jim, then Bernie and Bill.

DR. CHILDRESS: Let me join the chorus of praise for Ruth and Alice. I think their work has really been quite important and they have really been able to move us along in developing what I think will be in the end a fine report. I am sure with some difficult steps along the way yet to be taken.

If we draw a distinction between the general context for a debate about a variety of protocols in the international level and a particular context for a particular protocol such as AZT, a short-course trial, I think what Alta is pointing towards is something that really has to be part of the general context and it may

or may not have particular bearing on this protocol that is emphasized in this section.

I would really like to see her draft it and let us discuss it because I think it really would be good as part of the context in which some of the dilemmas arise.

Bernie's suggestions really relate much more to the particular protocol that is discussed here and I think they are very important and should be included as well.

So you are recommending to fellow Commissioners additional drafting but I think both of those would add to this proposed chapter.

PROFESSOR CAPRON: Bernie?

By the way, Trish and Rhetaugh, just say hands up when you want to get in the queue.

DR. DUMAS: Okay.

PROFESSOR BACKLAR: I am having difficulty hearing. I can hear you, Alex, but I am hoping that other people will make sure they speak very clearly into their microphones.

DR. LO: I wanted to pick up some comments that Bette made, which I agree with very strongly.

There are in a number of places sort of a tone of moral smugness about the language which I think

really needs to be taken out.

The problems that developing countries face are very largely the problems in this country, particularly with regard to HIV.

On page 10, I think, the description there of what is happening in the U.S. just is not accurate.

I mean, to second what Bette said, it is just not true that most people in this country, certainly not a lot of people with HIV, have access to adequate care. Medicaid often does not cover in many states state-of-the-art chemotherapy for HIV. In the states where it does, it is only because of tremendous pressure brought by AIDS advocates.

More to the point of this report, there is a long and disgraceful tradition in this country of using poor uninsured people for clinical trials.

The Wall Street Journal ran a feature series a number of years ago on a drug company in Indianapolis that recruits homeless alcoholic people for Phase I and Phase II drug trials because they are attracted to relatively low compensation that you cannot get other people to sign up for. And after those trials are over, they do not have access to medical care. They do not have access to the drugs.

So I think that all our points are valid. We

just have to say that our same ethical outrage that we are saying exists for discrepancies in developing countries has to also be focused on the discrepancies to the system in this country.

The Europeans laugh at us when we take these positions because of all the industrial countries, we are the only one that does not provide some sort of universal health care.

So that I think that for us to be taking the position of pointing fingers without recognizing that in our country we have many of the same problems, it just does not strike the right sort of moral tone. I think we should -- you know, we can make the same points and just include ourselves in the criticism.

PROFESSOR CAPRON: Bill?

MR. OLDAKER: First, I want to identify myself with Bernie's remarks. I really agree wholeheartedly.

Alta, I agree that it would be very good to have you do a draft here but I would suggest that when doing it that we not tilt too heavily at the intellectual property windmills, realizing that they are extant and we are not going to have a whole lot to do with that.

Second, recognize that while a compromise was reached in South Africa or Southern African, recently

there was a pricing compromise. It was not an intellectual property compromise and that, you know, we just want to be correct on those facts so that they do not come back and bite us.

I think that we have to realize that compromises like that also cause complications here, getting back to Bernie's statement, at least where I live in Washington and dealing with the political world.

Now there are cries saying that if the pricing is changed for AZT in South Africa, why is it not changed in the United States for the people who cannot afford it here?

So really complicated conundrums come out of this and I do not know if they are totally ethical but they are certainly -- they do raise outrage.

Now on a very minor point -- no, actually a major point to start with. I want to compliment the staff on doing a great job of putting this together.

But on a minor point we mentioned Puerto Rico as a country where an ethical lapse occurred in the '50s. I think we should keep in mind that Puerto Rico is part of the United States and it is not a separate country. It is a minor point but, you know, just for the point of accuracy.

PROFESSOR CAPRON: Alta?

PROFESSOR CHARO: First, I will go ahead and try to write something up and will obviously circulate it by e-mail to the Commissioners for their comments and will make sure that it accurately reflects the kinds of compromises that have been developed as well as the negotiations now about future interventions by WHO on the interpretation of the TRIPS agreement with regard to exemptions for countries that need life saving or health preserving pharmaceuticals.

I think that in light of Bette's comments, as well as Bill's, that there is something we might consider, Ruth, adding to Chapter 1 as a way of setting the stage for this report.

As I glanced through it again, I realized that for people who have not had the opportunity to travel in really poor countries, there may not be a kind of vivid imagination of the range of obstacles that are faced by people there who are trying to get health care.

Really concrete examples coming out of the contractor reports that we have may help us because it allows for the kind of complex presentation that Bette wants where you are talking not only about the cost of drugs but problems ranging from inadequate warehouse

facilities so that the drugs that you have rot on the docks before they actually get to the clinics, the absence of professionals, the difficulty with roads to get to the clinics, the difficulty of getting to clinics multiple times, phone service is chancy so that you cannot follow-up with people easily. I mean, all of these contribute.

MS. KRAMER: And the cultural part as well.

PROFESSOR CHARO: All of these contribute to a situation in which a variety of therapies that work here will not work there.

I absolutely understand that the pricing is only one of many elements but it is an important element and I did want to make sure we highlighted it.

Finally, on the comparisons with the United States, and the suggestion that we have the same problems in the U.S., it is fair to say we do. We certainly have them on a smaller scale but we do have them.

In some ways, I think we might be able to take advantage of that fact to say two things in the report. One of which is already there and one of which could be added.

One thing that is there is that we do not have these problems on the same scale and that leads to

different kinds of conclusions about what is really appropriate in developing countries.

The second thing is to play upon the fact that although we used to have a tradition of using the uninsured poor in charity hospitals as research subjects, we moved away from it. To note that when the Wall Street Journal covered that recruitment process that focused on homeless alcoholics, it was scandalous, not ethically justifiable because it was in the world of kind of a Libertarian analysis that the best possible deal that a rational alcoholic homeless person could make in terms of earning a few dollars in exchange for serving as a research subject.

The fact that we view these things as outrages here in the United States and that they get reported this way in the Wall Street Journal should point to our viewing it as an outrage when we thrust the same kind of thing on other people who are in similarly constrained circumstances.

And that may take care of the tonal problem and kind of present the U.S. and the complexity that it has.

PROFESSOR CAPRON: I have Eric and then Jim.

DR. CASSELL: Well, I just want to point out -- I mean, there are certain things that do not get

resolved in a discussion and this is one of them that will not get resolved.

Yet it is not the purpose of this report to resolve that particular discussion. It is to go ahead and make recommendations about research in international climates, and so what we have to do is make sure that every chapter of this goes and underlies the ultimate recommendations.

If there is a disagreement, it really represents the point of view of not just you but lots of people, and not just Bernie but lots of people, and so forth. The points of view should be put there so that we do not at that -- early on, at least, have to take a position about which one of these do we believe in.

There is no way to justify. If two percent of this country's population is unable to get medical care and 100 percent of some other, it does not make any difference.

What we ought to be doing is laying out the argument, including the stronger points that people make, and going towards a set of recommendations that we think can be justified in the face of disagreements and so forth.

PROFESSOR CAPRON: Jim?

DR. CHILDRESS: I agree with some of Bernie's concerns about tone and the smugness and so forth, and we will need to work on that.

But, I guess, Bernie, in looking at the paragraph on 10, which I believe you described as inaccurate, I am not sure if there is anything there that -- other than a tone matter that we would consider actually inaccurate.

If we distinguish between "universal access to health care" versus "adequacy of the level of health care," it seems to me the kinds of claims being made there are sound ones.

But I wondered if you had something particular in mind in that paragraph that you felt ought to be challenged?

DR. CASSELL: The word "majority" and you cannot argue as long as you say "majority," but that is --

DR. CHILDRESS: That is right.

DR. CASSELL: -- not Bernie's concern. It is not that the majority gets it, it is the size of the minority that does not get it.

DR. LO: Yes. I think it is one of those -- that sentence is literally true but it leaves out the sentence -- a couple of sentences that follow it say

but on the other hand a sizeable minority gets either no -- virtually no medical care at all or clearly substandard care by the standards of care in the U.S.

You know, again I just think that, you know, what we see with Medicare patients who have to pay out of pocket if they are not in an HMO, and Medicaid is just really spotty, and HIV is probably one of the worst diseases for coverage.

PROFESSOR CAPRON: If I may inject a comment here.

I have heard a lot this morning which would support the following suggestion, I believe:

I think we need from the very beginning of the chapter to be a little more direct in linking what we are talking about here with the human subjects regulations that already exist, which, of course, talk about a process of IRB prior review and talk about three basic principles. A favorable risk/benefit ratio, informed consent and justice in the selection of subjects.

I think we ought to begin not as you do now, Ruth and Alice, talking about lingering concerns and so forth. This kind of language tries to suggest by indirection what I think we can say right up front, which is the United States Government and private

pharmaceutical companies spend billions of dollars a year in research and a sizeable portion of that goes to research involving human subjects. Most of that research that they sponsor is conducted in the United States but some of it is not.

The question is, does research that is conducted abroad raise any questions or concerns as to whether the standards which have been established in this country are being followed in those countries or whether there are barriers to the implementation of the system that we have here in those countries.

I would then think we could catalogue the reasons why companies might conduct research abroad.

One would be such research may be necessary to get the regulatory approval for the sale of the drug in that country.

Another may be that the condition is something which occurs frequently in that country and infrequently in the developed country.

But there may be other reasons.

One of those reasons would be that although prevalent in both countries, the condition is much more prevalent in the developing country making it easier to recruit subjects and, therefore, easier to carry out the trial.

Now many of these points, by the way, Ruth and Alice, many of these points are in the report but I think they could be stated right at the beginning of the report and in the chapter quite straight forwardly.

Another reason would be that the cost of doing research might be less.

Another reason might be that the research could be done with fewer regulatory burdens.

Not all of these reasons raise concern.

Certainly the first that I gave does not raise any particular concern. You got a drug that is approved in the United States but Pakistan will not let you sell it there until you use Pakistani subjects if, that is the case.

Some of those concerns, however, give rise to concern within the existing U.S. regulations.

And, as I think has been pointed out by Bernie now, if research were done only on poor people, not only whose consent is less free but whose access to the products of the research are very doubtful, both concerns about justice in the selection of subjects and concerns about a favorable risk/benefit ratio are implicated, and the same would be true if that research were exported to another country simply because it was easier to recruit people there.

And I think we can make these kinds of statements. I would like to see them made much more straight forwardly.

I would then say these are not theoretical concerns. There have been for many years examples of research that has been conducted in other parts of the world. And, I agree with Bill, we have to note that, of course, Puerto Rico is a territory of the -- a Commonwealth. But in 1955 --

DR. OLDAKER: 1948.

PROFESSOR CAPRON: Thank you. 1948. A Commonwealth but not a state of the United States but a part of -- an extended part of the United States.

But I would actually ask our group now or otherwise, do we have no other examples between 1955 and 1996 or '97 of research conducted in Third World countries?

While it is true that we do not want to make this a report about the 076 regimen, it is also true that the issue was crystallized as a public issue for researchers in the United States and for government agencies with the publicity around the short-course AZT trial in Africa and, I guess, in Thailand as well.

Those events made it, I think, clear to us that the entire issue of research in developing

countries was one that deserved our attention as a separate item on our agenda, not just as a footnote to our overall examination of research regulation.

If we gather several other examples so that you have a very -- a page just giving a little sequence here.

Now when we get to the contraceptive trial, I do not think it is worthwhile doing what is done now, which is to say, "Well, actually the federal regulations were not in place then so this was not strictly a violation of the regulations," and so forth.

The point about it is judged by ethical standards, a trial in which women, particularly Catholic women who, of course, for whom birth control, as such, was a doctrival issue, were the subject of a trial in which, as subsequent examination showed, there was a lot -- there was not a lot of clarity apparently for them about what exactly was going on or the method that the contraceptive would use. Much less a question of if it did not work and they became pregnant, obviously these were women who were not in a position then to end the pregnancy given their own beliefs and the circumstances of their country.

It certainly raises questions about that selection or that group of subjects.

I suspect that if we look through the Annals of Research we can find a few other examples between 1955 and 1996 that would raise that question.

I do not think we have to say that these were conducted in violation of existing regulations.

The point is not to try the people who did that. It is simply to give an indication that these problems, the problems of exporting research, are ones which have been around for a while.

But I would prefer a much more straight forward description of the ways in which the issues here connect to the existing precepts, the Belmont Principles, if you wish, right from the beginning.

Is that --

DR. DUMAS: Rhetaugh has her hand up.

PROFESSOR CAPRON: Okay. We have Rhetaugh and then Eric has his hand up, and then Arturo.

DR. DUMAS: I would like to underscore the statement and the suggestion that has just been made, and I hope we will not lose it.

I think it is important to be straight forward and to have such statements right up front, and I think the context should be laid out very clearly.

And I think what I am hearing you say is that the context is the regulations for the protection of

human subjects. And then the issues, the ethical issues that arise, can be laid out.

I had some concern because it seems as if the examples over shadow the other major points in the report. And if we turned it around the way that is being suggested -- who was that who just spoke? Alex?

PROFESSOR CAPRON: Yes.

DR. DUMAS: Yes. The way that you suggested would take care of many of the concerns that I have about the perceived emphasis being on violations particularly having to do with HIV/AIDS and AIDS treatment and what have you. And that is not the major thrust of the report. The major thrust of the report is the protection of human subjects.

So I would like to underscore your suggestion, Alex.

PROFESSOR CAPRON: Thank you. Okay.

Eric, and then Bette, and Arturo.

DR. CASSELL: Well, following up on what Rhetaugh said. I think one of the solutions to this is to move the section on page 15 through 19, "Responsiveness to health needs of population," which is our major -- one of our central points that we are trying to get across -- much further forward, and opening with just some introductory material and go

right into what we believe is an absolute essential.

And then we can discuss individual instances which have failed to do that, as well as having perhaps other more or less egregious difficulties.

But if we do that, we go into a positive note right away. We are able to get in the difficulties of the previous research. We are able to solve the problems that some people see more outrageous than others, but still everybody having difficulty because we have stayed on the positive thrust of the report.

PROFESSOR CAPRON: Bette --

DR. CASSELL: And it is already written. That is another big advantage. It is already written.

PROFESSOR CAPRON: Right. Okay.

Bette is passing.

Eric or Arturo?

DR. BRITO: I agree with what Eric just said and I had raised my hand because I have some comments that -- about particular sections that I think adding a simple one or two or three sentences to those areas would really help with one of the problems that Bernie pointed out earlier about the moral smugness of this -- or what appears to be that tone.

One of them is that what is now page 17 on this, is when you -- when it is discussed about the NIH

and the CDC, I think in here, and the other federal agencies, how they have done all this research, what I found striking was that what is lacking is the fact of how resource poor countries have benefitted from research by this country.

More in the tone -- you know, there is no sentence saying that there is -- and then by -- some statement of the order of swinging the pendulum too far one way could actually put people in resource poor countries more at risk.

So I would like to see something to that nature in there somewhere.

I had other comments but I do not know if I should -- if anybody else has their hand raised or something -- in different areas of the report.

PROFESSOR CAPRON: You can -- different areas of the chapter you mean?

DR. BRITO: I mean of the chapter.

PROFESSOR CAPRON: I think we have fairly substantially departed from my initial suggestion that we walk through it section by section so I think you can feel free.

DR. BRITO: Okay.

PROFESSOR CAPRON: We have got about 15 minutes by our schedule.

DR. BRITO: This is a very quick suggestion.

One page 7, also, where it is discussed about the growth of research conducted by for profit organizations. If I -- my recollection is correct, we heard some comments, and I agree with these comments -- I cannot remember who it was that said it, but the academicians are not exempt from being motivated, not necessarily by financial gains always but by other things.

So I think it would be nice to put some sentence in there stating that people in academia -- while they are not under the same financial motivations, they have other motivations that have in the past and in the future can still make them do unethical research, et cetera. Because here it almost sounds like we are picking a little bit on the for profit organizations.

So once again a sentence or two in there to say something to that nature.

PROFESSOR BACKLAR: I have my hand up.

PROFESSOR CAPRON: Trish, why don't you go ahead?

PROFESSOR BACKLAR: I am just concerned about what Arturo said considering what has been going on about academics having financial motivation at the

moment. So I think one has -- we have to be very, very careful on how that is put out -- put down.

PROFESSOR CAPRON: Could you be more specific about the --

PROFESSOR BACKLAR: Well, I am just thinking about the recent discussion and that Marcia Angell has been talking about academics being -- having connections with -- being much more motivated for financial award than heretofore because of their connections to industry and so forth.

DR. DUMAS: Can I comment on that? Rhetaugh.

PROFESSOR CAPRON: Yes.

DR. DUMAS: This is Rhetaugh. Can I comment on that?

PROFESSOR CAPRON: Please go ahead.

DR. DUMAS: I do not think that we want to get into issues of motivation. I think we want to stick with whether or not the intent of the regulations to protect human subjects are being conformed to.

I think we would be in trouble to try to deal with issues of motivation. I do not -- my own feeling is that I am not as concerned about the motivations. I am concerned that whatever motivates researchers to do the research in the foreign countries that they carry them out in an ethical manner.

PROFESSOR BACKLAR: I agree. I just was concerned about refuting a remark that Arturo just said. That is all.

DR. DUMAS: Okay.

PROFESSOR BACKLAR: I agree.

DR. BRITO: Can I make a comment about that, Rhetaugh?

On page 7, the chapter between lines 7 and 18 talks and implies that motivation can lead researchers to do unethical things, et cetera.

But the tone of it is it is picking on the for-profit organizations and I think to be fair if we are going to include something like this, we also have to say that unethical research can also be done in academic settings. That is all I am saying. So we either include it, you know -- if we are going to say by "for-profit" organizations include the -- what the constraints they are under and motivate them to do certain things, we also have to do academics in there.

PROFESSOR CAPRON: Okay. Should we look at this just for a moment and make sure that we are all on the same page so that the staff knows what we want done here?

We have Troy Brennan's statement, which talks about the growth of for-profit research and a

concomitant emphasis on market principles. Now as I understand that, that can have two relevant impacts.

One is the choice of what things to -- what diseases to study are influenced by whether or not there is an economic pay off for doing so. Is that a fair reading of what he says, Ruth and Alice, do you think?

And another is that --

DR. BRITO: Lines 11 and 12.

DR. MACKLIN: Well, the next -- the very next sentence explains what that is supposed to -- what -- the meaning.

PROFESSOR CAPRON: Right. Right.

DR. MACKLIN: That is the emphasis created greater pressure for efficiency, which may produce compromises. That is any time --

DR. BRITO: Yes.

DR. MACKLIN: -- efficiency becomes a goal then other things may be overlooked so it is just explained by that. I mean, if you want more said, I suppose, it could spell it out but it is --

PROFESSOR CAPRON: Well, my impression of federally funded research is that the federal government does not regard research dollars as infinite.

Therefore, in looking at a way research is designed, an efficient design of a research project is a relevant and an appropriate thing to look for. If a study section sees something which goes about answering a question in a way which does not make good use of the resources, it is considered less good science than another project looking at the same question which would do it more efficiently.

So I do not think that market principles alone lead towards a desire for efficiency.

I had understood the point that Arturo was raising and that gets raised is whoever is conducting the research, if their own desire to receive the research funds is great enough, if they are in the position that they are being expected by our system, and perhaps by the subjects themselves, to play some sort of more disinterested protective role for the subjects, that role may be compromised, and that is what the --

DR. BRITO: Yes.

PROFESSOR CAPRON: -- that is what the word "compromise" here -- that role as a more disinterested person.

But let's face it. The person who is looking for tenure or for the Nobel Prize may have a motivation

at least as strong as someone being paid a generous amount by a research company to cut a corner, and that is a risk that always exists.

We can see it more easily because most of us are more aware of "filthy lucre" as the drive towards unethical conduct than other things. But people -- and I agree with Rhetaugh. I do not think we want to get into issues of motivation as such. We want to get into issues which involve the protection of human subjects and just be clear that people when they wear two hats, whether the hat is a drive for research or a drive for money, in addition to their hat as the physician with some role vis-a-vis the research subject, that is when we have to have other protections in place to make sure that somebody who does not have that particular compromise.

In the international area I have seen this in this report as raising the concern what about the other people such as government ministers or the people who run the academic research establishment in the country who also are in a position of having a second motivation. That is to say if the company says, "Well, we will build a research facility and leave it behind, or we will train some of your staff in our country and bring them back better trained," or any number of other

things.

Do we lose the usual ability to have some third party saying, "We are going to look at this with clear eyes and make sure that the appropriate balance of risk and benefit and the selection of subjects in a just fashion has been carried out." And that seems to me a question that we can ask.

Bette?

MS. KRAMER: Yes. Apropos of that, I think we need to be careful, in general, throughout the report not to bash for-profit companies acting according to market principles. I think that that would be a mistake.

PROFESSOR CAPRON: Alta, and then Bill.

PROFESSOR CHARO: This is going to return a little bit to what Alex was talking about earlier in terms of a presentation in Chapter 1 of material that appears elsewhere.

His suggestion that there be a kind of catalogue of the reasons that may lead to conducting research abroad, which, in fact, appears in another chapter as a kind of list, could be supplemented with each particular reason presented with an example so that the trials in the Commonwealth of Puerto Rico would be presented at a moment in which one is

cataloguing that in some cases there is an interest in running trials abroad because there is a perception that it is easier or more efficient.

The examples you give of a different kind of contraceptive, and I do not recall if it was an injectable or an IUD, I forget what it was, as well as, I think, a malaria intervention -- there were a couple of other examples of things which never appeared in those countries until 10 to 20 years after the trials, and after they had appeared in the First World despite having been tested in the Third World -- might appear in conjunction with the moment when you catalogue yet a different example for testing things abroad, and that is presumably because they might be used abroad.

And yet, in fact, in the end the absence of any real plan or any follow-up meant that they never did, in fact, yield a benefit for the population, and in this way might achieve the goal of helping everybody, even in the first chapter, to have a limited series of examples that tie motivations or reasons for doing research abroad with concrete examples of which there are many in the report already.

It would also, as an incidental fashion, allow us to kind of catalogue all the examples that are in the report and see if there are any that are missing to

illustrate a particular reason why you do research abroad and then to go out and search for it.

PROFESSOR CAPRON: Bill?

MR. OLDAKER: I guess, we are drawing to the end of this chapter here. Near the end you use some models as -- on the last -- I guess on page 22. And although I mostly agree with the concepts set out there, it makes me a little uncomfortable the way it is set up. And it could be -- I realize that "south only" is kind of a generic term used.

I think, though, you know, we are really talking about under developed countries and not necessarily just the south, and I realize that China in some international lexicon is considered part of the "south."

My feeling is that China is probably with the new areas of trade going to be a place where a lot more research is going to be done.

So I suggest that we change that somehow to deal with the world at least as I see it.

The second issue dealing with what I said before as far as tilting at windmills, I think that, you know, recognizing that the U.S. Government has gotten into the fight with South Africa, it has been much in the press, I think citing it there on page 23

really is criticizing the U.S. Government for basically enforcing its own laws.

I think that, you know, we have to recognize that they are -- there is a treaty between the South African Government and the U.S. Government.

So I agree that it creates difficulty, outrage for the South Africans, but I am not sure that it advances our report a whole lot though.

Thank you.

PROFESSOR CHARO: I am sorry. You know, I just realized looking at this that this is precisely what I was just talking about, and it is right there at the end of Chapter 1.

So I apologize, Ruth.

DR. MACKLIN: I knew it was in there.

PROFESSOR CAPRON: Bernie?

DR. LO: Alex, to respond briefly to your suggestion that we look for other examples of research conducted internationally that raises concerns, I think we might want to look at the hepatitis B vaccine trials as an interesting example.

As far as I know, there are no claims that the research was unethical in the sense that people were not informed or that it was -- the research was not relevant to a serious problem in many of these

countries.

I think by the standards of 2000 there can be concerns raised, which I do not think were raised at the time. First, did the people in the placebo group receive the vaccine after the trial was completed, which is a point that we make a lot of subsequent to the report. I actually do not know the answer to that but it would be worth sorting through.

Then analyses, there is the issue of availability of the vaccine in the countries where the hepatitis B is, you know, a serious health problem.

And there is a big time lag because these vaccines were under patent and they were really unaffordable for most developing countries.

Finally, there is another -- there is a third issue, which again for the retrospective scope you can look at, and that is what care was given to people who got hepatitis B, not because they were in the trial, but because being -- living in that country put you at risk for hepatitis B.

Certainly there was no consideration given, as far as I know, to giving the kind of care that would be given in this country to the people who got hepatitis B in those trials.

So, you know, it is an interesting example.

At the time, I think there was no criticism raised. Are we now going to sort of look at these studies and say, "Given that we think we have universal timeless ethical principles, are those studies now open for criticism?"

PROFESSOR CAPRON: And are we talking about the 1960's and '70s or what is the era?

DR. LO: '60s and '70s.

PROFESSOR CAPRON: Yes, okay.

DR. LO: Particularly the '70s.

PROFESSOR CAPRON: Further comments? Ruth, please?

DR. MACKLIN: I just have to ask a question here. I mean, to the extent that people are raising questions or making comments for adding new sentences, changing -- putting the material around, changing the tone, changing the emphasis, that is something that is relatively easily done at this late stage.

To the extent that some of these requests are requests to do research and include examples that are not in here now, I very much fear that we do not have the time or the resources to do it.

Now some of the questions Bernie -- the points that Bernie just made are matters of historical fact, and you say you do not even know the answer. I, for

one, would not even know where to begin looking and gathering this information, and then we would need to have it verified.

Others are asking for more examples of research that by today's standards would be unethical.

So I am really asking whether all of these suggestions are ones that you are asking us to take on board and for some of them at least -- I mean, not the tone and the adding of a sentence but anything that requires doing more research is actually going to delay this report because it is going to be physically impossible given the time between now and the next meeting to start doing research anew.

So I just want to know where we stand on these suggestions that are now coming out.

PROFESSOR CAPRON: Bernie, you were going to offer -- I think, by your body language, you suggested you had some way of offering a way of perhaps efficiently answering the question on the research project that you mentioned.

DR. LO: Yes. I would suggest, you know, contacting the principal investigators of the pivotal studies on hepatitis B vaccine and just ask them, you know, was it given to subjects after the -- subjects in the control arm after the trial. And those can be

tracked down.

I mean, they are sort of in -- the standard textbook of medicine or hepatology will cite -- Palmer Beasley, who is now at some place in Texas, dean of one of the schools of public health in Texas, was instrumental -- was the PI in a lot of those studies in Asia and, you know, he would be a good place to start.

PROFESSOR CAPRON: I can see the research staff sitting at the back table furiously taking notes and they will probably have the answer by this afternoon.

DR. DUMAS: Rhetaugh has her hand up.

PROFESSOR CAPRON: Rhetaugh, please.

DR. DUMAS: I would like to just caution against going into too much detail about the studies that have been done and the ones that were unethical or what have you.

Again, I think we should keep our focus on what we consider adequate protections for the rights and welfare of human subjects. And give examples, as best as we can with the data that we have, and balance them so that they illustrate the points that we are going to make.

But I think we can get into a lot of complex difficulties trying to test out whether or not

subjects' rights are being violated or not violated by particular studies.

PROFESSOR CAPRON: Yes. I gather from the comments I have heard that no one is asking that we, in effect, violate our charter and actually adjudicate the rightness or wrongness of any of these particular examples.

The issue is whether it would be helpful to say that in the last 50 years, as research has been conducted abroad, from time-to-time attention has been focused on the ethical difficulties that arose through the way in which that research was conducted.

If you have -- you could almost have a sentence or two on each of these, whether it is the testing of contraceptives in the 19 -- the original oral contraceptive in the 1950's in Puerto Rico, whether it is the development of hepatitis vaccines in whatever countries, Bernie, the research was conducted in, in the 1960's and '70s.

I think it would be appropriate to note in that process that when comparable research has been conducted in the United States in populations which themselves appear either to be particularly vulnerable because of -- as the report now says about the women in the Southwest who were the subject of a later

contraceptive study -- or are unlikely to have access to the research products, as Bernie notes from the research that was done in -- is it Indianapolis, Bernie?

That those concerns arise in the framework of the present federal regulations and so the -- a basic question when the 076 trial -- I mean, the short-term AZT trial presented this in Africa and Thailand was our existing regulations and the expectations being violated in those circumstances.

As we get into the subject, it becomes apparent that there is an additional set of questions, which is are there requirements in the federal regulations, which are either inappropriate to or very difficult to comply with under the circumstances of research done abroad and, if so, are there reasons to modify any of those requirements, or is this simply a way of saying that the requirements have to be enforced as written because they are important requirements, and if they impose greater burdens, that is something which the sponsors of the research will have to deal with, but that there is no reason to modify them.

And that is really, it seems to me, what the rest of the report goes on to address. I think we can frame it in that way.

And, Ruth, I think most of what you have heard there for -- is in line with what is already here. It is a matter, as you say, of editing and presentation.

And only a few of these little points, which I think really should not be that difficult because you are -- we do not need to have the complete recounting of the hepatitis B vaccine trials. We simply need to have an accurate sentence or two that suggests that they raised a particular genre of issue.

And, as Bernie has presented it, perhaps particularly the issue of what happened to the subjects who were receiving the placebo and what happened to the population of the country more broadly if they were unable to get the vaccine after it was developed.

Other comments?

Yes, Bette?

MS. KRAMER: Going back to the end of the chapter and the discussion around the models. On page 22, line 25, and then on page 23, lines 1 and 2, there are references to 15 to 20 years and then another 15 to 20 years, and then 10 or 15 years. Are those factual?

DR. MACKLIN: This was -- this came out of the testimony of Don Burke. I mean, in both answer to Bill's question and this question.

It is not noted here, I guess, or -- I mean,

it will be in the form of a footnote or a reference.

Actually it does say -- it begins on the top of page 22. It describes those models.

And he -- this was part of his testimony so these are facts as he stated them and when we have expert testimony what we are doing is citing the remarks of someone who gave us the expert testimony.

And it was his language, by the way, Bill, that used the "south only" and it does describe -- I mean, we can change this language and drop it all together but, you know, it says here, "For ease of reference and following common parlance, industrial country will be referred to as 'north' and developing countries as 'south'." Which of course is meant to recognize that this is not a geographic descriptor.

PROFESSOR CAPRON: Do you know what you could do to, I think, avoid the problem, Ruth? It would be simply to say, "Burke referred to industrialized countries as north and the other as south." And that would make clear that this language is a quote.

All right.

I realize that I am having problems with pagination because as my computer printed out the report the pagination is different and I was searching for Bette's reference, and Alta seems to have your

version.

So thank you, Alta.

PROFESSOR CHARO: Sure.

PROFESSOR CAPRON: We are now at a point where the schedule said we were going to move on and we will do so unless there are further comments and suggestions. I am sure that Alice and Ruth will appreciate anything you want to give them in writing.

And I believe I heard Alta agree to write out for us the suggestion vis-a-vis the licensing and availability, the price availability of licensed drugs.

And there was an assignment that Bernie was going to take on as well, is that right, earlier? Yes. It is not necessary that this be done today.

DR. MACKLIN: It would be helpful.

PROFESSOR CAPRON: I know. I am saying it is not necessary but it would be helpful if it can be done as soon -- but I do not believe it is appropriate to ask Commissioners to sit here and write when they should be discussing other chapters.

All right.

David?

DR. COX: Forget it.

PROFESSOR CAPRON: David is volunteering to write the report. He has got the whole thing on a

laptop right there in front of him.

DR. COX: Well, that is actually what I was going to discuss but I am not going to discuss it.

PROFESSOR CAPRON: All right. We will turn then to Chapter 2 on "Informed Consent" and ask Alice and Ruth if they want to introduce this with any highlighting comments.

CHAPTER 2 - INFORMED CONSENT

DR. MACKLIN: The only -- I guess the only comment here -- as I mentioned before, this is now a full text and what you saw months ago was basically the recommendations at the end.

We are not certain but there may be more interpolations of a factual nature in here. And what I mean is this: Remember long, long ago there were some commissioned papers, some studies commissioned, and we heard reports very early on from the consultants. This was Nancy Kass and Elizabeth Dawson -- Eliza, sorry. -- Liza Dawson and Adnan Hyder and Noreen Teoh. They -- in addition to Patty Marshall and Jeremy Sugarman.

All their -- all of the material from Jeremy Sugarman's report and Patty Marshall's final report is in this chapter.

However, we only have had preliminary

information. There was a brief presentation of preliminary data and some results of focus group discussions that both Hyder and Teoh and Kass and Dawson conducted.

Their reports -- they have promised their final reports on June 15th.

Now those reports will be in discursive form. It will not be -- they will not contain material only for Chapter 2, although I would say the majority of comments, although not exclusively, deal with Chapter 2.

So the question is whether or not there will be sufficient information or even necessary information to interpolate into this chapter or whether those reports will stand alone as -- because there is already some references, quite a few, as you can see, but whether any new material will simply be relegated to Volume 2 of this report.

But there is nothing that will be put in here that would either change the nature of the recommendations that now exist or add anything but either further support or additional descriptive material.

PROFESSOR CAPRON: Okay. That is the framework.

Jim has a comment.

DR. CHILDRESS: This is becoming a very rich chapter. I have three points I would like to raise.

The first is on page 1 where the claim is made that in all the documents that are referred to in the first several sentences, the requirement for consent rests on the respect for autonomy.

And I guess I wonder whether that might need to be qualified in some way. For example, even in the Belmont Report it is really a principle respect for persons with autonomy being a subset of that.

And if we look at -- and I have not looked at them but if we look at all these other documents, I am wondering whether -- particularly given the way in which respect for autonomy tends to be viewed as a very individualistic concern, whether some other justifications are not present in those documents such as preventing harm to subjects.

I guess the question I am raising in part is whether this claim is made in sentences -- lines 10 to 12 -- is a claim about the explicit justification that is given in those documents versus what we might offer as an interpretive justification of what really underlies those arguments.

So I guess this first paragraph -- I would

feel better if it probably were more -- developed a bit more and perhaps more nuanced in that regard.

That is the first.

A second -- on page 3, lines 4 through 6, which follows the presentation of two different views. One by Lisa Newton and then by Faden. The second one -- referring to the second view, it says, "We are persuaded that this latter view supports the application of substantive ethical principles," and it is, I think, true that that view does support that.

I guess what is not clear to me --

PROFESSOR CHARO: I am sorry, Jim. Can I interrupt?

Could you -- I think some of us have different page numbers. Could you just help us follow you a little bit better where you are now?

DR. CHILDRESS: Okay.

PROFESSOR CAPRON: Paragraph beginning with what language?

DR. CHILDRESS: Beginning with "exactly the opposite position." That would be on page 2 on mine and going into page 3.

PROFESSOR CHARO: Okay. I am sorry. Thank you.

DR. CHILDRESS: Okay. All right.

PROFESSOR CHARO: Thank you. I appreciate it.

DR. CHILDRESS: And then it says, "We are persuaded that this latter view supports the application of substantive ethical principles." Again I think that is right but what I am not clear is whether in this we have adequately argued for taking that view.

That is whether we argued for taking the Faden view in contrast to just that it would lead to this if one took it.

And then the last comment I would make is on page -- my page 5 but it is headed, "The basic elements of informed consent" in italics. So I think that one probably can be located fairly easily.

I would take what follows under the "Basic elements of informed consent" really not to be elements of informed consent but rather the elements of the obligation of disclosure, and that what appears there is what the federal regulations would offer as requirements for disclosing information to subjects.

So I think that just needs to be clarified there and at the end of that because elsewhere we talk about elements in informed consent. For example, on my page 3, we do include a variety of other things. So I just think that language clarification would be needed.

PROFESSOR CAPRON: Okay. Any comments? Any response, Ruth?

DR. MACKLIN: No, I take those -- all of those comments.

Actually your -- I agree with what Jim just observed. This language is directly from the regulations even though I think you are absolutely right and we can say it. It does say in the regulations basic elements of informed consent but, of course, these are the elements to be disclosed.

DR. CHILDRESS: Disclosure.

DR. MACKLIN: But those words, those italicized words do appear in the regulation so we can do better than the regulations in saying what we mean.

PROFESSOR CAPRON: Yes, Alta?

PROFESSOR CHARO: Two things that -- one, I guess, is pragmatic and one goes more to a substantive decision that we have made.

On the pragmatic one, when we get to the recommendations and we look at recommendation one, which says that U.S. sponsored researchers may not deviate from the substantive ethical standard of informed consent in the process of obtaining informed consent or in consent documents, I find that I am not sure that the typical investigator or IRB would be

absolutely sure yet what things are waive-able and what things are not waive-able from U.S. practice when it is being exported to a collaborative project abroad where practices might be different.

And when you go to the beginning of the chapter and you look at things that are identified as process versus substance or elements now of disclosure, one gets the idea that that is where this distinction is being made, but I would suggest that for the sake of clarity in any kind of explanatory text following the bold recommendation or in the recommendation itself we might want to try and more precisely define what it is that is waive-able and what is not so that the guidance is as clear as it can be.

I have watched my own IRB go around and around in circles. In fact, you cite the Vietnam protocol, which was our protocol, as an example of one in which we went for months trying to figure out what ought to be waive-able and what not with regard to truth telling.

Which leads me actually to --

DR. MACKLIN: Could I just --

PROFESSOR CHARO: Sure.

DR. MACKLIN: -- on that point --

PROFESSOR CHARO: Sure.

DR. MACKLIN -- are you asking for an enumeration or a set of examples because my own view, and I do not know about other's view, is that we will never come up with an exhaustive list.

PROFESSOR CHARO: Right.

DR. MACKLIN: If you start making a list, it will raise the question what else belongs on the list and very often you cannot tell it until you see it.

PROFESSOR CHARO: Right.

DR. MACKLIN: So, I mean, one possibility is to start talking -- is to try to describe or give criteria for what is waive-able and the only way to do that -- or what is and is not waive-able -- it seems to me the only way to do that is to elucidate a little bit more what "substantive" means.

PROFESSOR CHARO: I would be comfortable with either. I agree with you that the laundry list is probably doomed, although it is what everybody wants when they are doing checklists.

But anything that elucidates without getting us into kind of an endless loop of words that each need to be interpreted by reference to additional words would be helpful.

For example, within this recommendation or any, you know, small amount of explanatory text that

follows it, because that is all that people will probably look at in the end when they get the document, something that clearly identifies whether or not fully understanding the range of alternatives is considered a substantive requirement, because that was an issue in the Vietnam protocol.

Fully understanding the change in the fiduciary relationship of doctor-patient versus investigator-subject, is that a substantive part of the consent process or not?

These are the kinds of things that if we could communicate it a little bit more by describing what it is that makes somebody adequately informed would, I think, help the PIs and also avoid the kind of endless submission, amendment, resubmission, amendment, resubmission pattern that I think in my own IRB experience has dogged the international protocols.

Because since everybody is so uncertain, they keep going around in circles and the PIs eventually just want to -- they just want to cry.

That actually, though, led me to one of the more --

PROFESSOR CAPRON: Could --

PROFESSOR CHARO: Oh, I am sorry.

PROFESSOR CAPRON: -- before you go on, could

we try pressing this issue of substance versus procedure just to -- I am not clear where as a result of this exchange you think changes are going to be made, if any.

Because I heard in response to Alta's request for some enumeration an exchange which ended up saying, "Well, people want the laundry list but we are afraid that if we start the process the list is going to be incomplete so we --"

DR. MACKLIN: Well, we give examples at the very beginning of the chapter. We give examples of written versus oral, signing versus not signing. I mean, a whole -- they are listed as examples of procedures versus omission of information that is material to a person's being able to make a decision.

Now all that stuff does not follow the recommendations. It is in the text.

PROFESSOR CAPRON: I understand but you have -- you have also the statement, which I see as dangling unresolved, right before the basic -- that heading that Jim pointed out to us before, and it is on page 5 with me but I think my pagination is different than others.

"However, not everyone who was concerned with ethics in research agrees with the position that substantive ethical matters are more weighty than

procedural aspects.”

Now I am waiting for the other shoe to drop or something. I am waiting for us to -- do we -- do you feel that elsewhere in the report we come out on that or is that a statement that we already have come out, you believe, in the previous few sentences saying substance is more important than procedure because the previous two sentences -- few sentences to me say, "Gee, sometimes an accumulation, as it were, of procedural things rise to the level of substance."

So I am, frankly, not clear.

DR. MACKLIN: Well, you are not clear because it is not clear. I mean, there is a point at which the request for more clarity is going to do violence to both ordinary language and ethics and if we cannot resolve -- I mean, when something is procedural and rises to a level of importance that it is so important you want to say, "Hey, now, this is really substantive," I mean, we could probably engage in a treatise on that but I think it is naturally unclear. It is a gray area.

If we need to say more -- I mean, my own preference would be eliminating that sentence entirely. It is only because someone once said to me, "I do not think there is any difference at all. I think that

procedures are just as important." So, I mean, I put it in because that guy is going to read this report and he is going to say, you know -- so it is only acknowledging that some people make different claims.

If we have to say more, I would rather say less.

PROFESSOR CAPRON: Well, I guess my question in all of this is, is this something which is tonelogical in the sense that what we are saying is if -- if it is waive-able it is procedural?

DR. MACKLIN: No.

PROFESSOR CHARO: No. May I --

PROFESSOR CAPRON: We are not doing that? If it is substantive, is it waive-able?

DR. MACKLIN: Well, let's put it another way. Okay. In a lot of contexts, and we see it even in some of the quotations from one of these chapters -- I do not remember which one. People refer to ethical standards in the United States and they claim we should be exporting our standards to other countries.

Now what they end up referring to is signing the piece of paper. Now that is a procedure. It is not a standard.

A standard is something that can be defended by principles and that is, I think, the way we try to

elucidate it at the beginning of this chapter.

I guess one of the problems is if you look at the recommendations alone, they do not have this elucidation and that brings us to another question about how we are going to lay out or state the recommendations.

But I am not -- I mean, I am not going to fall into the trap of saying if it is procedural, it is waive-able and if it is not -- because it does not fit in that way.

PROFESSOR CAPRON: Well, see --

PROFESSOR CHARO: Alex, may I try something?

PROFESSOR CAPRON: Okay. Go ahead. All right.

PROFESSOR CHARO: Ruth, looking at the recommendation I find myself wondering if we might simplify it by eliminating the reference to substantive ethical standards and eliminating the reference in other places to -- in the text to procedures, and take a page a little bit out of the back of the recommendation.

I think I am getting the gist of it in the following way:

U.S. sponsored researchers must give subjects in other countries all of the same kind of information

that they would give them if they were in this country.

But the procedure -- the method by which the information is delivered, the method by which we ascertain that the information has been understood, and the method by which we prove later on that the information was given and understood is all amenable to tweaking based on local practice and needs.

So we -- by avoiding the phrase "substantive ethical standard" and just substituting in a sense "information" we may be, in fact, getting at what you were trying to achieve.

PROFESSOR CAPRON: What do other people think of that?

DR. DUMAS: Rhetaugh.

PROFESSOR CAPRON: Rhetaugh, and then Bette and Bill.

DR. DUMAS: I like that suggestion.

PROFESSOR CAPRON: Okay.

PROFESSOR BACKLAR: And Trish does, too.

PROFESSOR CAPRON: Let me -- before we all agree with it, let me throw -- one other thing is I gather besides being an informed decision maker, another criterion is being a freely consenting decision maker.

PROFESSOR CHARO: So that --

DR. DUMAS: Right.

PROFESSOR CAPRON: I believe that is --

PROFESSOR CHARO: -- in addition to this --

PROFESSOR CAPRON: -- I believe that is --

PROFESSOR CHARO: Okay.

PROFESSOR CAPRON: -- another basic substantive standard that --

PROFESSOR CHARO: Okay.

PROFESSOR CAPRON: -- or drop the word "substantive."

PROFESSOR CHARO: So it would be --

PROFESSOR CAPRON: Principled --

PROFESSOR CHARO: -- so let's try --

PROFESSOR CAPRON: -- principled conclusion that we insist on.

PROFESSOR CHARO: So trying this out would mean that you would say that U.S. sponsored researchers have to give the same kind of information, that people have to be judged free and competent by the same standards as we would apply here.

PROFESSOR CAPRON: I would think that sounds essential, yes.

PROFESSOR CHARO: Anything else?

PROFESSOR CAPRON: Well, what -- we can all think of whether there is anything else but this is a

direction that Alta has suggested, and we are filling in the substance, as it were, of that direction.

Bill?

By the way, I have Alta on the list to raise other subjects but I would like to keep us on this question for a moment.

MR. OLDAKER: On this issue, I realize we seem to be shying away from a distinction between substantive and procedural -- I am not certain why we are doing that but we can -- if we want to go in that direction, that is fine.

But I would think that, you know, as I would describe substantive types of matters, they are not waive-able and procedural matters may be waive-able with the appropriate amount of demonstration.

One of the things -- so, you know, I do not -- you know, wording of how you get there is fine by me but I think there are things that cannot be waived and we should specify what those are and what we are trying to protect.

One of my fears in reading this, and I must say I read it late last night so I may have not done it justice, was that it almost appeared too soft. I am not criticizing that first you have to maybe be a little too hard but, you know, I think we have to lay out --

and I do not know if it is possible to lay out where one cannot go. There have to be some examples of where the culture is so different that they have to conduct research in that culture and follow their norms.

We would be creating an ethical impermissible event and I do not -- and so it may be here and I may have missed it but I think that that is --

PROFESSOR CAPRON: Okay.

Bernie, I have Bernie on the list. It was on this point or do you want to raise another point?

DR. LO: No.

PROFESSOR CAPRON: Because if it is another point, I will go back to Alta.

DR. LO: No. On this point. I agree with trying to be very clear about, sort of, what is waive-able and what is not, and I think the ideas that Alta and you have put out are good ones. I just think that at various points in the text we can make that really clear.

I mean, it is sort of -- for instance, on page 8, lines 4 to 8, we kind of say that you have got to tell people about placebos, randomization and diagnoses but it can be rewritten to make it stronger.

And then I think, also, in the way the recommendations are written, rather than using the

language of substantive and procedural, to just say that you have got to tell people their diagnosis, the alternatives, the fact that it is randomized, and the fact that they may be getting a placebo. Those -- to mention those specifically rather than trying to have a basket phrase that we have a hard time defining.

There may be other things as well that people may later want to put in but at least those are the ones that, it seems to me, we can think of that every subject should be informed about.

PROFESSOR CAPRON: Jim, on this point?

DR. CHILDRESS: I think another problem with the substantive procedure language is, of course, a major procedure we are talking about that is very important and not waive-able is some kind of local review.

So I think that it can become confusing, but I think what is done in the text is quite adequate in that regard.

What Alta has proposed for the recommendation or some version of that would be the way to go.

And, obviously, as Ruth has already raised, a lot is going to depend on how we put these together, the recommendations relative to an explanatory and justificatory text.

But I think the directions that have been suggested are quite workable and desirable.

PROFESSOR CAPRON: Okay. Alta, you had another point?

PROFESSOR CHARO: Yes. And this one is -- this one is much more minor and I think it might be something that could be handled during the comment period.

There is on substantive direction here, to coin the phrase of substantive that occasioned a fair amount of discussion, and there is a conclusion here. I agree with the conclusion but I think it needs more justification.

And that has to do with --

DR. MACKLIN: Where are you?

PROFESSOR CHARO: I am in Chapter 2 and it has to do with truth telling. Telling people the truth about their diagnosis.

Now it was pointed out to us that this was very difficult in settings in which in a clinical care context people are routinely not told their diagnosis if it is terminal, serious, a variety of situations.

U.S. practice changed from that norm only 20-25 years ago and so if you look around, the other industrialized countries that are doing research within

their own borders and are doing collaborative research in resource-poor countries, you will find that the pattern, in fact, is often one of deception rather than truth telling with regard to serious illnesses.

I am comfortable with our conclusion that we wish U.S. sponsored researchers to follow U.S. practices when doing research abroad, but first I think that this is one of the examples of areas where we might actually see some conflicts in "north-north" collaborations with U.S. researchers working in Japan or certain parts of Europe, Italy.

And so I thought that during the comment period it might be helpful to try very specifically to get responses from people who work in countries that do not have the truth telling kind of tradition to find out two things.

First, how they react to the recommendations. How they perceive this affecting their own ongoing collaborations with U.S investigators.

And, second, to inquire how they handle this when they work abroad. I mean, I am kind of curious how other countries handle this dilemma.

France, for example, does have a code that governs its research with human subjects. I do not know the other European domestic codes but I do not --

I would be interested in finding out if there were provisions on this, and we could probably ask people in those research establishments to tell us.

DR. MACKLIN: Yes. Well, it is curious that you mentioned Italy because Italy has been changing its own medical -- I mean, this is sort of blurring what goes on in the medical therapeutic context --

PROFESSOR CHARO: Right.

DR. MACKLIN: -- and what goes on in the research context.

PROFESSOR CHARO: Right.

DR. MACKLIN: And Italy has actually over the last several years changed its medical ethics or its presumptions in therapeutic medicine from discretion on the part of physician to disclose to a requirement in using autonomy based language as a matter of fact.

PROFESSOR CHARO: Interesting.

DR. MACKLIN: You know, in Italy.

PROFESSOR CHARO: Right.

DR. MACKLIN: So this is changing, too.

PROFESSOR CHARO: Right.

DR. MACKLIN: And, in fact, even in Japan -- I mean, they have something that they refer there -- to there as Japanese informed consent, which enables it to retain its --

PROFESSOR CHARO: Right.

DR. MACKLIN: So we may be able to find that out.

PROFESSOR CHARO: Yes.

DR. MACKLIN: I mean --

PROFESSOR CHARO: And I appreciated and agreed with the justification that the research context will generate a demand for truth that is greater than the usual demand in a clinical context and justifies why we would not, kind of, do a cultural bow and say, "Do it your way."

But to the extent that there are some countries that have not made the switch yet, it would be interesting to get some responses.

PROFESSOR CHARO: Eric?

DR. CASSELL: I want to point -- I spent six weeks lecturing in Japan on truth telling and it is an interesting exercise. I will tell you the food is good.

(Laughter.)

DR. CASSELL: The change in the United States from concealment to truth telling did not just happen in medicine. There was a huge change in the whole population, the rise of individualism and many other things happened at the same time, which made that

possible, including therapeutic optimism.

In the absence of therapeutic optimism, truth telling is -- it can be a destructive thing.

So a lot of things happened in the area and this is one area in which I actually think local practice should rule but it should not rule automatically.

You know, "Oh, we do not do that" is not an answer. It is something that has to be addressed and it is another area of negotiation where negotiation should take place because there are two things.

The negotiation allows the local practice to be made clear but it also allows them to begin to be changed.

But I do not think that this is something where we ought to rule.

PROFESSOR CAPRON: Well, we will get to the recommendations as such in a few minutes but I guess, Eric, I hear you being pretty substantially at odds with what Alta just said.

DR. CASSELL: Yes.

PROFESSOR CAPRON: Is that correct? Okay. So that we will -- and I would like to talk about the part of the report up to page wherever -- whatever page it is with you, roughly page 30-31, where we get to the

recommendations and then we will take a short break and come back and start going through the recommendations as such.

DR. DUMAS: Alex, this is Rhetaugh. Before you go to that can I raise one observation?

PROFESSOR CAPRON: Please.

DR. DUMAS: On page 3, line 23, I notice that the -- in the --

PROFESSOR CAPRON: Could you identify the paragraph because we are not all reading from the same page as it were.

DR. DUMAS: Okay. This is the definition of "informed consent."

PROFESSOR CAPRON: Okay.

DR. DUMAS: It refers particularly to "trial" and I would like to suggest that we substitute "study or research project," or whatever for "trial" because "trial" has a particular connotation and I think this is broader than just clinical trial.

PROFESSOR CAPRON: Thank you.

I have Arturo and then Bernie. Did you --

DR. BRITO: Yes.

PROFESSOR CAPRON: Yes.

DR. BRITO: And I will try to stick with the

topic here because I have other comments obviously throughout it.

But I am not sure what pages you were referring to, Alta, when you started the discussion but one concern I have here is that on page 6 where under the heading "Cultural barriers to require full disclosure," the second paragraph. I think this is where it is introduced about the -- not truth telling. Okay.

We do not introduce the concept of therapeutic misconception until much later in this chapter. Okay. My concern here is that there is a blurring here of definitions because this on page 6 refers to the medical intervention.

Later on we talk about therapeutic misconception when people have a difficulty understanding what is research and what is medical care.

Somehow I think that concept needs to be incorporated earlier related to this because there -- particularly people that come from resource-poor countries, those cultural differences in making those decisions become more important.

In other words, a person in a resource-poor country who has no knowledge of what randomization is

or has a lot of difficulty, like we have heard before about what randomization or placebo controlled trials means, and when they are desperate for medical care and they allow someone else to make that decision for them on a medical level, they are going to be allowing them to make it for -- on a research level and not understanding that that is.

I am not sure if I am making any sense but somehow it bothered me that the therapeutic misconception was introduced so much later and not related to the medical -- the non-truth telling basically for medical interventions.

I do not know if I am making sense but does that -- I am just a little bit -- I do not know if we need to change it around a little bit and introduce therapeutic misconception in earlier.

DR. MACKLIN: Well, here is what I would suggest here: I understand what you are saying and it makes perfectly good sense.

The problem is, you know, you cannot introduce everything at once.

DR. BRITO: No, I understand. Yes.

DR. MACKLIN: So I would try to resolve this by perhaps adding a sentence and referring the reader to later in the chapter.

DR. BRITO: Okay.

DR. MACKLIN: Simply saying part of this barrier may arise out of the therapeutic misconception, refer the reader to later in the chapter, but go on with it here because it gets much more nuanced later on.

So would that accomplish it? I mean, just to say that this is further complicated by --

DR. BRITO: Yes, that would.

PROFESSOR CAPRON: Bernie?

DR. LO: I wanted to say a few thins about therapeutic misconception, which is a topic that has bedeviled us for months or years even.

I thought the discussion here was really very good and I think it just needs to be carried the next step further.

On the one hand, I would like to try and -- starting on page 22 forward but it is a whole section on the therapeutic misconception. On my version it is 22, line 3, and continuing.

I would like to see us give some examples, hopefully, from our contractors on how researchers have successfully addressed this issue in their actual studies.

I mean, my problem with therapeutic

misconception is we say it is a problem, it is a big problem. And then, you know, we do not give any advice on how to deal with it.

So if any investigators have -- if any of our contractors have found positive ways to deal with it, as they have for other things we have mentioned in this chapter, I would like to see the examples. I think that would be really useful.

Secondly, I think as I scan the recommendations -- I know, Alex, you wanted to get to this after the break. It seems to me there are about three or four recommendations on therapeutic misconception we might want to consider because it seems to me this is such a big area and we need to sort of try and do more with it as best we can but, I will hold off on the specific recommendations until later.

PROFESSOR CAPRON: Eric Meslin has some comments he may want to pass along from Harold Shapiro. Not right now?

DR. MESLIN: No.

PROFESSOR CAPRON: Okay.

All right. Well, then why don't we -- yes?

DR. BRITO: I just --

PROFESSOR CAPRON: You had a couple more?

DR. BRITO: Just a quick response to what

Bernie said about --

PROFESSOR CAPRON: Okay.

DR. BRITO: -- therapeutic misconception. I agree maybe some examples would be helpful but one problem I still have with therapeutic misconception is if we rely too much on investigators and how they have settled the problem, I think there is a therapeutic misconception on the part -- often on the part of investigators, too. So we just have to keep that in mind when we do that.

And then that line that we may have been -- we were talking about, Ruth, on page 24 of my version, lines 6 to 8, but it is a misconception to believe that the purpose of the research maneuvers to administer treatment rather than to conduct research. Something to that nature would be helpful earlier on.

PROFESSOR CAPRON: Okay. All right.

We will take a break now and when we come back we will turn to the recommendations which will actually, I am sure, get us back to some of these earlier pages if people have further comments.

Could we come back in ten minutes, please? I will see you in 15.

(Laughter.)

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

PROFESSOR CAPRON: Do we have Trish on the phone?

DR. CASSELL: They went to sleep.

DR. DUMAS: Rhetaugh is on the phone.

DR. CASSELL: Rhetaugh is on the phone.

PROFESSOR CAPRON: Hello, Rhetaugh.

DR. DUMAS: Hi.

PROFESSOR CAPRON: Trish, are you on the phone?

PROFESSOR BACKLAR: Yes.

PROFESSOR CAPRON: Good.

PROFESSOR BACKLAR: Who is this?

PROFESSOR CAPRON: It is Alex. I am reconvening you and I want to know who is present.

PROFESSOR BACKLAR: Okay. I am present.

PROFESSOR CAPRON: Physically or virtually.

PROFESSOR BACKLAR: I am present virtually.

PROFESSOR CAPRON: Very good.

DR. CASSELL: We still did not get Trish.

PROFESSOR CHARO: She said yes.

PROFESSOR CAPRON: Okay. We turn now to the recommendations and I would like to give staff as clear and helpful directions as possible so that the next time we see these we will have little reason to have to make modifications in them because we will not have as

much time at the July meeting for this report.

Recommendation --

DR. MACKLIN: May I --

PROFESSOR CAPRON: Yes, please, Ruth.

DR. MACKLIN: Let me just -- we heard some comments this morning that suggested or implied that some text would follow these recommendations.

Now let me tell you what we have in mind now and see what we are going to do --

PROFESSOR CAPRON: Okay.

DR. MACKLIN: -- and determine that.

When -- in previous incarnations of any of these chapters the recommendations appeared in exactly the place in the text that was either preceded by or followed by -- usually preceded by a discussion and a justification.

Apparently from what I understand, previous reports, I do not know how consistent we have to be, but previous reports from this Commission put all the recommendations in a chapter at the end.

What we would prefer is to have them -- if they are going to be at the end of anything, that they be at the end of each chapter because all we could produce by way of a Chapter 6 would be a repetition of what was in Chapter 2, Chapter 3 and Chapter 4 because

all of the justificatory material is there.

So we are, therefore, proposing that the recommendations, which were previously embedded within the chapter, now come at the end of each chapter in the hope -- and I hope it is not an idle hope -- that the justification from the chapter itself will be clear enough. That is from the material in the chapter.

Now I say this because we heard a couple of comments this morning that said, "Well, what will follow the recommendation will then explain it further, justify it." So we have to deal with that question as we discuss the recommendations.

PROFESSOR CAPRON: Okay. As an initial observation, Ruth, I think there are two types of textual material relating to a recommendation. There is the justification, which is usually some form of an argument explaining how the principles, which are enunciated, lead to a certain set of conclusions and here obviously surrounded by or include text about findings from research that we had conducted for us and so forth.

Then there is explanatory material which simply tries not to justify a conclusion but to go perhaps into greater depth than the black letter of the conclusion could as to what -- the recommendation could

-- as to what it means.

And so, for example, if we are trying to differentiate "waive-able" from "non-waive-able" and we find some global term that describes the non-waive-able and some other the waive-able, that we might have explanatory or text that follows that gives examples.

And it might, for example, say, "While not exhaustive, those things which derive from the principle of respect for persons would include a full explanation of the research project, et cetera, et cetera, and the free -- the position of the subject to be a competent and voluntary decision maker."

DR. MACKLIN: I got it.

PROFESSOR CAPRON: It is just so that you do not have to have a recommendation that goes on for a page but someone reading it would understand. Okay?

DR. MACKLIN: Yes.

PROFESSOR CAPRON: Now that does not answer the question that -- the other question you raised, which is one on which the Commissioners' view should be solicited.

Do we want to follow the model that we have done elsewhere where a subject -- a particular subject is discussed and then the conclusions that follow from it are made clear but not crystallized into a

recommendation until the end of the report?

Or do we want to follow the recommendation that Ruth has made here, which is that as those points crystallize into conclusions they also be stated as a recommendation so that the justification is linked sequentially with the recommendation rather than accumulating the recommendations for a conclusory -- yes -- chapter.

Yes, David?

DR. COX: So I really like the idea of having the recommendations stated following the -- or in association with the information by which it was derived but that at the same time having, you know, an overall list of recommendations some place.

But it is like a research paper. You have a summary or here is the recommendations. But then you do not have to search by going through the text for where the information was and where that recommendation came from.

So I think that having it tied to the text is a key thing to do and I do not think it limits having it listed as a series of recommendations.

PROFESSOR CAPRON: Well, we can put all the recommendations in the Executive Summary in any case.

DR. COX: Yes, exactly. Exactly.

PROFESSOR CAPRON: But the question is -- I think it is true in our other reports. We have had them both in the Executive Summary and in a final chapter. The final chapter -- it provides more discussion of them.

DR. MACKLIN: But there is no more discussion of them than what appears here.

PROFESSOR CAPRON: No, no.

DR. MACKLIN: So, David, do I understand your suggestion that they be --

PROFESSOR CAPRON: He is agreeing with you.

DR. COX: I am agreeing with you, Ruth.

DR. MACKLIN: Wait a minute. Agree -- let -- there were still two possibilities. Not -- forget the chapter at the end.

DR. COX: Yes.

DR. MACKLIN: Now we have the possibility of the recommendations at the end of each chapter.

PROFESSOR CAPRON: Yes.

DR. MACKLIN: Or inserted into the chapter at various points and I am -- at the points at which the argument is made. Now I am not sure which one you are --

DR. COX: So I actually like them inserted at the points where the argument is made because what I

will do is look at the Executive Summary to see what the hell the recommendations are and then I will go in, okay, and try and understand where did that come from and so if it is there next to the text into the discussions the examples and where they came from. That is how I would use the report personally.

PROFESSOR CAPRON: Now that actually is, I believe, a fair statement of what we have done at least in some of our reports. That is to say the points at which the recommendations come, they actually have pages of justification, recommendations, some explanation; next discussion, recommendation and so forth.

So are people comfortable with that? And I think we could -- we could --

DR. DUMAS: I am.

PROFESSOR CAPRON: Yes? That was a yes from the phone?

DR. DUMAS: Yes.

PROFESSOR CAPRON: That was Trish?

DR. DUMAS: Rhetaugh.

PROFESSOR CAPRON: Rhetaugh. Thank you, Rhetaugh.

PROFESSOR BACKLAR: May I ask you a question?

PROFESSOR CAPRON: Please.

PROFESSOR BACKLAR: Okay. So because it is sometimes very hard to hear exactly what. The point that you are making, Alex, is that you would -- that it would be as we did in previous reports or we would do it as Ruth is doing it now?

PROFESSOR CAPRON: Well, actually neither. I believe in previous reports -- and we may not have been consistent in all of these, Eric. I do not have them all typographically committed to memory. Eric says he does.

But we have had discussions -- we have had a chapter on ethics and a chapter on law and a chapter on religion or whatever, and in each of these points have been made and conclusions have been reached but then one gets to a final chapter --

PROFESSOR BACKLAR: Right.

PROFESSOR CAPRON: -- conclusions and recommendations, which itself has text and then a recommendation and then more text and a recommendation, and so forth.

What Ruth is suggesting is the draft we have in front of us of Chapter 2 has discussions and then at the end of that chapter are the recommendations.

She is actually suggesting and David just agreed that we would, indeed, keep the recommendations

in that chapter but now distribute them throughout the chapter at the point at which enough explanation and -- excuse me -- justification had been given to that conclusion that would lead to the recommendation.

Is that correct, Ruth?

DR. MACKLIN: Yes.

PROFESSOR CAPRON: Okay. And that is the proposal that is before us and, as we have heard from staff, if we are going to have a report, which is ready for our final review and approval next month, they need to be able to rely on the conclusions, which we reach today, so that subject obviously to the way the pudding looks when we get it -- it is always possible that we can give very clear directions and they can carry them out and we will look at them and say, "This does not work." But subject to that, that we are now committing ourselves to tell them, "Please, put the recommendations at the appropriate point in each of the various chapters where they would come. Not all at the end of a chapter nor at the end of the report."

They will also appear in the Executive Summary, which is a separate issue.

DR. CASSELL: And also appear.

PROFESSOR CAPRON: Yes. They will appear there because we always -- you have to be able to pick

up the Executive Summary --

PROFESSOR BACKLAR: Right. Right.

PROFESSOR CAPRON: -- without looking at the report. It is published separately as a separate brochure as well.

PROFESSOR BACKLAR: So, Alex, then as I understand it, in a sense each chapter will look like our -- what our chapters look like where we put all our recommendations together.

PROFESSOR CAPRON: Yes. They --

PROFESSOR BACKLAR: Where there was discussion, recommendation, discussion, recommendation.

PROFESSOR CAPRON: Right. But -- that is right.

PROFESSOR BACKLAR: And it will be not in one place but throughout the report. Okay.

PROFESSOR CAPRON: On the different -- depending upon the different subjects of informed consent or research design.

PROFESSOR BACKLAR: Right, exactly.

PROFESSOR CAPRON: Or duties after the fact and so forth. Is that everybody's understanding? That is what we are talking about. So that is the plan that we are asking the staff to carry out.

PROFESSOR BACKLAR: Right.

PROFESSOR CAPRON: All right. Now let's turn -- Bernie, a comment on that, please?

DR. LO: I like the idea of integrating the recommendations into the chapters with the appropriate text but I guess I would like to suggest -- and I do not think we can do this in the Executive Summary -- that sometimes the recommendations in toto are more than just the separate recommendations.

Often our recommendations are aimed at very different people so we have recommendations for researchers, IRBs, funders, NIH.

One of the things that is hard to do if they are just listed in each chapter is to sort of bring it all together. So to the extent we can do that in the Executive Summary without having a separate chapter in the text that does that, that is fine. But I would like to see at some point our sort of bring it all together into sort of a coherent report as opposed to just a series of recommendations in each chapter.

PROFESSOR CAPRON: Well, that is going to be -- that, I think, we should ask perhaps the Executive Director or someone to look at. It may be hard for Ruth and Alice to do that in addition to redrafting because as I would -- I would anticipate that we would otherwise number the recommendations consecutively

throughout the report. So we are going to not have a recommendation one in Chapter 3 if we have already had a recommendation one in Chapter 2.

What you are saying is if we -- if the recommendations fall into those that are particularly for researchers, those which are for IRBs, those which are for health ministries, those for U.S. companies, or whatever, that those would be gathered, which might mean that in the Executive Summary, it goes Recommendation 1, 2, 5, 7 or something like that if we were gathering them.

Now is that acceptable, do you think?

DR. LO: Well, I think it is not just a matter of gathering them so that everyone knows what they are supposed to do. But to have some discussion that -- to make this work lots of different people are going to have to do things differently than what they now do.

And one of the things I think is going to be a problem is that some people are going to say, "Well, I can do what you are asking me to do," but that is only a small part of the picture and we have got to expect other people to do their role.

I think that kind of level of tying together is what I think we need here because so much of this is so different than what currently takes place and unless

we have kind of a rah-rah, let's really do it and pull together, I think it is going to get diffused.

PROFESSOR CAPRON: Eric Meslin?

DR. MESLIN: Just two quick things. There are two conventions we can use.

The first is the Executive Summary can be more than simply a compilation of the recommendations. They can do more work as you have described.

Secondly, the cover letter to the President that describes what the report is, which is often picked up by most people before they even read the entire report, can also frame that for you.

So, Bernie, your worries can be met in those two ways at the very least.

Just as a reminder, I think Ruth may have said it while I was outside, the format of this report is different from past reports in that there is not a science chapter, an ethics chapter, a legal chapter, and forcing previous reports aesthetic model into this one just did not work and probably would not work for a number of the reasons that have been mentioned but your worries can be met by those two conventions at least.

PROFESSOR CAPRON: Trish, were you able to hear that?

PROFESSOR BACKLAR: Actually I am sorry,

something else was going on here. I am very sorry.

PROFESSOR CAPRON: Okay.

PROFESSOR BACKLAR: I will get it from Eric later.

PROFESSOR CAPRON: Well, I just want to encourage everyone -- I know Trish and Rhetaugh are having some difficulty hearing -- that we be very vigilant about speaking directly into our microphones.

Let's turn then to Recommendation 1. We have already, at Alta's urging, looked at this recommendation somewhat. I guess I had a question to start off with, which is whether there is some advantage to having this parallelism within one recommendation between researchers and IRBs.

I mean, it seemed to me either there would be a reason to state these as separate recommendations or simply combine into the same sentence the research sponsors and IRBs must assure that the research adheres to but I do not see that repetition adds anything since the -- as far as I could tell, the substantive requirement was the same for each.

But do I -- Ruth, do you have a reason --

DR. MACKLIN: They were written like this -- remember this chapter was only a bare bones outline when you last saw it and the recommendations remain

the same. It is just the text that has been added.

At the very early stage in which these recommendations were formulated, there was some discussion of whether or not they should be directed to specific individuals or agents so that researchers was one group. On the assumption, as we just discussed a moment ago, that there might be in the Executive Summary, recommendations for IRBs, recommendations for researchers, recommendations for sponsors if it is going to be broken down that way this reflects that breakdown.

On the other hand, if it is not going to be broken down that way then the repetition is not needed and we can put where needed. If we are talking about all these guys, we can put it in.

The one thing we tried to do, it did not succeed everywhere, but tried to put these in an active -- named an agent who had to act rather than --

PROFESSOR CAPRON: Yes.

DR. MACKLIN: -- put it in the passive voice.

Now it is pretty clear just for one second when you look at Recommendation 2, when it says, "The provisions of the U.S. Code of Federal Regulations" should be modified," it is quite clear who the agent there is. You can put it in the passive voice. We are

not there talking about the researchers.

But what we have tried to do is say who has to do what actions by naming the agents. So depending upon what you would like to see, you want to see it all lumped into one and then it will be repetitious or are they going to be broken out according to who the agents are.

PROFESSOR CAPRON: Well, for myself, if it is all in one recommendation, I would like the sentences to have both actors in it.

DR. MACKLIN: Right, that is what it will be but it is --

PROFESSOR CAPRON: But if we think that there is -- this is a question for my fellow Commissioners. If we think that we want to be able to say here is a recommendation for researchers, here is basically the same recommendation for IRBs, then they should be separate -- there should be Recommendation 1 and 2, precisely so they can later be sorted and identified.

So what is people's preference? Is there any reason to separate them out?

Bernie, and then Bette?

DR. LO: Well, before we get to that question, which to me -- you are going -- we -- at some point we need to do it both ways. But one of the things that I

would like to see is to make the parallels really explicit so it seems to me the general flow is researchers need to make explicit how they are proposing to change, give adequate justification.

IRBs have to ensure that the justification is adequate. It seems to me sponsors also have an obligation to ensure that any deviation from practices that would apply in this country is adequate as well.

So I would like to -- it almost invites sort of nitpicking if some of the recommendations have all three actors having duties and others do not to say does that let somebody off the hook.

So I would like to just be very careful and to make sure that we are as explicit as possible as to what people should do.

As to Alex's question as to whether -- how we stylistically present it, I do not have strong feelings one way or the other, other than to say that I think we ought to do it both ways at some point in the report, that it ought to be topic and by actor at two different places.

PROFESSOR CAPRON: Bette?

MS. KRAMER: I like the way it reads as all together. I think it has a cohesiveness.

PROFESSOR CAPRON: Well --

MS. KRAMER: I think it is a big issue.

PROFESSOR CAPRON: -- Bernie has, in effect, raised an additional question to my mind and that is do we want always to identify on the sponsoring side two actors. The actual sponsor, the company or the governmental agency that is conducting the research.

And, secondly, the scientists who are carrying it out.

Yes, Ruth?

DR. MACKLIN: I think you have to look at each recommendation to answer that question because, as you will see from the recommendations in Chapter 4, some things go only to sponsors because researchers do not have the wherewithal to --

PROFESSOR CAPRON: Right.

DR. MACKLIN: -- make products available.

PROFESSOR CAPRON: Right.

DR. MACKLIN: So -- and then a question is who is doing the negotiation. So I think you have to take up that point, point by point --

PROFESSOR CAPRON: Okay.

DR. MACKLIN: -- to see what fits.

PROFESSOR CAPRON: In this first one was there any reason to leave sponsors out?

DR. DUMAS: It says, "U.S. sponsored

researchers." That includes sponsors.

PROFESSOR CAPRON: No, I do not think so. "U.S. sponsored" is an adjective.

DR. DUMAS: For what?

PROFESSOR CAPRON: For modifying researchers.

DR. MACKLIN: But wait a minute.

DR. DUMAS: Yes. But if you are talking about sponsors then the researchers are sponsors.

PROFESSOR CAPRON: No. The sponsor is Merck. The researcher is Dr. Jones. The IRB is something at the University of Idaho at Dares Salaam (phonetic) University. I mean, those are the -- I mean those are different actors.

And, as Ruth says, sometimes we explicitly want to separate the sponsor from the researcher because --

DR. MACKLIN: And here is an example: I mean, the sponsors do not get the -- are not involved in the process of obtaining informed consent, the researchers are. So that is precisely why sponsors are not in here.

We are talking about who does what in the informed consent.

PROFESSOR CAPRON: Bernie?

DR. LO: Don't sponsors have an obligation to

review the protocol they are sponsoring and ensure that it meets ethical standards?

PROFESSOR CAPRON: They do both for FDA and for NIH.

DR. LO: So that if there is a -- not so much in one --

PROFESSOR CAPRON: Or CDC or anybody else.

DR. LO: -- but for --

PROFESSOR BACKLAR: And Trish has her hand up.

PROFESSOR CAPRON: Yes, Trish.

PROFESSOR BACKLAR: And the other aspect of this is it is important to have a list of sponsors because sometimes it means that they have to put in more money because it costs more to do this.

PROFESSOR CAPRON: Yes. That is true.

So do we want language, which, in effect, says, "United States agencies and companies in the research which they sponsor; United States investigators and the research which they conduct; and Institutional Review Boards in the research that they review and approve should ensure that --" and then we get to this question of what they are ensuring but using the language that is here now that the substantive ethical standards of informed consent is adhered to.

They may, however, vary the procedure by which informed consent is obtained. Is that a fair summary of what we want to do?

Yes, Bernie?

But we have to come back to this question of -- I thought we had made some progress earlier with the suggestions that were made and we have to refine them a little bit as to what is required and what is waive-able.

DR. LO: Right. In addition to that point, I think your last thing you said, Alex, they may vary "procedures." It seems to me we need a clause saying "provided they give adequate justification for the variation." So that is language that is in some of these other recommendations that you cannot just do it, you have to justify it.

PROFESSOR CAPRON: Yes.

DR. LO: I think that should be there.

PROFESSOR CAPRON: And, in fact, obviously a number of the recommendations that follow this one address that issue.

Now perhaps we do not want to say both of those things in one recommendation. That is to say perhaps we should say that certain things are not waive-able and hold for the next recommendation or the

next recommendations those points which we are going to say may be waive-able and, indeed, with Recommendation 2, in effect, calling on federal regulators to change the regulations to allow such a waiver.

Is that fair?

So if that is -- yes, Ruth?

DR. MACKLIN: I just have a little problem now that we are making -- putting all the agents in here -- using the word "waive-able."

The IRBs, according to the regulation, may waive. Sponsors do not waive. They do something else. And researchers do not waive. They omit or they alter.

So I think you just have to be careful because of who is charged with doing what.

I do not mind taking up any of these. I have no investment in any of these alterations but every time you say "put it all together" and then you start talking about what is waive-able, you do not have the right people doing the waiving.

PROFESSOR CAPRON: Right. So that if we -- if we start off with what is required, we have no problem saying that in the research which they sponsor and the research which they conduct or in the research which they approve as each of those agents, there should be

no deviation from those requirements which flow from the basic principle of free and informed consent.

Is that --

DR. DUMAS: Rhetaugh has her hand up.

PROFESSOR CAPRON: Rhetaugh, and then Eric.

DR. DUMAS: I like the idea. I like the format that is used in the Recommendation 1 and I would like to suggest rewording that, I think, would take care of the concerns that are being raised.

"U.S. sponsors should ensure that researchers adhere to the substantive ethical standard of informed consent," et cetera, et cetera. Or "They should ensure that there is no deviation." Whichever you would prefer. And then all the other things follows.

Does that make sense?

PROFESSOR CAPRON: Some.

DR. DUMAS: Recommendation 1.

PROFESSOR CAPRON: Yes.

DR. DUMAS: "U.S. sponsors of research should ensure adherence to the substantive ethical standards of informed consent." The process of obtaining informed consent or informed consent documents.

PROFESSOR CAPRON: I think, Rhetaugh, we are going to have to go around on this issue of what it is that they are ensuring and get the language of that.

DR. DUMAS: That is right but if you start out with the sponsor's responsibility and it is global. And then this means that researchers, you know, there is certain flexibility for the researchers and then there are certain expectations of the IRB.

PROFESSOR CAPRON: Bette, did you have a further comment? I had your hand before.

MS. KRAMER: No.

PROFESSOR CAPRON: All right.

Eric, did you want to weigh in?

DR. MESLIN: Well, I have two comments. One is substantive and one is procedural.

The substantive comment is that if you go with Rhetaugh's suggestion you have to add something at the end of that first clause that describes where they are doing the ensuring. In the process of awarding money and that sort of thing? So you have to simply add that in.

The procedure -- the two other procedural comments are (1) it is 11:00 o'clock and we have a discussion of Chapter 5 looming.

More relevantly, Harold Shapiro has sent to all of you some thoughts in a fax, which I just received moments ago, some of which are relevant to the discussion now, some of which are relevant to the

discussion later.

I am going to circulate them with his wish that you read them and I will direct you through it. I have been on the phone with him going over this.

So I just make those for your benefit.

PROFESSOR CAPRON: Okay.

If we are getting to the level of wordsmithing, I think the message is we will not have time to do that.

I would take so far from the summary that we do want to address as to this first recommendation all three actors and that appropriate language should be crafted to do that.

I also saw some nodding of heads affirmatively when I suggested that we separate out the affirmative obligation to ensure things are provided from the steps that would follow in subsequent recommendations about varying the standards or waiving the standards as to things which are not as required or the procedures.

Bette, I had Eric and then David.

MS. KRAMER: I just wanted to make a suggestion to maybe help us move along on this.

Why don't we just ask Ruth and Alice to just draft it both ways, all in one and broken out, and we will just be able to quickly see what it looks like and

pass on it.

PROFESSOR CAPRON: Is that the way you would prefer to operate? Is that easier for you?

DR. MACKLIN: Well, I do not know what is easier but since we have 11 recommendations in this chapter and we are only dealing with number one now, I think we have to think both of how we are going to get through them right now to see what we are going to redraft and how we are going to get to Chapter 5, and how we are going to get to Harold's memo.

PROFESSOR CAPRON: Okay. I have Alta, Eric and David.

Alta?

PROFESSOR CHARO: I only wanted to say that I thought that this is a stage of report writing where the actual words of the recommendations do not strike me as being as crucial as a clear explanation in the text of what we are trying to accomplish.

This draft is for public comment. This is not a draft of regulatory language so that if it would be at all helpful, I would personally urge that we worry far less about what particular words appear in the bold type and far more about explaining what we want to get to.

And at the end of the day if that is signed

off on, worry about the words here and then look into whether things like decision charts become the best way to communicate to individual actors what to do versus language.

But it might be a way to kind of break the time barrier here.

PROFESSOR CAPRON: Okay. Eric?

DR. CASSELL: Well, I just want to say that the more complicated the thing is, the easier it is to evade. That is on the first hand. And the easier it is not to understand clearly step by step. So I would rather see it broken out.

I actually also think that when you call it U.S. sponsored research and leaving out researchers in the first section of that will take care of all the actors in it. And that you should identify -- that should be one section and then the next section should be researchers, however, maybe. Make it a separate recommendation as simple as it conceivably can be. Not to cover everything in one thing but simple. Or clear -- not simple, clear.

PROFESSOR CAPRON: David?

DR. COX: So I agree with what Alta just said and I am going to make a comment in that respect with respect to informed consent and this first

recommendation.

Not to have people agree with me but to put forward sort of my simple minded view of this.

So Jim Childress said early on the concept of respect for persons being a fundamental ethical issue, which I understand sort of what that means. So what we do in the United States, at least, is we represent that very often by the process of informed consent.

But informed consent is not the ethical principle. Respect for people, persons, is the ethical principle.

So our regs deal with informed consent. We have to have a rule for international work with informed consent but one of the problems becomes is that different people have different views about personal autonomy, which is tied up in the concept of informed consent.

So that what we do then is we say, "Listen, we start with respect for persons. We in America do it with informed consent." When you take that into an international context, it makes life complicated because other people look at autonomy differently.

So what we can do is have some other ways that we can have informed consent and these are them. Autonomy may be one thing that is different in

different places. So we use that as an example. All right. And that we do not get tied up. That is not in here right now. I do not see that written in a place where I can understand that logic.

So I am not saying to agree with my train of logic but have a train of logic that starts with the principles, goes into what it is that -- what the statutes use as implementation. In this case, informed consent. And why that is more difficult in international situations.

I use the example of autonomy as one thing that you have to face up front because we know that people disagree with that.

PROFESSOR CAPRON: Yes. I think that a lot of that is in Chapter 2, frankly.

Ruth, I think that a lot of that is in Chapter 2.

What I conclude -- I want to make clear what I understand, however. We do not think that individual informed consent can be put aside for consent given by third parties for otherwise competent adults. That is to say a husband cannot consult for the wife, a Chief cannot consult for members of his Tribe or whatever.

In other words, when we talk about those things in the report we see those as perhaps additional

procedural things that would be allowed. That is to say you get -- you go through a process of negotiation before you go to individuals in the group by looking to group leaders.

But we do not see -- so that we do not say autonomy is just this U.S. requirement. We believe that you still are going to have to get the free and informed consent of individuals before they are in research even if that is not the standard in that country and either the standard is so difficult to accommodate that you cannot go to the people in that country and do the research or the people who you go to are going to be going through a somewhat unfamiliar process.

Is that a fair statement of where --

DR. MACKLIN: Yes.

PROFESSOR CAPRON: Okay.

DR. MACKLIN: It is a rock bottom requirement.

PROFESSOR CAPRON: Yes.

DR. MACKLIN: Individual consent.

PROFESSOR CAPRON: Yes, right, and we do not think -- and I took our discussion that Alta prompted earlier today to lead to the conclusion that we will try to explain in the language here that follows this that what we -- not to touch every possible example

someone could come up with, but we are talking about those things which relate to being informed of what the research -- that there is research and what is involved in the research. And the person be situated so as to make a free and competent judgment about whether they wish to participate is something which does not get waived.

And if we split this up into our first recommendation that deals with what is not waive-able, that is the core of it, and we are going to -- you know, we might -- if this follows the point where we have discussed in the text procedure and substance, say that some people describe it in those terms, that these are the substantive requirements.

But that they derive, as you just suggested, David, from -- and as Jim suggested earlier -- from the principle of respect for persons, which plays out to this rock bottom requirement.

Are we all comfortable with that?

DR. COX: So, Alex, can I just comment on your comment on my comment?

PROFESSOR CAPRON: Yes, please.

DR. COX: I think it is in Chapter 2, all of these words are in the chapter, but when we look at the recommendations and the point that Ruth wanted to put

forward, which is what is the logical trend by which we derive these conclusions. Right? Is that it is not clear to me where this one -- precisely the things that it comes from.

And the second thing I would like to say, Alex, is that the -- what you did -- okay -- just now is basically said we have already reached a conclusion, okay, in terms of what the rock bottom principles -- and I would like to come back to Jim Childress, and maybe I misunderstood your point, Jim.

But I heard when you made the point about autonomy, right, that that was not a clarified issue yet.

DR. CHILDRESS: Or at least in the -- if we are referring to all the codes in different countries and internationally there might well be different statements of the justification.

DR. COX: Indeed.

PROFESSOR CAPRON: Jim, I think David is taking something different from your comment than I took from it.

DR. CHILDRESS: Okay.

PROFESSOR CAPRON: I took you to be saying that if we look at those statements, we would do better to generalize that they all embody a respect for

person's view as to which a particular language about autonomy might be thought to be particularly a Western or U.S. way of deriving from that.

But respect from persons in the Belmont Report had not only autonomous consent but other aspects to it.

Is that correct?

DR. CHILDRESS: That is correct and I think respect for persons would come closer to being more generalizable.

But even there I just do not want us to rest everything on that as -- because even in the U.S. many have argued for first person voluntary informed consent as a way to protect subjects, not as a way to respect autonomy. That is there are many --

PROFESSOR CAPRON: Yes.

DR. CHILDRESS: -- and you have one of the famous lists of --

PROFESSOR CAPRON: Right.

DR. CHILDRESS: -- the different kinds of functions, for example.

So, I guess, I just did not want to over simplify in this first paragraph exactly why we think voluntary informed first person consent is important.

PROFESSOR CAPRON: But you do not differ from

the conclusion that it is a rock bottom requirement?

DR. CHILDRESS: Right, absolutely.

PROFESSOR CAPRON: Okay.

Now let's turn to some of the spelling out that occurs in the subsequent recommendations of those aspects of the U.S. regulatory requirements that may be waive-able and talk about how this plays out.

In Recommendation 2 the present statement is that "the provision of the U.S. Code of Federal Regulations requiring written signed consent documents for all research involving more than minimal risk should be modified to allow for waivers of one or both of these requirements. Researchers must provide adequate justifications for requests for such waivers."

Now I understand that implicit in that latter sentence is the notion "justifications based on local customs, which would make written forms or subjects signing such forms culturally unacceptable."

Is that the correct reading of that?

DR. MACKLIN: No.

PROFESSOR CAPRON: No. What is -- what more do you have in mind?

DR. MACKLIN: Because, for example, if a signed consent form by a person who is engaged in illegal behavior but is a research -- a subject of

research, if the signed consent form can identify the individuals and may put them at legal risk, that is a different kind of justification.

Similarly, in some HIV research, it has nothing to do with the local customs but it has to do with the possibility of the information being revealed.

So there are other justifications. It need not be only local customs and I think it is better -- it is preferable to leave it general because these other conditions may also obtain.

PROFESSOR CAPRON: Yes, Bette?

MS. KRAMER: My recollection is in reading it that it flowed very naturally out of the earlier discussion so I think when it is put back where the discussion is it is going to be very consistent.

PROFESSOR CAPRON: Okay.

MS. KRAMER: And clear.

PROFESSOR CAPRON: I left out that parenthetical clause and it just reminds me -- I do not know at what point, I guess, each of us should try to give you language that rewrites the language.

I did not find that some of these recommendations read like recommendations in our other reports. They read more like a statement of the topic and a conclusion.

But other than that, concerns of that sort, are we all comfortable with this as a conclusion?

Recommendation 3 states, "In addition to the basic elements of informed consent and any optional elements deemed relevant and appropriate for the proposed research, the informed consent process and document should include information about what will and will not be made available to subjects when their participation has ended."

On this one I thought that that first language made it sound, as Alta said a moment ago, that we were trying to write a regulation, which I did not think we were.

Perhaps it would be more direct simply to say, "Subjects must be informed what will and will not be available to them when their participation has ended. The IRB should ensure that this information will be adequately conveyed by researchers in the process of obtaining informed consent and in all informed consent documents."

Recognizing that there may not be, for example, a written form and so forth.

But is the substance of this agreeable?

Now this actually, of course, refers readers, the text surrounding this is going to have to refer

readers ahead to Chapter 4 because that is where the substantive discussion of that comes but you would like to have that here in the informed consent chapter.

DR. MACKLIN: It was not here earlier but since we now have Chapter 4 and that is one of the things we are saying in Chapter 4, it belongs in both places.

PROFESSOR CAPRON: Well, I would, frankly, leave to you in the polishing of the next draft the question of whether when you get to this point you decide that there has to be so much forward referencing that this conclusion actually belongs in Chapter 4 because after all we are now saying that the recommendations are spread throughout.

Not every recommendation that says the word "informed consent" has to be in this chapter but I would leave it to you to see that -- whether it flows more acceptably here or later.

Eric?

DR. CASSELL: Well, since this part of the recommendation is about something we have not even resolved and it is open to so many individual variations, depending on the kind of research and whether the trial is successful or it is not successful, and so forth and so on, I just -- I do not

see a point in having it here until we at least have discussed it thoroughly in Chapter 4.

I would like to leave it out myself.

PROFESSOR CAPRON: Jim?

DR. CHILDRESS: Let me respond to Eric.

I think it ought to be included because it does not really at all say what policy or practice has to be present. Only that whatever you have you need to disclose that to the participants.

MS. KRAMER: Just say nothing.

DR. CASSELL: There will be no follow-up in this trial.

MS. KRAMER: Right.

DR. CASSELL: But what does that mean? What does no follow-up mean? I do not understand that. It is just too vague. There will be no follow-up. That is it. We will never say another word. No other word will ever follow. I mean, you can just think of --

PROFESSOR CAPRON: Well, that probably would not be a very helpful description is what you are saying.

DR. CASSELL: No, exactly.

PROFESSOR CAPRON: But would a description which says, "At the conclusion of this trial the sponsors will not provide you with any product

developed in this trial."

DR. CASSELL: Well, I can think of a situation where they would say, you know, you will have a piece of boilerplate that says that but it does not have anything to do with that particular trial.

It is just too vague.

I think that the issue has to be argued out later on and then the recommendation should be that that should be part of the informed consent.

If you put it in here without the discussion about it -- I was reading it and I was thinking what am I supposed to say. I mean, I am writing a trial of a particular -- I do not know if it is going to work. It is a phase this trial. Somebody else -- I am only trial number two. I know four more trials are coming. They will not really know the answer until trial seven. What am I supposed to say now?

There will be nothing following this trial, which sounds like I am taking something away from you. You know, when you write down I am not going to give you anything, that says I am taking something away.

Whereas, after trial seven we are going to really know whether there is something coming out of it.

So you are sticking people with something that

does not apply to them and it may not -- it makes them look bad when they are not being bad.

I do not think we ought to put this in here. I think we ought to argue it out completely where it belongs and then if it looks like we can come up with language, that is a different issue.

PROFESSOR CAPRON: Yes, go ahead on the phone.

PROFESSOR BACKLAR: Trish has her hand up.

PROFESSOR CAPRON: Go ahead, Trish. And then Arturo.

PROFESSOR BACKLAR: It may be that one could have the discussion in the text somewhere that whatever is relevant -- it is understood that whatever agreements are made that are relevant for the subject to have knowledge about this will be -- the subject will be informed.

This is not at all the language I would mean to put it in but it seems to me that this is something that could be discussed in the text itself.

PROFESSOR CAPRON: I have Arturo and then Bette. On this point?

DR. BRITO: On this point.

PROFESSOR CAPRON: On this point.

DR. BRITO: Because it just occurred to me that there is no recommendation here -- okay. Earlier

in the chapter we describe the basic elements of informed consent that we already -- that Jim earlier talked about the rephrasing that as obligations of disclosure instead of calling it informed consent.

And there is no general recommendation, which -- it just seems to me there should be somewhere here -- about -- because you start off "in addition to basic elements of informed consent..." what would be wrong with making a general recommendation to say that all these basic elements of the obligation of disclosure or whatever phrase we use need to be discussed, and then later on in Chapter 4 being specific if we decide to -- what will be made available to subjects when their participation has ended?

I am not sure if I am missing something here from the recommendations but it just -- there seems to be a gap here somewhere especially if we are going to go back and put the recommendations following the text.

PROFESSOR CAPRON: Bette, do you have a comment on this as well?

MS. KRAMER: No. I think it ought to be in both places and perhaps it would -- perhaps we could just include at the end of the recommendation just a note that a broader discussion follows in Chapter 4.

PROFESSOR CAPRON: Well, let me see --

MS. KRAMER: Or in addition.

PROFESSOR CAPRON: -- I am not clear whether anyone agrees with the most sweeping version of what Eric said, which was that somehow -- wherever it is that the information that you would be conveying in many cases would be something you should not either have to convey or would be harmful to convey.

DR. CASSELL: Well, yes. I say if you have nothing to contribute at the end of the trial because it is that kind of a trial and that you are obligated to say I will do nothing following this trial in one form or another, you have just made a negative statement when you have done anything negative. You have nothing you could have done.

PROFESSOR CAPRON: Well, you have -- I gather that the thought here is similar to the present requirement that people be told whether or not there will be any compensation if they are injured in the research, that people could go into it with a misimpression that they will be taken care of because they are being research volunteers and they should know if the policy of the institution is if you are injured, whatever compensation, medical care you get is on you and your present insurance mechanisms. We do not guarantee to do anything for you. It is thought to be

important to say that.

Now you may regard that as a negative statement, Eric, but it is --

DR. CASSELL: Well, I would like to see language then, I guess, you know, or see it discussed. And I guess that is my problem with it.

PROFESSOR CAPRON: No, I understand. That was a separate.

DR. CASSELL: Yes.

PROFESSOR CAPRON: The more modest version of what you were saying is it will only make sense in context of a discussion of the point and that is going to occur in Chapter 4 and, therefore, the recommendation should be held until Chapter 4.

DR. CASSELL: I will take the cloak of modesty.

PROFESSOR CAPRON: The more modest. Okay.

DR. BRITO: Alex?

PROFESSOR CAPRON: Yes, Arturo?

DR. BRITO: I am sorry. I just -- I think I have figured out what -- where the problem is here with what I am saying.

I agree that it probably should be in Chapter 4 so I agree with Eric on that.

But going back to this recommendation, we have

got to go back to Recommendation 2. The way Recommendation 3 reads right now, "In addition to the basic elements of informed consent," and then it talks about the process and document.

The implication is that we are assuming there is going to be a written document but yet in Recommendation 2 we are allowing for modification or waiver of one or both of these requirements, which is the written -- one of them can be the written document. Right? A written signed consent form.

PROFESSOR CAPRON: Yes. I do not -- Arturo, I do not think that is a problem. I mean, in other words, if there is not a written signed consent form, there still has to be information conveyed.

DR. BRITO: I understand that but what I am saying is there is -- Ruth, maybe you can help me here. There is really no recommendation here saying that on international research settings if there is no written document that anybody has to be obligated to follow the basic elements of informed consent --

DR. MACKLIN: Well, those must be disclosed in the process. Those are the substantive requirements that must be disclosed in the process whether or not there is a document.

DR. BRITO: Right. Where in the

recommendations does it say it?

PROFESSOR CAPRON: I have a sense that as reformulated, Recommendation 1 is going to say that. Isn't it?

DR. MACKLIN: Yes.

PROFESSOR CAPRON: Yes. The Recommendation 1 is going to say, "This is the core requirement of what must be conveyed," and now we are going to get later on to the process of conveying it.

DR. BRITO: Okay. If that is the case, once it is reformatted, then I agree with Eric that it should be put --

PROFESSOR CAPRON: And I would suggest, frankly, right here, Ruth, that it may very well work out in the commentary on that first recommendation to note that one of the things that is -- that may be at issue is what will be given to the participants, and that is addressed in Chapter 4. That signals the reader that there is going to be further discussion and the discussion then gives -- in the view of some people -- probably a better way of understanding the recommendation.

Why don't you see how that works out because I think now we are getting to the point of trying to anticipate what the next draft is going to look like

and I think we have to let Ruth and Alice try to work it out.

They have gotten advice and they have gotten Eric and Arturo's concerns.

Recommendation 4. Is there any discussion of that? "Researchers should develop culturally appropriate ways to disclose information that is necessary for adherence to the substantive ethical standard of informed consent." That language may have been modified.

"Researchers should describe and justify in the protocol the procedure they plan to use in disclosing information to participants."

Yes, Bernie?

DR. LO: Just to say that I think we need a parallel sentence that says, "IRBs have an obligation to ensure that..." blah, blah, blah. And if you want to put another one in for sponsors as well.

PROFESSOR CAPRON: Okay. Any further comment? Is the substance of the recommendation agreeable?

David?

DR. COX: So this comes back to the same issue that if in a culture, all right, it is not culturally sensitive to go to the individual, all right. So, I mean, I understand our rock bottom thing but that if it

is not culturally sensitive to go to the individual in the first place, right, then it is impossible for researchers to develop culturally sensitive ways to do what we are asking them to do.

So to make it so that it is not logically totally inconsistent with what we are doing, we have to say up front -- and Harold had suggested this earlier -- that there are just some types of research that under these rules it is not possible to do in other places.

PROFESSOR CAPRON: I believe that --

DR. MACKLIN: Could I just say here --

PROFESSOR CAPRON: Yes, Ruth.

DR. MACKLIN: -- this recommendation does not go to the question of who may be approached. It goes to the earlier discussion about disclosing fatal illness and in the text where this is going to go back it should be clear from -- with the inclusion of some examples that are in this text that this has to deal with how you break news to people that is required in order for you to be disclosing the basic elements of informed consent if, in fact, it is one of these cultural situations where people are not usually told that they have a fatal illness.

So this does not go to the question of whom, the approach to an individual so much as the content

that is disclosed.

PROFESSOR CAPRON: But you would agree with David's bottom line that the result of this would be to say if you are dealing -- you are doing cancer research in a country in which patients are not told they have cancer, you either have to find a way of conveying that fact to them, which is sensitive and so forth but that conveys it, or you cannot do the research there.

DR. MACKLIN: Exactly.

PROFESSOR CAPRON: That is what I take to be the conclusion.

DR. DUMAS: But when you convey it back it might be considered culturally inappropriate.

PROFESSOR CAPRON: Right. And, therefore, if it is culturally inappropriate you either -- you decide that if that cultural inappropriateness is so great a barrier that there is no means to develop appropriate ways of overcoming it.

DR. DUMAS: Right.

PROFESSOR CAPRON: You cannot do the research. Is that what we are saying?

MS. KRAMER: Yes.

PROFESSOR CAPRON: Yes. Yes. Yes, David. Yes, Bette. Yes, Arturo.

DR. COX: I just want to make that clear for

the researchers because what you are going to be doing --

PROFESSOR CAPRON: Yes.

DR. COX: -- and for everybody -- is that there is going to be some ways where you try and figure this out and it just will not compute. And what that means is we are saying that, you know, that is life because we have got certain rules that we do in the U.S. and if we are using U.S. money we are using these rules.

Now Harold said this before. I really must say I have thought a lot about it myself as the bottom line. But that the -- if that is what we are saying, which is I think the whole sort of logical foundation about what we are doing, we have to be clear about that up front.

DR. MACKLIN: Yes. I guess I do not want to buy into the phrase that it is "U.S. rules" and if you are using U.S. money you have to rely on U.S. rules.

The chapter starts out by pointing out all of the other international documents that buy into the principle of disclosure of relevant information so that people give an understanding and knowing informed consent, and it ticks off the names of those documents.

So there is no more specificity in the U.S.

rules than there is CIOMS or in the ICHGH, et cetera. So I just want to resist because that is a different claim. If you are going to use U.S. money you have got to pertain to U.S. rules.

What we are trying to say about these requirements for informed consent is that they are universal even in Uganda and India, which buy into the principle, and I think they do use the word "autonomy" by the way but we will check it.

PROFESSOR CAPRON: Diane, you had your hand up before.

I want to welcome the Commissioner from Massachusetts. Steve Holtzman has joined us for the record.

DR. SCOTT-JONES: It seems that the phrase "culturally appropriate" is too ambiguous to use here because the recommendation does not say anything about how that would be determined. I think cultures change as ours has changed over time. It just seems to me that this should have more specific information than can be conveyed by the phrase "culturally appropriate."

PROFESSOR CAPRON: Alta?

PROFESSOR CHARO: I have a feeling that there is, in fact, a very common understanding here of what

is going on and that if you -- if we were to simply say that when U.S. researchers work abroad the subjects will receive the same information that they would have received in the United States, which would then incorporate the truth about their diagnosis, but that researchers should feel free to vary the way in which that information is communicated to take into account local conditions.

We will have clearly stated what is here in different words that maybe convey it more clearly to other people.

DR. MACKLIN: Alta, I guess I want to be very careful. This is goes back to the same point I just made to David.

There is so much, as you will see later on, of people saying, "You are imposing U.S. standards, rules, practices, behavior on other countries." And phrasing it in the way that you have, even though I know what is behind it, it is saying it should be the same everywhere, is going to make it look as if once again we are saying this is the way we do it in the U.S. so you better do it elsewhere and people are going to object to that.

PROFESSOR CHARO: Ruth, I sympathize with your objection and I -- but the reason why I am phrasing it

the way I am is because these recommendations are being made by a Presidential Commission to the Federal Government to tell the Federal Government how it ought to behave, which means what we are saying is how should U.S. researchers behave.

Now we could say they should behave the way all researchers around the world in places that use any of these various international codes behave or we could say they have to do what they ordinarily do here.

The first would be more politic. The latter would be a lot easier to implement because the IRBs have lots of experience in applying U.S. domestic standards to U.S. domestic situations. And if you tell an IRB, "Do with your U.S. research in Uganda what you would have done with U.S. research in Massachusetts," they will know what you are talking about.

DR. MACKLIN: Yes. And remember then that the other people who are going to have to deal with this are the IRBs in other countries and they are likely to give -- because you are talking about collaborative research, and all these other countries have or will have or are required to establish IRBs, and they are the ones who are going to look at this and say, "Ah-ha, you see yet again they are saying you should do here what you do in the United States."

Whereas, if you make it neutral to the country, it is now the other IRBs are not going to say what we have in Chapter 5, and maybe too many quotations in Chapter 5, of people saying, you know, be more flexible and do not -- we do not want any more imperialism.

PROFESSOR CHARO: I see your point. But now I have got a problem of kind of infinite regress because I do not know how those other international documents have been interpreted.

For those places that are following CIOMS guidelines or interpreting the World Medical Association statements, I do not know what their views are on things like truth telling with regard to the diagnosis somebody has prior to enrolling them in a clinical trial.

So I do not know if a directive that says follow the rules on truth telling that are embodied in all those documents will actually accomplish what I am hoping to accomplish because I am substantively, whether we admit it or not on paper, trying to, in fact, export the U.S. interpretation of truth telling.

DR. COX: Exactly.

PROFESSOR CHARO: And so can you tell me from your own experience with places that work with those

documents instead of our own regulations whether the equally vague language has resulted in similar interpretations?

DR. MACKLIN: We heard from Christopher Plowe, who said they are inscrutable.

(Laughter.)

DR. MACKLIN: I do not think we are going to know the answer to that question, Alta, and I think this is at this point a somewhat political point and I think there may be a way of saying it and saying that the standards in the world for the disclosure should be the same without making -- using -- saying explicitly researchers should do elsewhere what they do in this country.

PROFESSOR CAPRON: I have Bernie, Bette, Arturo.

DR. LO: Yes. I guess I would like to go back to sort of what is it we are trying to get across here and then separate that from how we are going to justify it and explain it in a way that people are going to accept it. And if what we are really trying to say is that researchers should tell people their diagnosis, that they are being randomized, and they may get a placebo if those, in fact, are going to happen, then I would suggest we say it just straight forwardly

and not sort of take the back door approach that we now have in Recommendation 4.

Then how we justify that in text, I think, we should have this whole discussion encapsulated. I like actually Ruth's approach that this is universal. It is not just the Americans exporting. But you can say -- and that we are sensitive to the notion that, you know, it is cultural imperialism.

But I think I would sort of then make Alta's point that from the point of view of the IRB or researcher this involves doing the same kind of balancing they do in this country of what is clear, what is feasible, what is understandable.

But I think I would -- if we are just dealing with the recommendations I would sort of first clarify what it is we are recommending and trying to say.

I guess I would lean with what David was saying that we need to say pretty explicitly that these things which are -- that these issues of diagnosis -- and I think it is diagnosis, randomization, placebo. There may be others I am missing. If that is part of your protocol, you need to explain that in a way to your potential subjects -- in a way that they are likely to understand it, period.

And then the cultural appropriate really comes

more into sort of the language you are using and the concepts but not to the mandate to convey that information.

PROFESSOR CAPRON: Okay. Bette?

MS. KRAMER: I pass.

PROFESSOR CAPRON: Arturo?

DR. BRITO: This -- I think one of -- I agree with what Alta said about that this is a document meant for the Federal Government and I also agree with Bernie that in the text that we should include discussions that Ruth mentioned about international regulations.

One of the problems I have with this recommendation is the word "should develop." That to me has a tone of arrogance to it.

And I think what we are talking about here is that the U.S. sponsored research in other countries should utilize culturally appropriate ways to disclose the information. Not develop them and it may sound like a minor point but I think this gives it a tone of we are telling -- once again here we are the big bad U.S.A. telling other countries how they should do things and we are going to develop systems.

So I know -- so I would just change the wording around here so that -- or culturally appropriate ways should be utilized by U.S. sponsored

researchers, et cetera, in foreign countries.

DR. MACKLIN: What if we said "in consultation with --"

DR. BRITO: Okay.

DR. MACKLIN: "-- people in the host country," or something like that?

DR. BRITO: That is perfect. Perfect.

DR. CASSELL: Well, if you --

PROFESSOR CAPRON: Now I have Diane.

DR. SCOTT-JONES: I just wanted to comment again about this notion of culturally appropriate and it is related to what Arturo just said about should develop.

There is still an air of cultural superiority here because we in the U.S. need to remind ourselves to adhere to these standards and this reads as if we are somehow doing things in a perfect way and we are not by any means, and that we are going to somehow relax our very high standards when we go to other countries.

I think we need to reframe this along the lines that others have said so that we are not giving this air of cultural superiority.

PROFESSOR CAPRON: Jim?

DR. CHILDRESS: And there are variations in the U.S. and if we distinguish, for example, diagnosis

from prognosis, and look at Nicholas Christakis (phonetic) book Foretelling Death, there are tremendous variations in U.S. professional norms regarding disclosure of prognosis as distinguished from diagnosis and yet the two are often very closely related.

So I am not so sure in relation to Alta's standard that she wants to export that we actually have it as clear cut in the U.S. as she suggested.

PROFESSOR CAPRON: Now -- Bill, did you have a --

MR. OLDAKER: Just one point of follow-up.

Whatever we do here we have to realize that we are exporting a standard and the standard that we are putting forth here, as Alta said, is a standard of the Federal Government.

I realize that we want to be culturally sensitive to that but on the other hand we are setting the standards for how research is going to be conducted with U.S. money in underdeveloped countries. I mean, we cannot overlook that fact.

So, therefore, the less clear we are as to that, the more problems we cause by our very writing of it.

So I know you are trying to divide -- you know, make a very difficult division here and trying to

be culturally sensitive and put the guidelines down at the same time.

PROFESSOR CAPRON: Now, as I understand where we are then, if in Recommendation 1 we have made the strong statement about what is required, we are addressing here the notion that it is appropriate for researchers -- and we are talking here about researchers in U.S. sponsored research -- to adopt and utilize culturally appropriate means of conveying information with the bottom line being that the information that is necessary for informed consent not be compromised and not be omitted as a result.

Is that -- that is what we want to get across.

In some ways, frankly, this whole discussion seems more a commentary on -- I guess it is a recommendation but it is a recommendation not that they should adopt but when they do adopt or utilize such standards that these modifications should not lead to an omission of any of the essential elements.

Is that what we want to get across? Okay. We are done with that one.

Now Recommendation 5, which is about men and women. "Researchers should use the same --" Sorry.

DR. LO: Alex, earlier you made a comment which I think ties together with 5, 6 and 7 and 8,

which was that where you have a competent adult subject, they need to give their informed consent. And although you may wish -- they may wish -- or it may be appropriate to have additional authorization from a group leader or a spouse or the family, such additional sort of authorization should not substitute for first person consent.

PROFESSOR CAPRON: Yes. Yes.

DR. MACKLIN: Now that consolidates the three, right?

One problem is if, in fact, we adopt what everybody said we should do, namely putting these recommendations back into the text, each one of these items is discussed separately with a separate discussion and a separate justification. So consolidating it here would mean making a different recommendation for the Executive Summary than we would have individually because we are going to put each one into the text. We are going to discuss women and men, we are going to discuss community members, et cetera.

So we have to be clear which you prefer because having decided we are going to put these back in the appropriate place, they have to be broken out in these separate ways.

PROFESSOR CAPRON: Frankly, I do not see the

problem quite that way. I think we can make both the global statement that the -- freely given voluntary individual consent is required.

And then explore the issues that have been raised about situations in which spouses, particularly male spouses, consent for the treatment of their wife or wives is accepted.

And say as to this kind of research that is not going to wash and have a recommendation that says that.

And then we have a discussion in the text of the cultural -- the customary leaders and other leaders of groups and then we have a conclusion.

So, Ruth, I do not see the problem with the broader statement having come earlier and still elaborating, in particular, these recommendations as they flow from the text that you have.

So if you were seeing problem -- and there is -- in other words, there is a slight redundancy. Having stated the global, these are all self-evident but since they are the very points which have been discussed around these issues, they ought to be addressed and it is reasonable to have a conclusion and a recommendation.

Yes, Alta?

PROFESSOR CHARO: On the other hand, I am not sure that all three of these are precisely the same. There are slight differences in what is going on here.

An initial question is whether a third party ought to have the privilege of preventing an individual from enrolling in research.

If you look at the text that has been proposed for Recommendation 7, which talks about community leaders, it says that researchers should adhere to local customs where you are supposed to approach a community leader first.

What might be inferred from that is that if a community leader refused that the researcher ought not then go out into that community and start recruiting individuals. So that in a sense the community leader has prevented individuals from enrolling.

Recommendation 6 is a little unclear about that because it says we should adhere to custom about involvement of families but at the end it also says the potential subject should be told about the risks and benefits of involving them, and that suggests that maybe they have a chance to say do not involve them at all. So that one.

And then Recommendation 5, which involved men and women, we never start by saying you should adhere

to local custom even if that custom were to approach men first to ask their permission to approach their wives for enrollment.

So obviously there are some subtle differences in the thinking going on here. Whether we all agree with that, I am not sure yet. But it does seem to suggest that these are not, in fact, all of a piece.

DR. MACKLIN: I think that is right.

PROFESSOR CHARO: And I would actually appreciate a chance to talk about each of them individually to make sure that we are all on the same page as to what we want the rules to be.

DR. MESLIN: So let's start talking about them. Let me just give you a quick time sequence here. For those who have been looking at your agenda and were wondering where Chapter 5 at 11:00 o'clock went, Alex elected to continue the discussion so that we could finish Chapter 2.

We will reorganize the agenda for tomorrow afternoon's discussion to ensure that Chapter 5 is not short-changed at all. So we will continue with the discussion of Chapter 2's recommendations now up until lunch time.

For the public who is here, just to let you know, we will try and break around 12:00 o'clock or

12:15, and reconvene as quickly as we can after our lunch, which will just be a lunch in the hotel or locally for Commissioners.

The Public Comment session scheduled for 1:00 o'clock, we will try and adhere to that plus or minus a few minutes so we do not disrupt our afternoon schedule.

So we are on Recommendation 5. Alta, were you proposing to continue on with 5 or do you want to go on to 6 and 7 to flesh these two out?

PROFESSOR CHARO: Well --

DR. MESLIN: I want to put you on the spot because you proposed it.

PROFESSOR CHARO: Right. I am very comfortable, in fact, with suggesting that American researchers should feel comfortable deciding that they are going to approach women first regardless of local custom and ask women if they would choose to participate in research, and then leave it up to women whether or not they wish to involve their spouse.

So I am very happy with that but I can certainly imagine some people here who would not be.

DR. CASSELL: So say again in one simple sentence what it is you are comfortable with that some people might not be going directly to the women.

PROFESSOR CHARO: Regardless of local custom.

DR. CASSELL: I see.

MS. KRAMER: Doesn't that --

DR. CASSELL: I hope you do not have to do that research.

PROFESSOR CAPRON: I have Bette and Steve.

MS. KRAMER: Doesn't that fly in the face of everything that we have been saying -- that we have said about being -- what is the word I am looking for?

PROFESSOR CHARO: Culturally sensitive.

MS. KRAMER: Right, thank you.

DR. DUMAS: Rhetaugh wants to ask a question.

PROFESSOR CAPRON: Okay. Well, Rhetaugh, we have Steve first and then you and then Diane.

DR. DUMAS: Okay.

MR. HOLTZMAN: I certainly agree with the sentiment, Alta, but what I am having trouble with is the consistency. Right? I have a pragmatic concern with the first sentence in 5 where it says we have to use the same procedure. That may be tantamount to saying that no trial can take place here because you cannot use the same procedure, you know.

DR. MACKLIN: This is Harold Shapiro's.

MR. HOLTZMAN: Right. Excuse me?

DR. MACKLIN: This is Harold Shapiro's wording.

MR. HOLTZMAN: Right, and I have a -- so I would -- I can imagine plenty of scenarios where obeying the local custom of talking to the male spouse, as long as the female retains the right to assent, which again is consistent in all of these. We are saying --

DR. MACKLIN: Like a child, right? Like a child.

MR. HOLTZMAN: Well, do not put me on the other side of this, Ruth, because it --

DR. MACKLIN: That is where we are.

MR. HOLTZMAN: Well, okay, but then help me understand why you make the distinction there but not in the case of 6 and 7. All right. So why is it we are saying that gender trumps other relationships of authority? I understand in our culture right now that is a very important issue at this moment and it has always been an important issue, and I know the way I would like the world to look like with respect to all power relationships.

DR. MACKLIN: It happens to be an important issue for women in other countries even though men would like to keep it just as it has been for

centuries.

You know, every single country has a women's movement. They have NGOs and they would support this.

So it is -- the -- Alta made the distinction, I think, quite appropriately between what the community leader is being able to do and what a spouse is being able to do.

So each of this -- one has to look at the nuances and it is not even clear in the case of Recommendation 6 where we talk about the family members that it is because they are in a position of authority. It is a kind of custom that families are involved in these.

MR. HOLTZMAN: So have we articulated that argument sufficiently well in the chapter, do you believe? The one you were just making.

DR. MACKLIN: Of course, I am going to say I did, we did, but I am not sure you would agree.

(Laughter.)

MR. HOLTZMAN: Okay.

DR. MACKLIN: It is going to go right into the place in the chapter where we talk about those distinctions.

PROFESSOR CAPRON: Rhetaugh?

DR. DUMAS: I had a question. We have deliberately limited this to consenting adults, right? Because I was wondering about the case of minors.

PROFESSOR CAPRON: Do we have any reason for deviating from the standards that apply to the United States as to minors? I think we have been discussing entirely adults, competent adults here.

DR. DUMAS: Yes.

PROFESSOR CAPRON: Okay. Is that --

DR. DUMAS: Is that the intent?

PROFESSOR CAPRON: That is the intent, yes, competent adults.

DR. DUMAS: Okay.

PROFESSOR CAPRON: Diane?

To tell you, I have Diane, Alta and David at the moment on the list.

PROFESSOR BACKLAR: And Trish.

PROFESSOR CAPRON: And Trish now.

DR. SCOTT-JONES: I want to say again that I think we are on shaky grounds when we use the phrase "culturally appropriate." I think that we are promoting the notion that we are in the United States one unified culture with one set of beliefs, and I think we are letting our own beliefs about particular issues come to the front as universal and not as an

instance of a cultural belief.

I just think we are in trouble because we are using the phrase "culturally appropriate" at times and at other times we are pushing components of our own culture. As much as I might myself believe in them.

And I would just like us to remind ourselves that within our own culture there are different views and there are some members of our own culture who are very much against what we are seeing as universal. I think we need to revamp Recommendations 4, 5, 6 and 7 to somehow get a consistent view of what we are meaning by culture here and how we are going to use it.

PROFESSOR CAPRON: Alta?

PROFESSOR CHARO: I want to return again to a distinction I make in my own mind between third parties that can preclude somebody from choosing to enroll versus third parties that can force somebody to enroll by giving substituted consent.

I think in the latter case, a third party who gives substituted consent, the husband for the wife, the community leader for the person in the community, that there has been no debate about the fact that this is one of the issues on which we want to insist that U.S. sponsored researchers must make sure that only the individual himself or herself has actually consented

when we are talking about competent adults.

And that we can ground that not on U.S. custom but we can actually take advantage of the discussion from the human rights people to ground that in a variety of documents that now reflect a growing consensus in the international community and a developing kind of norm of individualism that is beginning to universalize around the planet.

I think that we are comfortable with that, in part, because the idea of being enrolled against her will seems to be such an intense violation of one's personal autonomy.

I think that the first problem, however, whether a third party could preclude someone from choosing to enroll is genuinely more difficult since we do not assume that there is any actual concrete benefit to enrollment from a medical standpoint since it is research.

The notion of an entitlement to access to the trial is certainly weaker than the notion of an entitlement to refuse to participation.

Certainly there are other kinds of benefits people might want. Secondary health care, payment, a chance to interact with people from a different setting. There are a variety of reasons why people get

involved in these things. None of them seem to rise to the level of entitlement that we are used to talking about, although it is a good reason why somebody might want to enroll.

And so it is for that reason that I am personally comfortable with the idea that when you are talking about political authority that we recognize the political authority of municipal leaders to say yes or no to recruitment within their municipality, whether it is a village or a town or a city, because there is not necessarily a strong entitlement or need on the part of the individuals to enroll and we recognize that there is political authority. Sometimes we might call it more legitimate than others but it exists.

I distinguish, however, although I -- and I understand the problem of consistency, I do distinguish, Steve, the situation of allowing husbands to preclude their wives from enrolling reaffirms (sic) a norm that has been attacked by those same international documents that we are using to justify the idea that individuals have a chance to refuse.

The Convention on the Elimination of Discrimination Against Women, which has been signed by many countries, although not by the United States, as well as a variety of other international documents,

have argued consistently for equal treatment of men and women with regard to civil rights.

And, although I do not think enrollment in a trial rises to the level of a civil right, I think the analogy is strong enough that this is distinguishable, that gender-based authority is distinguishable from political authority in the human rights documents and that, therefore, we are also entitled to make a distinction and how strongly we insist on a more individualistic notion, both in choosing to enroll as well as refusing to enroll.

PROFESSOR CAPRON: Right now I will tell you where I am. I have David, Trish, Eric and Diane, and now Bernie. And I think we need come to a division of the house on this issue, which is the basic framework for 5, 6, 7 and 8, I guess.

Go ahead, David.

DR. COX: So I am going to make a comment directly pertinent to that point and support very much what Diane just said, and that if -- I do not want to guise -- okay -- putting forward our own personal beliefs in the context that this is what the whole world thinks everybody else has to do.

The -- I do not care how many international documents are put together. To go into a country that

does not sign off on those international documents and say the rest of the world feels this way so that makes it ethically right for the world, I have a real problem with, particularly when even the United States does not do that.

So if we simply state, okay, which Bill said earlier on, what we are sitting here trying to do is take and set a set of rules, okay, that we can use U.S. money to do research with.

And I do not -- I think we are getting that confused with a whole variety of other issues to make the world a better place.

I am in favor of making the world a better place but if we try and do that in this report, okay, at the expense of saying what the rules for the researchers are to do to use U.S. money, we are going to end up with a mishmash, I believe.

PROFESSOR CAPRON: Trish?

PROFESSOR BACKLAR: Well, I want to say that I think that what I have said is important and I think ways to deal with this is the way Dickens actually talked about it, and talk about this in ways -- researchers develop ways that are responsive to the host country so that I do not know if somebody has used the word "responsive" before in the discussion.

I think that is very important but the other issue is that I am very concerned about the -- enrolling women in research in which a spouse or a man -- in research in which the spouse has some power over deciding whether or not that person may be asked to be in a research protocol.

I just wanted to make sure that --

PROFESSOR CAPRON: If I understand you then, you would agree with the present thrust of Recommendation 5, Trish?

PROFESSOR BACKLAR: I think the way Recommendation 5 -- I think it is important because I think you want to look at nobody could recruit anybody else without getting permission from the individual. Yes.

PROFESSOR CAPRON: Let me -- I am trying -- as I see the issue, we have access to individuals and then their own consent to enroll. We have, as far as I know, universal agreement around this table that on the latter point no competent adult may be enrolled without his or her own informed consent.

Is that correct?

DR. CASSELL: Correct.

PROFESSOR BACKLAR: Correct, yes.

PROFESSOR CAPRON: Okay. So the question is

in terms of getting access to individuals, if the local custom is to go to the community leader and approach that person before any research is done in the community, is that acceptable?

DR. CASSELL: Yes.

PROFESSOR BACKLAR: Yes.

PROFESSOR CAPRON: Then the question -- and do we have yes around the table from people? That is what the -- that is what draft of 7 says now. Is that -- is there any dissent from that? Okay.

Now we come to the point on which we are faced with are we going to be consistent with that or are there reasons for a different view when it comes to access to an individual through his or her spouse?

MS. KRAMER: No, it is "her" spouse.

PROFESSOR CAPRON: Well, okay. It is basically --

(Laughter.)

PROFESSOR CAPRON: -- "her" spouse.

(Simultaneous discussion.)

PROFESSOR CAPRON: There I am being sex neutral and getting called for it.

MS. KRAMER: Right, exactly.

PROFESSOR CAPRON: All right. Of going to husbands to ask if their wives may be enrolled before

you go to the wife. What happens after he say, "Yes, you may talk to my wife" is a separate issue. We have agreed that you have to get consent and this document would say you also then say to the woman, "Do you want me to continue to involve your husband," and go through all the pluses and minuses of that.

But this is the threshold issue and Alta has said, yes, we should; David has said, no.

PROFESSOR CHARO: Yes, we should what?

PROFESSOR CAPRON: Yes, we should treat men and women the same. We should not -- I am sorry.

DR. COX: David did not say no.

PROFESSOR CAPRON: No.

DR. COX: Because I was not addressing this particular issue. I am happy to be in a situation where I would say no because that is what, I think, the standard in America is. But I do not want to go to these people and say you have got to do it because it is a universal ethical principle.

DR. CASSELL: It is not an ethical principle at all.

PROFESSOR CAPRON: I think this is the perfect illustration of the question that we got to earlier. Is this a substantive or procedural thing. Right? And that is to say is it waive-able? Is the requirement

that you go to individuals and ask them as individuals if they want to participate or you go through a filtering process first just a procedural thing, or is it something that is basic to informed consent?

Bette?

MS. KRAMER: Just as a practical matter, if the custom is that you cannot approach a woman without first approaching her husband, and we say we will not do it that way, isn't -- the whole thing is going to fall anyway.

PROFESSOR CAPRON: No. I think David told us before the upshot is sponsors and researchers would be told if you cannot get a modification of that local custom, you will not be able to do the research in that setting.

MS. KRAMER: Right, exactly.

PROFESSOR CAPRON: Yes. That is the bottom line. Okay. I have Eric, Diane, Bernie and Alta.

DR. CASSELL: Well, I want to address just exactly the question you have.

PROFESSOR CAPRON: Yes.

DR. CASSELL: Is it a substantive issue or a procedural issue? I know of no ethical principle that applies and research principle that applies and makes it a substantive matter.

Now the bottom line we all agree about. The person has the right to consent or refuse individually, no one else.

But beyond that, I want to hear the derivation of the research ethic. Where it came from. Not what other countries say, not what documents say. I want to hear where it comes from and how somebody who is not a research subject, who is a gleam in my eye doing malaria research -- I want to hear how that works.

I do not want to hear that it would be desirable. I want to hear its derivation from existing principles.

DR. MACKLIN: It is not a principle that derives from research ethics and, in fact, when you talk about it in the United States -- no where in the U.S. Federal Regulations does it say anything about who may be approached by whom under what circumstances, whether it is families, spouses or community leaders. It is silent.

We are now talking about something that does not derive from research ethics but not all of the principles that we use -- and this happens to do with equal respect for women and men, not every principle that we want to apply has to come from the research context. This is a broader context than the research

context.

So that is how I would answer it. It is being applied to the research context but it is equal respect for persons. Equal respect for persons. That is how I would name the principle.

DR. CASSELL: Well, excuse me but we are dealing with research subjects. We are not yet at a subject and I understand exactly what you are saying. I understand why you want it. I could not argue with you for a moment. We are now talking about directions for people who are trying to do research in another country.

I can tell you there are places in the United States -- and I took care of a large population of them -- that you will no more get that woman to consent in the research without her husband's permission than the man on the moon.

And you will go along with and that is the Hasidic population because it is a different relationship of family and community just as you will no more take care of that man without the wife's permission.

PROFESSOR CAPRON: Okay. And the question is -- I do not see, Eric, I do not see that as the issue that is posed here.

I see that as the statement which apparently comes from Harold Shapiro, "Researchers should use the same procedures for recruiting men and women" is based on the notion that respect for persons means treating persons the same regardless of their sex. And that means that no one else decides before I am offered the opportunity to make the choice myself. No one else decides whether that choice should be posed to me and the research regulations in the United States are apparently silent on that because it is simply an assumption that that will be the case.

Now it may well be that I say this is not my choice at all not because I am a woman but because in my culture people who are sick do not make their own treatment choices because they are sick they look to others to make it. And I say to the investigator, "You have to ask them. I do not decide." We allow that. That is my delegating the choice.

I gather that is not the issue that is at issue here, though. The issue is whether or not before you speak to a woman you have to go to her husband and say, "Do you give permission," is her consent dependent upon your consent from the beginning and that is the issue here.

Do we think that that derives from a basic

understanding of what respect for persons is and, therefore, is part of what we were describing before as the principles which are not waive-able or do we regard this as merely a custom which dependent upon local circumstances is as waive-able as the notion of not going into a village until the village elders have said, "You can come in."?

Yes?

I am just trying to pose the issue because I see us drifting.

Diane?

DR. CASSELL: But, you know, the thing is that --

DR. SCOTT-JONES: Okay. My turn.

PROFESSOR CAPRON: No, it is her turn.

DR. CASSELL: All right.

DR. SCOTT-JONES: If you read the first sentence of Recommendation 5 and then the first sentence of Recommendation 6, you can do under Recommendation 6 what we are claiming we would not do under Recommendation 5 because a husband is a family member.

So if you adhere to Recommendation 6 you could, in fact, involve the husband in the decision from the beginning.

PROFESSOR BACKLAR: Right.

DR. SCOTT-JONES: I think we have to read these and be consistent.

PROFESSOR CAPRON: Well, I -- whatever the language here now says, I understand that there is a difference and we should not belabor -- that is what I have been trying to avoid having us do.

There is a difference between saying that people often in the room with the doctor or afterwards or whatever involve their families in their decision making. That is different than saying do not approach a person until you have gotten permission from someone else.

I gather that a researcher is not free to come to my elementary -- my child's elementary school and approach them about being in research without having gotten my permission first. That is a rule.

Now the question is, is my wife in the same position as my child?

DR. SCOTT-JONES: But we are not addressing children in this --

PROFESSOR CAPRON: No, I know. I am giving you an --

(Simultaneous discussion.)

PROFESSOR CAPRON: Excuse me. Diane, I was

trying to give you a clear analogy. That is to say something -- where we do not say, yes, obviously we could then say when my child goes through the research process I have to be there. But we say more than that. We say do not ask my child to be in research until you have asked me.

DR. DUMAS: But that is just the problem here and it is treating women as if they are the children of men.

PROFESSOR CAPRON: That is right and --

DR. DUMAS: And I am opposed to that.

PROFESSOR CAPRON: Right. I understand and that has been a view expressed by several people here and now I am trying to get a division of the house.

Why don't we just see as of now how many people -- I think we have resolved all the other later steps about you have to have consent but the question is as to husbands for wives, just to use the shorthand, how many agree that that is something which is a requirement that you -- that is not waive-able that you approach the woman herself, that is not waive-able based upon the local custom that as to health care or other matters --

DR. CASSELL: It cannot be waived, period.

PROFESSOR CAPRON: It cannot be waived. You

cannot -- it cannot be waived. How many agree that that is not a waive-able thing?

(A show of hands.)

PROFESSOR CAPRON: Well, then what are we disagreeing on?

DR. DUMAS: Well, it depends on whether or not you are getting consent or whether you are involving people -- other people in the process.

PROFESSOR CAPRON: Yes. I do not think there is any disagreement that it is perfectly appropriate as Recommendation 6 says for an individual to involve his or her family.

The question is -- and we are apparently -- despite the last 20 minutes of heated discussion -- we are all in agreement --

DR. CASSELL: Except --

PROFESSOR CHARO: No. I do not think that people understood what you asked.

PROFESSOR CAPRON: Okay. Let me just ask it again. Recommendation 5 is intended to say something different than Recommendation 7; 7 says it is okay to follow local custom and get the community leaders' permission before approaching people for research.

DR. DUMAS: Yes.

PROFESSOR CAPRON: We all said that was okay.

DR. DUMAS: Okay.

PROFESSOR CAPRON: Recommendation 5 says it is not okay to approach husbands before getting their wives -- asking their wives if they are interested in participating in research.

DR. CASSELL: Even if that is local custom.

PROFESSOR CAPRON: Even if that is local custom. Local custom does not trump the requirement that persons be treated as persons here, equal whether they are married, not married, male or female, or whatever.

DR. DUMAS: Right.

PROFESSOR CAPRON: Is that -- now do people disagree with that as a recommendation? Do not worry about the way it is worded. We will get the wording right if we have agreement on the substance. Do people agree with that as a conclusion? We have to come to the conclusion of this discussion.

(A show of hands.)

PROFESSOR CAPRON: Bill, you do not agree with that as a conclusion?

MR. OLDAKER: For the reasons stated before, I have difficulty in seeing why a community leader should have a greater say than a spouse. Possibly equal.

PROFESSOR CAPRON: Well, that is -- but let's

just say with the spouse. In other words --

MR. OLDAKER: I understand but I am saying if we go to 7 then I --

PROFESSOR CAPRON: What I am trying to say to you is you could say, "I, therefore, think that women should not have their husband's consent first and I, also, think that we should change number 7."

MR. OLDAKER: I could live with 5 the way it is.

PROFESSOR CAPRON: You can live with 5 the way it is.

Bernie, with 5 the way -- I mean --

DR. LO: Before I cast a vote, I think there are a couple of issues that we have not got to despite the heated passions here.

One, respect for persons is not the only ethical principle at stake and we are losing sight of beneficence.

I mean, if we say, "Fine, you either play by the U.S. rules or we just do not do the research," the consequence will be some research will not get done.

A dilemma facing many women in Sub-Sahara in Africa is they are trapped in a dilemma. On the one hand they would like to be equal and want to move towards that. On the other hand, they are

disproportionately affected by the very research that we are trying to deal with in this report.

And to walk away and say, "We will be pure and say you cannot do the research because the custom there is that you have to approach the husbands and, therefore, we will pack up and send our research some place else," leaves them with a very tough --

DR. DUMAS: Well --

DR. LO: Let me just finish. Okay? I have sort of been patient in trying to get in on this.

PROFESSOR CAPRON: Go ahead.

DR. LO: So I think that if we need to enlarge the discussion to say if we are saying we are just not going to do the research, I think we have to address the question of do we feel comfortable walking away from a lot of research.

This comes up at several points in our report where if we are purists we will say the pure approach is we will not sponsor that research and we will not let our investigators do it. That means, frankly, a lot of research, which is uniquely addressing the health care problems of that population in ways that are not otherwise going to get addressed is not going to get done.

The second point is that anybody who does

research knows that there always is a filtering process. Very few research goes directly to the people as individuals. You get people through community-based organizations who will deny you access to not just people in their organization but to people in their geographical area.

The director of the clinic, the people that run the clinic, if you do not get them to agree, you are not going to approach their patients.

So then to think that people are autonomous and that you can reach them directly independent of the social structures they live in and seek medical care in, I think is a fundamental misunderstanding of how research works.

I think the problem we are trying to do here is that we have an ideal that is very far away with reality and in the long-term, yes, we would love to be able to approach people as individuals regardless of their sex and gender.

But we live in a very imperfect world and we have to make decisions as to whether we stand up for a principle or we do things that are compromises that allow other things that are good for other reasons to take place.

DR. DUMAS: Rhetaugh wants to speak.

PROFESSOR CAPRON: Okay. Rhetaugh, you are on the list after Alta and Diane.

DR. DUMAS: Okay.

PROFESSOR CHARO: Bernie, I completely sympathize with what you were saying but I think first, I think, we are beginning to view this problem as worse than it is because I know I have not suggested that we rewrite this recommendation to say that husbands could never be approached.

What I wanted it to say clearly was that husbands could never refuse to allow their wives to be approached. That is you might find that local custom is husbands are involved in these things and so you are going to approach them.

But what I did not want was for them to have a veto on the ability of a woman to subsequently be approached independently and asked do you want to be recruited.

Second, with regard to research that would not take place, a very important point, but what is the research that is most needed? What is the biggest health threat for women around the world? There was a wonderfully dramatic piece in the last week's news about the rate of violence against women and how as a public health matter this dwarfs many of the medical

conditions we have in mind when we think about what women need in terms of an understanding of the health problems and possible solutions.

And what is the one area that would absolutely be impossible to research if we allowed ourselves to buy into local customs where husbands have to give permission for their wives to be approached?

It would be things like violence against women.

So that there is going to be research lost whether we go with husbands allowed to refuse their wives' permission or husbands not allowed to refuse their wives' permission. It will just be different kinds of research. There is going to be research lost regardless of which way we go.

Finally, I do think that there really is a difference between recognizing the right of a husband to refuse access to a wife and the right of a political leader to refuse access to a community because what it does is it makes us complicit in a kind of authoritarian regime that is not based on any kind of political legitimacy but is based on the rankest kind of discrimination that we have been fighting for decades and centuries.

I do not think there is a person here that

would have taken this discussion for 20 minutes if what we were talking about was in old Apartheid South Africa, whether householders could refuse access to their domestic -- their Black domestic workers before we could do research on them.

I do not think that we would take this discussion seriously if we were talking about householders giving access to their slave labor in other parts of the world, which still has slavery.

And yet we continue to mark out gender hierarchies as somehow cultural rather than political discrimination and it has been a fight within the human rights community for years to change the rhetoric and the thinking about the degree to which this is a central form of discrimination as opposed to one of those wonderful cultural variations that we do not buy into but we have to respect.

I do not respect it.

DR. DUMAS: Hear hear.

(Laughter.)

DR. CASSELL: Well, Alex --

PROFESSOR CAPRON: I have Diane, Rhetaugh, Steve, Eric, and you know I want to point out, ladies and gentlemen, that we are now at about a quarter after 12:00. We have to be back here for 1:00 o'clock

comment period. We are at a place where we probably do not have very fast food available to us so I want to encourage us to try to focus in on our conclusions.

Diane?

DR. SCOTT-JONES: I would like to return to the points that Bernie made and despite Alta's very inspiring statement, in reality we cannot override existing social structures. They are here in the U.S. And to give you an example from my own research, we tried to study adolescent mothers in southern parts of Illinois where they are extremely poverty stricken but husbands of these very young women would come to the door and turn us away no matter how much we believed in that young woman's right to speak for herself. We could not overturn the existing social structure and that is a different point from where we believe in the rights of women or not.

We simply cannot go in and change a social structure by proclaiming that we believe in the rights of women.

PROFESSOR CAPRON: Rhetaugh?

DR. DUMAS: I think we -- there are two comments I wanted to make and I will be brief.

I think we tend to confuse access to community with consent of a person to participate in a project.

And I think we are pretty much agreed that access to the community is something that may require contact with community leaders but I feel very strongly.

And I like the statement that says the same procedures for recruiting men and women and obtaining their informed consent should be used.

And I do not think that -- I do not think that we are talking about forcing countries to accept the American way. I think that they have the right to say no.

And the other thing is that I also think that the other countries and the people, the leaders and the authorities in those countries have some responsibilities to seek solutions to those problems.

And we are not totally -- we do not -- the researchers who go from this country should not feel that they bear total responsibility. If, yes, we believe that certain principles are important here then we believe that they are important in other places, and that does not mean that you cannot be flexible.

But the things that you feel that are really important -- if you -- you are not asking them necessarily but you must live by them.

PROFESSOR CAPRON: Thank you.

Steve?

MR. HOLTZMAN: Well, first, I want to express some appreciation to particularly Alta, Diane and Bernie for that little exchange because it really crystallized it for me.

I agree with you, Alta, that there is a difference between -- let me call it the fact that there could be de jure authority of a political regimen and de facto it is corrupt versus there is no de jure authority of a man over a woman. All right. That is appropriate.

And so what I really come to is the struggle of whether picking this place as the place for that -- the battle is the right in virtue of what could be lost in the research.

And when you raised the question of what if we were talking about South Africa ten years ago, twenty years ago, and would you go to the householder, really -- I mean, you assume the answer was, of course, we would not. We would go right out to the workers. All right. But would we?

It really makes you stop to think about it. If the result of that is they would be beaten -- you just need to think through really whether the context of research is the place, to use Diane's word, that we can try to redress and should be trying to redress

these kinds of systemic problems.

It is not obvious to me that it is, which is not to say that that is a good.

PROFESSOR CHARO: May I answer --

PROFESSOR CAPRON: Eric, and then, Alta, a final comment.

DR. CASSELL: Well, it is a debate that is un-resolvable because we are talking not only about women's rights. We are talking about family structure. There are many who believe -- other countries that might believe that the United States family structure could use some help.

And these are not easily resolvable issues yet we have to come up with something that we can have in the report.

Now I see no reason why the issue cannot be argued in the report but for myself the bottom line thing we all agree on is that nobody can consent except the person themselves.

And we want to stay with what we can all agree on and then put in the body copy what the argument is and move on because otherwise we will never move on.

PROFESSOR CAPRON: Alta, final comment?

DR. CASSELL: It is not a matter of -- you know, it is not a matter where you are going to just

vote and that is going to resolve it. You know, it is not that kind of an issue.

PROFESSOR CHARO: I am not sure if it is or not, Eric, because we have not had a chance to try putting it to a vote in a way that is clear enough that everybody really understood what they were voting on.

But if that ever happened or if the discussion continues at the next meeting, I would only want to point out that I know that I am not arguing for something as extensive as what I think Diane and Steve have in mind when they raise objections to it.

I am not suggesting that we write a recommendation that says you may not approach people through the filter that is usually used in that city, culture, whatever.

All I am suggesting is that we do not tell researchers that they must permit those filters to be the final word on whether or not the individuals can subsequently be approached but instead researchers are permitted if the filters are uncooperative to nonetheless see if it is possible.

And it may not be, Diane.

But if it is possible to insinuate themselves in a way that allows them to approach the individuals and that the individual women themselves can then, as

it is said in the recommendation, be told, "Look, you want to do this, we would love to have you, of course if you do not involve your husband, we understand that might be risky so you should think about that for yourself, and it is up to you if you want to enroll and it is up to you if you want to involve your husband before you enroll."

What I am saying is that I do not think researchers in the United States that go abroad should be precluded from approaching individuals and letting individual women decide for themselves simply because there is a local custom that says that the filter, the husband, has the right to refuse.

I think it is insulting and I think it is inconsistent with our own civil rights laws. I think it is inconsistent with international documents and I do not think it is necessary in order to protect women from being beaten or assaulted, and I do not think that it is going to preclude all forms of research.

DR. CASSELL: Well, why didn't you say it straight then? Where possible, individuals should be individually contacted and let it go at that.

PROFESSOR CHARO: All I wanted to say was that husbands should not be able to refuse to allow their wives to be recruited. That is a little different than

what you just said, Eric.

DR. CASSELL: Well, how about fathers? How about fathers?

PROFESSOR CHARO: I refuse to equate women with children and so we will not -- and will not argue that we have to be consistent on parents and child and with husbands and wives.

DR. CASSELL: No, but adult children by the father.

PROFESSOR CAPRON: As I understand the argument as it has now played out -- and, Alta, I want to say I find the position that you are pushing just very hard to operationalize. If what you are saying is you are designing research and you come up with a statement, you will recruit women and men in the following fashion, and the local collaborator says, "Oh, no, you have to go through the husband before you go to the wife."

There are two responses -- there are three responses to that. One is fine, that is what you do, we will do it, and if he says -- he has a say, he has the say.

The second is the position I gather you to be taking, which is, fine, but if he says no, we do not have to listen to the no.

And the third is to say no, we cannot -- we cannot get approval under our understanding of what informed consent involves to people who are -- in which the design is that you go through someone else before you go to them when that person is their spouse.

Now, Diane, I do not find the objection that sometimes when you are trying to seek consent from someone, someone else bars the door, that to me is not what is at issue. This is a question of whether it is designed in that way.

Are the three alternatives clear enough that we could have a straw poll on them as to -- and people -- the first alternative is that the researcher would say, "I will adopt a local custom," just as we say that researcher can adopt a local custom about seeking community leaders' permission first?

I will adopt a local custom and get the husband's consent to involving the wife before I approach the wife and before she can participate. That is one.

The second is I will approach the husband but what he says is irrelevant to my making attempts to get the wife.

The third is I will not be able to do research under those conditions. Either I have to persuade the

local people that we are going to use a different method here or I will not do the research in that setting.

Is that -- are those three alternatives clear? I do not know how I can make them any clearer.

DR. SCOTT-JONES: Alex, I think there is a different issue --

DR. MACKLIN: To make it more credible, let me just give the example of where --

PROFESSOR CAPRON: Yes.

DR. MACKLIN: -- the opportunity would arise to approach the woman directly and that is in a reproductive health clinic.

A very large amount of this research would take place in a reproductive health clinic where a woman is coming for whatever services in a medical clinic and research is going to be conducted there. You are not going to have her husband there at the door and you are not going to have to approach him through any other mechanism. She comes to the clinic.

PROFESSOR CAPRON: But your local collaborator says that before we would ask --

DR. MACKLIN: All right. You can leave that. I am just saying the practical barrier -- someone said before how would you ever get to her. You get to her

right where she comes for --

PROFESSOR CAPRON: Right.

DR. MACKLIN: -- medical services.

PROFESSOR CAPRON: Right. But the issue only arises, Ruth, because someone says you really cannot ask her until you ask her husband first and the question is (a) the first alternative is you listen to what the local custom is and you go to the husband before you ask the wife; (b) you go to the local -- you follow custom and ask the husband but if he says no, you do not allow that to be a barrier to enrolling her; (c) you say we cannot follow the local custom, we have to treat the woman the same way we would if we were asking a man to be involved.

Can we just see a straw poll? How many favor our taking (a)? The view that you follow local custom and the husband becomes the filter to whether or not the wife is involved in research.

No hands for support.

DR. SCOTT-JONES: Alex?

PROFESSOR CAPRON: Not that this does not happen but you do not design it in.

Diane?

Yes, you cannot vote.

DR. SCOTT-JONES: I just wanted to say that I

do not see that as the issue that we were discussing.

In my view we were discussing whether we need a special statement about women and men in addition to Recommendations 6 and 7. Recommendations 6 and 7 already cover these issues.

The question in my view is whether we need in addition a special statement asserting the equality of women and men in Recommendation 5. That is a different question from what you are posing.

PROFESSOR CAPRON: Diane, I really do believe that the way I have posed it has been the bedrock of the debate here and I agree with you. It might not emerge from the way that Recommendation 5 is worded now but let's just try this because we have had a long discussion of it.

Does anyone favor the first, which is to say if local custom says wives may not be involved without the prior permission of their husbands that research may go ahead under those circumstances with U.S. sponsorship?

MR. OLDAKER: I would if we were to make Recommendation 7.

PROFESSOR CAPRON: Okay. To be consistent.

MR. OLDAKER: Right.

PROFESSOR CAPRON: You are saying to be

consistent with 7.

MR. OLDAKER: But if we do not then I can --

PROFESSOR CAPRON: Okay. So it is a conditional yes.

Steve, you are saying yes?

MR. HOLTZMAN: Yes.

DR. CASSELL: Yes, yes.

PROFESSOR CAPRON: Okay. Eric. All right.

DR. CASSELL: The same thing in 6. I think it is the same as 6.

PROFESSOR CAPRON: Okay. That is -- How many favor the second --

DR. DUMAS: I am confused about what we are voting on now. Is that the (a) option?

PROFESSOR CAPRON: That was the (a) option.

The (b) option is Alta's suggestion. That is to say if custom requires you to go to the husband, you go to the husband but the husband's veto does not count. You could still go to the wife and inform her, her husband has vetoed, but you are asking her anyway and if she wants to participate, it is still her choice.

How many favor that? Alta. Alta.

The third is to say that a protocol should not be accepted if it is based upon the husband as the

decision maker of whether or not the wife should be involved. How many favor that as the alternative?

PROFESSOR CHARO: I will go with that instead.

PROFESSOR CAPRON: Well, you can go with that instead.

David, Alta, Arturo.

DR. DUMAS: I think I would go with that one.

PROFESSOR CAPRON: You have been speaking in favor of that one, Rhetaugh. That is --

DR. DUMAS: Yes.

PROFESSOR CAPRON: Okay. That is four. That enjoys the larger support. We have not heard from Bette, Jim and Bernie on this.

Can you give us any -- this is a straw poll.

DR. CHILDRESS: Well, in part, because I am not sure. It seems to me that Ruth's example is actually a somewhat different one.

PROFESSOR BACKLAR: I actually -- I know this is not what you want but I think that Diane is right. I think that probably the best way to do this would be to look at 6 and 7, and maybe address this within 6 and 7 but I know you do not want that.

PROFESSOR CAPRON: My understanding is that there are many cultures in which family members are very actively involved and, indeed, it would be unusual

not to have a discussion with all the relevant family members in the room.

PROFESSOR BACKLAR: Right.

PROFESSOR CAPRON: And I do not understand that that is implicated in number 5 because that would be true whether it was a male patient or a female patient. And it does not say that those family members have to be consulted first and asked may you talk to the patient. The patient who would be a subject, let's say. I mean, the person who would be recruited whether they are a patient -- I suppose if you have a normal volunteer, a normal volunteer. You would not presume to have a discussion but -- without those people present.

PROFESSOR BACKLAR: Well, then I would --

PROFESSOR CAPRON: And that they can participate --

PROFESSOR BACKLAR: Alex?

PROFESSOR CAPRON: Yes.

PROFESSOR BACKLAR: I would vote with Alta's suggestion that if it is -- if I am correct in understanding this. That is that if it is the custom and the convention that the spouse is asked permission to approach somebody, one would follow that convention. But if it is refused, if the permission is refused,

then you go directly to the prospective participant. Is that -- am I understanding that correctly?

PROFESSOR CAPRON: That is what Alta -- that is alternative (b) and we may have to do this --

DR. DUMAS: That is what I voted for.

PROFESSOR CAPRON: You were voting for (c), which is --

DR. DUMAS: Yes.

PROFESSOR CAPRON: Yes. -- do not use the husband as a filter.

One last comment for Bette.

MS. KRAMER: No, it was a question. Would you just restate (c) once more? That if --

PROFESSOR CAPRON: (c) is if you were told that local custom is you go to the husband, you say we cannot make that part of our protocol design. We either have to persuade you local people that we will deviate from that or we cannot do the research here. We will not make a woman's participation contingent on her husband first being asked if she can participate.

You are for that?

MS. KRAMER: I will go with that.

PROFESSOR CAPRON: Okay. That now has five adherent. There are a number of people who are not here. It would seem to me that that -- if we are to

have a majority view -- obviously these recommendations have to be worded in such a way that the distinction between what is being said in 6 and what we have just said is clear. That one is a question of involvement in decision making, the other is as a prior barrier or a filter to asking the person to be involved. And we recognize that there is a difference between what is practically attainable and what is designed as part of the research.

We have reached the point where we have to break. I would ask people to make every effort to be back here.

Do we know what the public comment situation is? Whoever? Who is in charge of the list?

DR. MESLIN: Fred, do you want to check?

PROFESSOR CAPRON: We have no one signed up as of now. Please try to make it -- we will use a few of the minutes if we can get them before 1:30 so that we can try to finish this. We are obviously going to use the time tomorrow afternoon for Chapter 5 since we have lost the discussion of Chapter 5 this morning.

PROFESSOR CHARO: What time did you say come back? I did not hear you.

PROFESSOR CAPRON: Try to come back by 1:10 then. It is about 35 minutes for lunch.

(Whereupon, at 12:35 p.m., a luncheon break was taken.)

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