**38th MEETING**

**NATIONAL BIOETHICS ADVISORY COMMISSION**

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# I N D E X

**I N D E X (Continued)**

**P R O C E E D I N G S**

**OPENING REMARKS**

**HAROLD T. SHAPIRO, Ph.D.**

**DR. SHAPIRO: I would like to call this morning's meeting to order, please.**

**First of all, let me welcome the commissioners and thank them for being here today. We have a very busy agenda both today and tomorrow.**

**We will have a number of very distinguished guests who will be speaking to us today, of course, on -- we will have some guests dealing with perspectives from other countries dealing basically more broadly speaking with our international -- what we call our International Research Project.**

**I will welcome -- they will be welcomed separately in a moment.**

**The rest of the day, though, once this morning's panel and discussion with this morning's panel is done, will really be spent in discussion between ourselves and Ruth and Alice on aspects of chapter -- what we are calling chapter -- called chapters 3 and 4 if I remember the numbers correctly, which were distributed to you early or late last week and we want to really get into important discussion there and try to resolve issues and focus on the**

issues that really matter in those chapters.

So that will be mostly -- take up most of today once this morning's session is done.

Tomorrow we will return, of course, to the oversight of human subjects here in the U.S. We will also have some visitors tomorrow. Indeed, we have quite a number of visitors tomorrow as we try to put together the information we need to carry this project forward.

Indeed, tomorrow, I think, we have four or five panels who we will be dealing with during the day. I think we are scheduled to go to roughly 3:00 or 3:30 tomorrow afternoon.

So it will be a busy time and we have a lot of work to do ahead of us in the next day or so.

Before we turn to Ruth to just give us a brief overview of work to date that she -- there is a memo in your materials and so -- but Ruth may or may not want to add anything to that.

Let me turn first of all to Eric who has a few words.

I think, incidently, the scheme today with today's microphone is you just press this, the light goes on, and then you speak.

DR. MESLIN: Let me just again welcome

everyone. Especially our guests from overseas.

We have handed out a number of things in the briefing book and many of those additional items are in your table folders for commissioners. They are also available for the public.

We are hoping that the method of using briefing memos by many of the staff is helpful to commissioners. If you have questions about particularly the legislative update from Ellen Gadbois or the report that I have presented to you, the Executive Director's Report, please feel free to ask us at any time.

We are not trying to overwhelm the commissioners with this material but we think that with the addition of the legislative update you will be more caught up on where activities are in Congress.

In my report handed out this morning a couple of items of interest, only one of which I will mention briefly, that relates to follow-up from our reports.

There is a slight typo in the report but I wanted commissioners to be aware that we are able to write to agencies requesting responses to our reports and we can do that for previous reports as well as those that are being presented, both our former charter and our current charter allow us to do this.

So with that, Harold, the only thing I will add is that we have only one person signed up for public comment today. I do not know whether they are here in the room at the moment but as a reminder to all members of the public as a federal advisory committee you are welcome to make comments before the commission.

If you wish to do so, please let our staff know at the outside registration desk. The public comment period is scheduled for 1:00 o'clock after lunch today.

That is all.

DR. SHAPIRO: Thank you very much.

Any questions for Eric?

DR. DUMAS: I would like to thank Eric for the reports. I find them very helpful.

DR. SHAPIRO: Thank you.

Steve? But you do not want to speak, right?

Okay. Thank you very much.

All right. Let me now turn to Ruth.

Ruth?

## ETHICAL ISSUES IN INTERNATIONAL RESEARCH

### OVERVIEW OF WORK TO DATE

### RUTH MACKLIN, Ph.D.

**ALICE PAGE, J.D., M.P.H.**

**DR. MACKLIN: Thank you very much. I want to add my welcome to the guests here this morning.**

**I never know whether to repeat what is in this memo as a reminder or just to assume that everyone has memorized it but I will mention just a couple of highlights.**

**DR. SHAPIRO: Well, as long as you do not distance yourself from it.**

**(Laughter.)**

**DR. MACKLIN: No. I take full responsibility.**

**Alice and I have been transforming the bits and pieces that we have presented over the last several months into drafts or partial drafts of chapters and, in fact, as you will and as the memo notes, and as Harold has already mentioned, what we are referring to as chapter 4, that is obligations to subjects, communities and countries, is now a portion of what will be chapter 4 and this follows from some of the -- several of the propositions that we introduced and discussed briefly last time.**

**We are going to discuss that first today -- I mean, this afternoon in our discussion section, and the reason is that this is the first time you are**

actually seeing the draft materials.

The other chapter, chapter 3, which we will turn to second, is one that you have already seen.

I mean, that -- much of the text was there before but it is very much expanded now with the addition of the material that Elisa Eiseman prepared and that material followed from -- I forget which meeting. It was the October meeting, I believe, when we had the presentations on the study design.

So that is the progress of what we hope will be drafts of chapters or are now partial drafts of chapters.

Also, as the memo notes, we have not yet returned to the informed consent discussion, which was the very first substantive material that we discussed. In part because we were waiting for Patty Marshall's final report and, in part, because we are awaiting the results and analysis from the empirical studies that Nancy Kass and Adnan Hyder and Noreen Tesh and Liza Dawson were preparing. So we will return to that and provide a more substantive draft in due time.

One other thing to point out, you will notice in the memo there is mention on the second page of a chart. Now this has come to be known around the office as "Stu's chart." Stu Kim has been primarily

responsible and working diligently and responding every time Alice or I or anyone else says, "Well, we have to add something else to the chart."

It is now -- the last I looked -- I think 44 pages. Is it something like that? It is a very comprehensive chart. Probably the first of its kind in the world.

And I have just recently communicated with a European colleague who has a grant from the European Union to do very much what this commission is doing. His name -- some of you may know him -- his name is Ryder Lee.

And I shared with him the chart in progress and he made some comments so Stu's chart may have to be copyrighted and world renowned.

So we did not distribute it partly because of its large size but if anyone would like a copy it can be made available. Okay. We did not think everyone would want to see it immediately but anyone who wants it may have the full 44 pages if you promise to read it.

So I think that is all I will say by way of introduction.

DR. SHAPIRO: Ruth, when are we expecting -- I am sorry. When are you expecting the results of the

studies that you are waiting for on the informed consent issue?

DR. MACKLIN: Nancy Kass has communicated with us begging for a little more time. She actually was very heartened by the response rate to the empirical study and said it was extremely good news. I mean, I, not being an empirical scientist, I do not know what the usual response rates are but people who do social science surveys are often disappointed at the response rate.

Interestingly and just coincidentally, I happened to be at a meeting and spoke to someone whose husband was sent the survey and she said he probably would have tossed it in the wastebasket but for the coverage page which said, "National Bioethics Advisory Commission."

So the imprimatur of the commission apparently has led some people who otherwise would have ignored the study to respond.

So Nancy Kass will be coming to the office, I guess, to share with the staff current -- the current status and some preliminary findings and I think we will be able to use those in beginning a draft of that chapter but realistically the completed study -- and this is Nancy Kass' study -- is slated for June, I

think, she said.

DR. SHAPIRO: Thank you. Jim?

DR. CHILDRESS: Ruth, in your memo you mentioned some of the difficulties you have had in trying to get the pharmaceutical industry involved and yet you also say we hope to hear testimony from private industry later.

Could you say a bit about the reasons that are given for declining to participate?

DR. MACKLIN: I cannot but I am going to ask Eric and Harold to say what they know and perhaps Alice has something to add.

DR. SHAPIRO: Eric?

DR. MESLIN: We were hoping that Nancy Kass' survey, which is principally involving academic researchers, could be replicated identically with industry itself and with discussions that we have had with representatives from industry we were made aware of concerns that they had about that actual replication.

So while the involvement in the survey itself, the identical survey, is probably not going to occur, we have communicated with them our hope that there are a number of ways that they can be engaged and to participate, both by giving testimony, by

commenting on drafts, by submitting white papers and doing as many things as possible to reflect their views and concerns.

Our goal was obviously to get as much information as we could and we still hope to get that information.

DR. SHAPIRO: Alex?

PROF. CAPRON: Two points. Where do you stand with Nancy Kass and Joan Atkinson on the subjects study? That is the first question.

DR. MESLIN: As with all studies that we commission where human subjects are involved we have to both ensure that there is domestic approval and because we are a government agency to obtain the necessary clearances from OMB we are inquiring about the OMB issue right now.

I do not know whether Rachel has any more information but we have begun the process of inquiring as to whether that will occur, meaning OMB approval is required for this type of study. If it is, then we will have to make a decision as to whether the time period that it will take to get the approval is permissible for the commission. And if it is not required then obviously the study can begin ASAP.

DR. SHAPIRO: Rachel, do you have any further

information?

DR. LEVINSON: As Eric and I discussed when we first -- he sent in a note about this. It looked like a much more extensive survey than the original one and that it would probably require OMB approval as the other one did but OMB has not made a formal decision on that.

DR. SHAPIRO: Alex, your second question?

PROF. CAPRON: Yes. The second point is I think the answer you just gave to Jim Childress alleviates some of the concern I had but in Ruth's memo the notion that private industry was in some sense going to be unresponsive when so much of what we are talking about here, and many of the most problematic issues that have arisen have involved privately sponsored research struck me as totally unacceptable for our report.

And I was thinking of times -- I mean, when we are in Madison we are not all that far from Upjohn in Kalamazoo, and there are other times -- I mean, I cannot imagine Pfizer and Schering and others not being responsive. I mean, it would just seem to me unacceptable for our report and I hope that whatever is going to happen by way of negotiation with them that we will have at least as much data as we have

gotten from looking at work that is sponsored by CDC or the World Bank or whatever.

I just cannot imagine that we would have that huge lacuna and basically say that industry had been unwilling to be responsive.

DR. MESLIN: I agree with your point and I think both the staff and others agree as well. The issue is not whether they will be involved but how and in what way. And the concern at least with respect to the survey instrument was that it was not the most effective way of them to communicate those views.

So we are exploring every possibility and making available as many opportunities as we can, and we hope to see if not a roundtable at the next meeting in April then one in May that will allow for the private sector to communicate to the commission not only their views about the international report but about the oversight report as well.

So there is not -- it is not focused on one project but rather the goal of private funding and issues related to industry sponsorship.

DR. SHAPIRO: Ruth?

DR. MACKLIN: Well, one more point.

Alex, you used the word "data."

We wanted or hoped for responses to a survey,

which would provide data.

PROF. CAPRON: Right.

DR. MACKLIN: Any other approach, including the round table, will give us information but not data in the sense that would be analogous to what we are getting from the others. So the only way we could get data would be either by a response to our overture or by a willingness on the part of the organization to conduct a similar survey.

PROF. CAPRON: Well, you made a comment earlier, which I found to be true of the President's Commission as well, that is to say that Nancy was reporting -- I guess actually it was our chairman who said that Nancy was reporting that she got a better response -- no, you. Excuse me. You were the one who said it, yes. In any case she got a better response rate because it was a presidentially appointed commission and I think that is a general experience.

I would hope that if it requires a vote of this commission to indicate that we are not in a situation where a researcher is asking for some information but that this commission wants that information and it would strike me as exceptionable for the drug companies to basically say that somehow their researchers are unable to provide comparable

information. And, indeed, in effect to give responses to the same kind of survey.

I am amazed that that should be the case. We are not talking here about the kinds of points that ought to raise the sensitivities. I mean, we are not asking for proprietary data.

And if, Mr. Chairman, we -- it requires this commission to go on record that you personally request that information -- I gather there have been some conversations, perhaps informal conversations with a couple of the drug company executives, I would like the commission to give you and our contractor and our staff as much backing as possible to get data from that source.

And I agree with Ruth, data, not simply some anecdotal statements at a roundtable as important as it will be to hear from those executives.

DR. SHAPIRO: Well, we are currently in discussions on exactly these kinds of issues and I will just take it the commissioners strongly support our attempts to achieve that, and we will report back at the next meeting if not before on that issue because I think it is important. I quite agree with you.

Tom?

**DR. MURRAY: I have been waiting a while to ask this so some of it has gone under the bridge but, Eric, in your description of your interactions with pharmaceutical companies, you gave us nothing of the substance of their objections. You just told us that they were not going to complete the survey.**

**I wonder if we can hear anything about the nature of the reasons cited for that?**

**And I have a second question that is unrelated to this.**

**DR. MESLIN: I can make available to commissioners the correspondence between the Pharmaceutical Manufacturers Association and the staff relating to this issue with whom we have had these discussions but without going into extensive detail of the pieces of paper which will provide that information, and we will do that, I will summarize it as follows:**

**There were concerns about the applicability of some of the questions to privately sponsored researchers as contrasted with academic researchers. And we will also make available the survey instrument to commissioners. You have seen this before but we will share it again so you can make that assessment.**

**Secondly, there were concerns about the time**

that it might take to do this.

Third, there were concerns about the type of interpretation that might be made of the survey responses.

I think that summarizes the three areas of concern as fairly as I can.

DR. SHAPIRO: It does not sound too reassuring, does it, Tom?

DR. MURRAY: No.

Can I follow-up?

DR. SHAPIRO: Yes.

DR. MURRAY: This is not about the international survey. This is about the Executive Director's memo, Eric's memo to us that was in the folder so I just saw it this morning.

A very helpful memo. Thank you.

It was in this folder and it reminds me that we have a -- we have the power at NBAC to direct our recommendations to particular agencies of government and then they must respond within 180 days.

Have we done this as a routine? I guess I -- given the human biological materials report, have we tasked any specific agency or agencies of the government to respond to that and, if not, should we -- I think we should do that and then we have to decide

which one and, in fact, we should always make it a practice it seems to me any time we issue a report to specifically identify the agencies from which we would like to have a response.

DR. MESLIN: The answer to the first part of your question is, no, we have not specifically tasked agencies to respond to recommendations in the report on research involving persons with mental disorders that may affect decision making capacity, the report on human biological materials, or the report on stem cell research.

Those -- the first two reports that I mentioned, the "Capacity Report and the HBM Report," have been sent, as has the stem cell report, to the NSTC as is required.

As I mentioned in my memo the first of those reports is being reviewed and, if I hear what you are saying, should we be doing this, then if it is the will and wish of the commission that a letter be sent then I am more than happy to prepare a letter or Dr. Shapiro would.

I can tell you that I have had conversations with some agency representatives as well as individuals from OPRR and others and I do not think anyone would be opposed to receiving such a letter

because, in fact, this review is either underway or is intended to be underway.

It is, however, a particular instrument. The requiring of a response in a particular time that I would just remind commissioners, you know, should be used in an appropriate way because we have many consumers of the recommendations. It is not just agencies. There are some subdepartments. There are private sector companies -- private groups as well. But there is nothing to prevent us from sending a letter even a letter about a report that predated the October 20th revision of the charter.

DR. SHAPIRO: Alta is next. And then we will have one or two more questions, then I want to turn to our panel.

PROF. CHARO: This is brief. Thanks very much.

First, let me say on the record what I said privately before, which is that I thought the materials on this topic in the book were extraordinarily well-developed and now that I have seen the chart that Stuart is preparing it looks like something that should be sent up by NASA, you know, for contact with extraterrestrial species all the things we do here.

Specifically on it, however, I was gratified to see something here about compliance and enforcement provisions and the sanctions that can be applied. I think this is a crucial area but it has been my experience as a law teacher that many things exist on the books that are rarely used in practice.

How realistic is it to try and match the provisions for sanctions with the actual use of those provisions in any situation ever for each of the countries that have been listed?

DR. MACKLIN: I think you asked how useful it would be. The answer --

PROF. CHARO: How realistic?

DR. MACKLIN: Yes. Okay. Well, the question is how one would go about doing that. One hears frequently probably in this country as well as elsewhere but I have hard -- particularly I can think of a colleague in Argentina who says we have all these laws -- and in Mexico. Two places where I have colleagues.

We have all these laws on the books but there is very little enforcement, and these are laws of all sorts. Everything from informed consent -- I mean, in this area, everything from informed consent to review of research by independent, ethical review committees.

So to find out something realistically who would one ask and how would we go about doing it? If one asked people in official capacity, my guess is no one in an official capacity is going to say, "Oh, yes, we have these laws but we do not enforce them."

So one would then have to develop another instrument or have some kind of systematic survey in the countries or in the places where the answers on Stu's chart say, "Yes, there is an enforcement mechanism and there are sanctions," and try to find out from the individuals in that country just what really happens. So realistically I fear it is probably something we cannot do.

PROF. CHARO: Just -- and, of course, you could say exactly the same thing about the United States in terms of laws on the books that never get enforced but maybe we can pursue this later with the staff, a discussion about possible ways to identify people to ask.

DR. SHAPIRO: Thank you. We, of course, can come back to any of these subjects later but, Larry, you had a question and then I want to really -- we can come back to issues later. I want to turn to the panel.

DR. MIIKE: Just a follow-up. A follow-up to

Tom's question. Are we tracking what has happened to our reports such as HBM and Impaired Capacity because we have very specific recommendations in there directed at specific people?

DR. MESLIN: If -- by "tracking," do you mean finding out whether government agencies have implemented any? Yes. And the answer is none of the recommendations in either of the reports have been implemented yet by any agency.

DR. MIIKE: But I would like to see more than that, which is that how receptive are they, are they actually looking at it. We do not need to wait until they actually formally accept certain things.

DR. MESLIN: The second version of the answer is there are a number of indirect ways of finding out that the recommendations from the Capacity Report are or have been implemented in some ways, including things that NIH has done to follow-up with their intramural program at NIMH, for example.

With respect to HBM, I mentioned at the last meeting that not only have many IRBs and investigators informally been telling staff that they have found the HBM report to be very helpful.

So, too, has OPRR mentioned to us informally that they have felt that the report has been very

helpful to them in responding to requests for information and interpretation of the federal regs regarding this area of research.

So the -- we are tracking both the formal responses and waiting for the Committee on Science and HHS to respond to the recommendations on both of those reports but we are also tracking informal responses, which I must say are quite gratifying particularly on the HBM report.

**DR. SHAPIRO:** Thank you.

We can revisit any and all of these issues later on this morning or this afternoon as need be but we do have a wonderful panel here this morning, including one member of the panel who is here in a delayed fashion having been delayed and unable to make our last meeting when it was scheduled.

Let me turn to Eric or to Ruth to introduce the panel.

## PANEL I: PERSPECTIVES FROM OTHER COUNTRIES

**DR. MACKLIN:** Thank you very much.

We are honored to have the panelists seated at the table and, unfortunately, one of the invited panelists at the last minute was unable to join us.

This was Dr. Doumbo from Mali and apparently there was some problem with a visa, some technical

problem or bureaucratic problem, and that is unfortunate.

But the panelists who are here -- and I will just briefly introduce them all at the outset and then their words will speak for themselves.

First, we have Dr. Jean Pape from the Faculté de Médecine et de Pharmacie de l'Université d'État d'Haiti in Port-au-Prince, Haiti.

Dr. Grace Malenga from Queen Elizabeth Central Hospital and University of Malawi College of Medicine in Malawi.

And Dr. Christopher Plowe from the University of Maryland Medical School who is representing the American Society of Tropical Medicine and Hygiene.

So without further ado, let's begin with Dr. Pape.

**JEAN W. PAPE, M.D.,**
**FACULTÉ de MÉDECINE et de PHARMACIE**
**de l'UNIVERSITÉ d'ÉTAT d'HAITI**
**PORT-AU-PRINCE, HAITI**

DR. PAPE: Thank you very much for the opportunity to present to you and share with you some of my experience working in Haiti for the past 20 years.

(Slide.)

I have been wearing two hats for the past 20 years since I have been -- I am still a faculty member at Cornell University Medical College, a faculty member at the University of Haiti, and director of a nongovernmental organization in Haiti.

My field of expertise is infectious diseases and what I hope to do is present to you at this time as a Haitian the difficulties of complying with U.S. regulations and at the same time presenting to you the positive and negative aspects of collaborative research and some suggestions to improve things in this area.

(Slide.)

The Cornell experience in Haiti has involved research, training and services.

(Slide.)

I will be mentioning something about each of them.

In the area of research we can say that the collaboration has had a direct impact on the life of the Haitian people, both the impact on diarrheal diseases, on HIV/AIDS, to only mention those two.

The possibility to apply and obtain NIH support. We have had NIH support continuously since 1982.

**And Cornell involvement has supported the creation of a Haitian AIDS Research Team that was initiated in 1982.**

**(Slide.)**

**Now let's turn to infantile diarrhea. This was our first project in 1979, which essentially involved determining the causes of infantile diarrhea and improve the management of children with dehydration.**

**We are able to decrease the in-hospital mortality from 40 percent to one percent.**

**This project led to the creation of a national program to fight diarrhea with our unit as a training center. To date over 13,000 medical personnel and over 100,000 parents were trained.**

**And the overall impact has been a decrease in national infant mortality from 140 per 1,000 in 1982 to 74 per 1,000 in 1994. This occurred despite the presence of AIDS and worsening economic conditions.**

**(Slide.)**

**This is a slide that depicts the case fatality rates for diarrhea at the State University hospital where we work. In orange is the admission curve from 1968 to 1993 and in green is the mortality curve. The arrow indicates when we started working**

and as you can see there was a rapid decrease in infant mortality to a low of one percent, which is the level it is now.

(Slide.)

There has been also a major impact on HIV associated diarrhea in adults and children. Our research found the causes and treatment of HIV associated diarrhea for isospora and cyclospora. We have trained over 800 physicians in the management of these conditions and actually it has been very difficult to find any such cases at least in metropolitan areas since physicians know how to treat them.

(Slide.)

Perhaps the greatest impact has been psychologically to remove the CDC 4H label for Haitians. I remind you the 4H was -- meant the risk factors were homosexual, heroin addicts, hemophiliacs and Haitian was the fourth H.

Two risk factors that are found in most countries, including one of the first time that Haiti (sic), was sexual transmission was found as a major risk factor.

(Slide.)

Now in the area of training I will be very

brief. You can see that there have been almost 3,000 people trained in HIV, STD's, tuberculosis and counseling from 1992 to 1999, including laboratory technicians, social workers, nurses, physicians and community leaders.

(Slide.)

But also a major impact has been on patient care. Our centers receive 100,000 patient visits per year. It is the National Referral Center for Infantile Diarrhea, the National Referral center for HIV/AIDS, the National Referral Center for sexually transmitted diseases, and the Main Referral Center for Tuberculosis.

(Slide.)

Closer to home, this project, the Cornell Program, has had a major impact on the creation of ethical committees. First our own committee in 1984, which was the first in Haiti, and with the coming of HIV vaccine trials we have been pushing very hard for the creation of the National Bioethics Committee, which actually took place last year.

(Slide.)

This is the composition of our institutional IRB. As you can see of the ten members only three are related to GHESKIO. The others are not.

**(Slide.)**

**Now let's turn to some negative aspects of the collaboration and with Cornell and other U.S. universities. There has been a feeling with my colleagues that there has been the patronizing influence of US IRBs. That is we know what is best for your study participants in your country and we know how best to inform volunteers in your own country.**

**And although I am familiar with IRBs at Cornell in particular and know that members of IRBs mean well, I also realize that it has been difficult for IRB members to understand anything with which they are not familiar. Most members have never worked overseas and most of them have never set foot in developing countries.**

**(Slide.)**

**This is the example of one thing that happened with a drug, thiacetazone, that was used in most countries, in developing countries, to treat tuberculosis. This drug was approved by the World Health Organization and the Haitian Ministry of Health.**

**In 1982 we observed nine cases of Stevens Johnson syndrome. This fatal dermatologic disorder**

occurring all in patients with AIDS being treated for tuberculosis. And we had planned already at that time in 1982 to study 40 AIDS patients. Twenty would be treated with thiacetazone and 20 not on the drug. Please note that we were not placing those patients on the drugs. This was common policy to put them on the drugs by the National TB Program. And our endpoint was the occurrence of dermatological reactions.

Well, thiacetazone not being FDA approved for use in the U.S. this study could not be done and we had to wait eight years later for a similar study conducted in Zambia that showed that AIDS patients on thiacetazone were much more likely to develop Stevens Johnson syndrome and, therefore, the drug was banned for patients who were jointly infected with HIV and TB.

(Slide.)

Another example involved the U.S. Agency for International Development. It is an ethical principle that research patients should benefit somehow and the minimal acceptable benefit is the treatment of diseases diagnosed during a study.

Because USAID regulations prevent the purchase of non-U.S. manufactured drugs, although in the project we had funds to purchase the drugs, we

could not do so. This barrier was eventually overcome by a national agency called PROMAS, financed by USAID that provided the drugs not manufactured in the U.S.

(Slide.)

Now I will turn to the complexity of ethical clearance because I think that this is the area where collaboration has been the most difficult. Both the complexity of the IRB process, the IRB forms and consent forms.

(Slide.)

The complexity of the IRB process. As you know for any given project there are multiple IRB clearances. Each IRB meets once a month at different times. Each IRB uses different presentations and consent forms. Each IRB has a different set of rules. Some accept oral consent. Others written consent. Others written consent with witnesses, without witnesses. And depending on who the witnesses are, each IRB responds with different comments that must be addressed, a different time period for approval and, therefore, different time for yearly renewal.

This process can take six to 12 months before all the obstacles are removed for a project whose duration is 12 to 24 months.

(Slide.)

**This is an example. We are ready now to start HIV vaccine trials in Haiti. We needed the approval by our own institutional IRB. The project had to be translated in French. The consent form in Creole. We needed approval of Vanderbilt IRB because Vanderbilt was one of the partners. Approval also by Cornell IRB, which required actually the back translation in English of the consent form that was translated in French and this had to be done by an independent person.**

**We needed approval of the National Bioethics Committee, the benediction of UNAIDS Ethics Committee and eventually the approval by OPRR with the issuance of an SPA number.**

**(Slide.)**

**Now although I am essentially on the staff at Cornell, we have the possibilities to work with other universities, both in the U.S. and in other developed countries. And, therefore, every time a French or Canadian project that we do in collaboration has to be approved, it must be submitted to Cornell and our friends in Canada and France feels that this is viewed as U.S. imperialism.**

**(Slide.)**

**Now there is a very specific problem that may**

occur and that occurs when local and overseas IRBs disagree about specific issues. There is no mechanism to resolve this conflict anywhere.

(Slide.)

Now the complexity of the consent forms. They are clearly too lengthy and over the past 22 years I have found that they get more and more complicated. The language is too complex. They appear to be more concerned about legal implications for sponsor agencies than concern with the welfare of the volunteers.

We cannot read them to volunteers because the only time a volunteer had legal or a document like this read to him was when he was in a court of law and had to sign some kind of papers. So this is changing the trust relationship that we have with our participants and, therefore, we have to explain it step-by-step.

The required back translation is often inappropriate. And, most importantly, it does not guarantee that volunteers have really understood the objective of the study, the risks and advantages, and their voluntary participation.

I have heard many people in developing countries say, "Okay. You give us a 20 page form. We

**will have people sign it if this is what you want." But what is the guarantee for the volunteer?**

**(Slide.)**

**Now I would like to make some suggestions to improve the process. First, to decrease the complexity of ethical clearance. We feel that there should be a unique IRB and consent form for all U.S. NIH sponsored studies.**

**This is crazy that we have to fill out different forms for Cornell, different forms for Vanderbilt and, since Harvard is sometimes involved, for Harvard as well. With the aim eventually of having forms that would be applicable worldwide.**

**(Slide.)**

**How to solve conflict between IRBs from developed and developing countries. We feel that very often the IRBs do not trust each other. They do not understand each other. Therefore, we propose a yearly meeting of IRB members from sponsoring and host institutions.**

**And those meetings could take place alternatively in each country and perhaps to decrease costs it could be the head of one IRB that would go and meet and work with them and see that there are sets of rules and working documents. And eventually**

the host country should decide on the details on how best to proceed as long as the general ethical principles are respected.

(Slide.)

We feel that U.S. IRBs, and this is the reality, they have no mechanism, and this was just mentioned here earlier before the presentation, to ensure compliance to ethical principles. And we feel that it should be the responsibility of the host country's IRB to ensure compliance with ethical standards. And, therefore, if they understand each other they can define the sets of rules and regulations that would make the process work.

(Slide.)

In our experience we have had one person totally dedicated to ethical issues. That person prepares and submit with the head researcher in charge of that study IRB forms and consent; counsel potential volunteers about all aspects of the project; help develop a test questionnaire which all potential volunteers must pass before obtaining a consent form, obtain the consent forms; ensure that one copy stays in the chart, another one with the volunteer, and the other one in our file; obtain all IRB renewals that come at different periods; and most importantly be

available to answer all volunteers' concerns and comments.

(Slide.)

We feel that we should use the waiting ethical clearance period to counsel and inform potential volunteers. It should not be a period where nothing is done. A simple questionnaire should be developed that addresses the most critical concerns. Perhaps 22-24 questions at most. The potential volunteer should pass that test before obtaining a much more simple informed consent. If he has passed -- if he passed that questionnaire test we know he has understood because that questionnaire test involves multiple counseling sessions before he can arrive at passing that test.

(Slide.)

But now in a practical way this very often cannot be done because there is no support for such a person and we feel that every grant should include 10 to 20 percent to support an ethical person or an ethical unit in the host country with the primary responsibilities to prepare and submit to the head researcher all IRB forms and consent, consult potential volunteers, develop the test questionnaire that will be administered by the local IRB.

But to make this happen the funds should be available for the ethical unit or person before final ethical clearance.

(Slide.)

In summary, we at Cornell and in Haiti found that the 20 years experience has been very positive and we feel that it is possible for research teams to meet the highest ethical standards in developing countries provided the following:

Consent process must be simplified.

There is a greater understanding of the role of IRBs from host and sponsored country or countries.

And there is support of ethical unit in host country.

Thank you very much.

DR. SHAPIRO: Thank you very much.

I would like to take a -- if there are questions now I would like to take at least a limited number of questions dealing with the presentation while it is fresh in our mind before turning to Dr. Malenga in just a few moments but we cannot go on too long since I want to be able to get to the other panelists.

Tom, then Larry and then Alex.

DR. MIIKE: Just a very specific question.

**You mentioned in terms of the percent of funds from the grant to support the consent process, 10 to 20 percent, is that -- that seems a lot in terms of the proportion of the proportion of the grant monies.**

**DR. PAPE: Well, it depends. If it is a grant, $150,000 grant, 10 percent would be $15,000 that would be available to help support one person that is fully dedicated to that and we feel that unless there is one person fully dedicated to that everything that is being prepared by U.S. IRBs here and your regulations that is being asked will not be implemented.**

**DR. SHAPIRO: Okay.**

**Tom?**

**DR. MURRAY: Thanks, Harold.**

**Dr. Pape, you mentioned that back translation of consent forms is sometimes inappropriate. I would appreciate hearing more about the reasoning behind that claim. We realize that translation and back translation can be complex but what makes you skeptical about its usefulness?**

**DR. PAPE: Well, very often the meaning changes and particularly when it is translated in language like Creole, which does not have many of the complex wording that exists in English or in French.**

It makes it very hard afterwards to be translated back into English.

DR. MURRAY: How is a research ethics committee, an IRB, then to know how accurately the translation conveys the information about risks, benefits or lack of benefits at all?

DR. PAPE: That is exactly my point. I think that you have to work with local IRBs. It should be their concern and even if you have the best back translation you still do not know whether this is actually implemented and it should be their role since they are right there to make sure that this is done and this can be done very easily. We just need understanding between IRBs from both countries.

DR. MURRAY: Thank you.

DR. SHAPIRO: Alex?

PROF. CAPRON: I want to thank you for one of the most interesting and informative and challenging presentations I think we have had in our existence.

I wanted you to clarify one point in your example about the drug that was being used for the TB patients and the inability to study it.

Did that inability arise specifically because you were a U.S. based researcher? Was that the origin of it?

**DR. PAPE: Yes, essentially.**

**PROF. CAPRON: And so that a non-U.S. based research in Haiti could have done the study because the drug was in common use in Haiti. Is that --**

**DR. PAPE: Absolutely.**

**PROF. CAPRON: Okay.**

**DR. PAPE: Absolutely.**

**PROF. CAPRON: Thank you for the clarification.**

**DR. SHAPIRO: Bernie?**

**DR. LO: I also want to thank you for a really stimulating presentation and I guess first I hope that you will be able to make available the text of your remarks so we can read them and think about them some more. There are some excellent suggestions.**

**One of the things I heard you say was to make a very clear distinction between the consent form and the actual understanding of the research participant about the nature of the research, the risks and the potential benefits. And it seems to me you made some very thoughtful suggestions as to how you might ensure understanding rather than sort of create longer and more complex consent forms.**

**And two of the things you suggested were first to use this long waiting period to get the**

**ethical clearance to educate potential subjects and the second one was to actually directly assess what potential subjects -- participants understood about the project.**

**I am particularly interested in the second suggestion which seems to have implications in the U.S. as well as other countries. Have you devised such questionnaires and could you make them available to us that might serve as sort of models for others to consider?**

**And, secondly, is there agreement among your research team as to what the essential -- I think you said 20 -- aspects of the study had to be?**

**Some of the things we have heard in this country are that people really do not understand it is research. They think it is therapy. They do not understand the idea that treatment is assigned by chance if it is a randomized trial as opposed to the judgment of the individual physician.**

**At what level -- what sort of things -- I mean, I think the ethical issue is what do people need to know about a study to be able -- for them to be able to give truly informed consent? And if you could help us sort of establish what those criteria are and how to test them I think that would be a very useful**

**contribution.**

**DR. PAPE: Thank you for this question. I think it is very important and we feel that the very lengthy consent form describes risks that are minimal and putting them at the same level as very important ones.**

**For instance, when you tell a participant that you are going to have a black and blue mark -- well, first of all, in black patients it is not a black and blue mark but a mark because you are -- and you may feel faint because you have your blood drawn. Most people know that. They have had at least once in their life their blood drawn.**

**We feel that it is very different than telling them that the study will involve taking 200 cc's of blood in a manner that they will understand each three -- every three months or every six months.**

**This is very different and we would put that in our questionnaire that are you aware that this study will involve taking, let's say, two bottles -- one bottle of Coke every six months or every three months of blood, something that they can relate to.**

**DR. SHAPIRO: Thank you.**

**Diane?**

**DR. SCOTT-JONES: Thank you for your presentation.**

**I was wondering if you could say a little bit about how -- about the extent to which U.S. researchers are working in Haiti. For example, is your project one of many or one of a few projects that involve U.S. researchers?**

**And, also, I was wondering how typical it is for there to be researchers who both have an appointment at a U.S. university and also an appointment in Haiti so that they are genuinely of both the foreign country and the host country?**

**DR. PAPE: Well, to answer the second question first I think I am the first one at Cornell to be working as a full-time professor overseas. In Haiti, unfortunately, we have lost some researchers from Johns Hopkins in particular and this was related sometimes to bad press publicity, which is very unfortunate.**

**Actually this is another point that I would like to raise. The lay press has become the judge on how research is conducted in developing countries and I think it is fine that the press should be involved and discuss such matters but at least one should have some opportunity to reply. And even in cases where**

**you are allowed 100 words your answer is not guaranteed. And, therefore, the public only has one side of the story and you never have any other way to present the other side.**

**From our standpoint we had an article in the Times that described one aspect of the research. We sent a reply that was never acknowledged, which in the four days period never published, and if we had not been working there for a long time and people were not aware of what we were doing, this would have flushed entirely a 20 year program and the end result would have been bad for the Haitian people.**

**DR. SHAPIRO: Thank you.**

**Alta?**

**PROF. CHARO: I would also like to add my thanks, Dr. Pape.**

**I am sure you know that as somebody who is a faculty member of Cornell many of your concerns resonate even domestically with the problems we have here with this system. It is certainly magnified when we cross boundaries.**

**I would like to ask you to comment on something that goes a little bit beyond your talk but is the focus of a lot of interest for the commission and that is to discuss perhaps your experience**

concerning the provision of services and medical devices or drugs that are being studied after the study has completed.

What has been your experience in terms of the expectations of the investigators and of the subjects themselves with regard to what will happen after the study? Do your national guidelines say anything about this? Indeed, you mentioned national guidelines but I am not familiar with them. So to the extent that you would like to say a few words about the national guidelines, in general, that would also be helpful.

DR. PAPE: Well, first of all, from our standpoint we have always refused to be involved in drug studies that would not be provided or where the population would not benefit in some ways either from reduced costs or -- this is why we have never been involved in any of the retroviral studies. We were approached by many companies but when I told them if this is successful what would be the advantage for the population, and they said they will get back to me, and they never did.

So I cannot tell you. We do not have any experience with that because we have never been involved with it and the only time we would be is there would be some guarantee that the population

would be involved.

We are interested in the vaccine because we think that this is the hope is that it would be made available at a price where we could purchase it but clearly we cannot be involved with the drugs because we can never purchase them.

DR. SHAPIRO: Thank you.

Larry was the first and he will be the last before we turn to the next speaker.

DR. MIIKE: Thank you.

DR. SHAPIRO: Larry?

DR. MIIKE: Dr. Pape, I would like to hear a little bit more about the relationship between the sponsoring and host country IRBs. You had mentioned that what you would like to see -- and I know you are just being perfunctory in the presentation -- that the sponsoring country IRB should, say, have an agreement on general ethical principles and then leave it up basically to the host country but general ethical principles are embedded in the rules and regulations that govern IRBs already.

So could you expand a bit on that about the kinds of issues that have come up between those two IRBs?

DR. PAPE: Well, first of all, there have

been no contact between -- and this is unfortunate -- between IRBs from -- our IRB was set up in 1984 and that IRB never had any contact with the Cornell IRB.

I have had contact with both. In Haiti we found it helpful to go and present a project to the IRB staff by giving them ahead of time the project to read and answer their questions.

But it is unfortunate -- this is why, you know, I feel frustrated because I think that a lot of the problems that arise could be easily solved if one IRB did understand the other because I have found that in both places the members are very interested in providing the best ethical standards for patient involved in studies but they have their own set of rules and they do not understand each other.

So this is why I think that the first step would be to have them work with each other and the best way to do that is for the head of one IRB to go and work at specific projects that are submitted and vice versa.

DR. MIIKE: Just a follow up.

When you mentioned something about a uniform consent form or whatever you had mentioned that it would be universally used. Are you talking more in terms of not so much the mechanics of it but sort of

guidelines for how relationships should be set up between the host and sponsoring IRBs? Or is that -- it just sort of says this is the way that the relationship should, in general, be established?

DR. PAPE: I am looking at it from a very simple and practical way. A project that involves three U.S. universities require for us to fill out three different forms. Those forms are very different and the consent forms are different as well.

Why can't we have, since NIH is the sponsoring agency, that they have one form that all universities comply by? That would make life much easier for everybody. That would simplify the consent process.

DR. SHAPIRO: Thank you very much, Dr. Pape.

I hope you will be able to stay since I am sure there will be more questions later on today.

I am struck myself by your testimony here this morning.

I kept on going back in my own mind to words -- a single word, namely "trust" -- a building of trust between partners here as something which would help a lot in trying to expedite these projects and it was very inspiring what you had to say.

But now let's turn to our -- ask Ruth to

introduce our next panel member.

Ruth?

DR. MACKLIN: Well, I had introduced all three together.

But, please, I want to introduce now Dr. Grace Malenga, who comes to us from Malawi in Africa.

Dr. Malenga?

GRACE MALENGA, M.D., QUEEN ELIZABETH CENTRAL HOSPITAL AND UNIVERSITY OF MALAWI COLLEGE OF MEDICINE, BLANTYRE, MALAWI, AFRICA

DR. MALENGA: Thank you, Madame Chairman. Is this on? Yes. Okay.

Could I have somebody to project the overheads, please?

(Slide.)

I am basically a clinician and maybe details about research processing and things may not come out as clearly as my colleague did. I am a clinician and have always worked as such. Mainly in the district hospitals in Malawi, in the rural district hospitals, and for the past four years I am a member of the College of Medicine and, therefore, working at the -- one of the tertiary hospitals, Queen Elizabeth Central Hospital in Blantyre, which happens at the same time to be the only teaching hospital in Malawi.

So my presentation may be a little more clinically oriented than research oriented. I thought I should give that background. Thank you.

(Slide.)

Simply to give an overview of the types of health research oriented activities in Malawi, you have those that are based within the Ministry of Health or rather coordinated by the Ministry and also those based in the College of Medicine.

(Slide.)

The Ministry of Health based research activities are usually part of the disease specific operational research, which are part of the multilateral collaboration that the Ministry has with the donor agencies like WHO and we have had partnership with the CDC especially in relation to the diarrheal control program and a lot of these usually assess the impact of cultural influences on established primary health care interventions usually looking at knowledge, attitudes and practices of the community.

Also, assess the health systems performance and they sometimes look at drug efficacy, especially in relation to malaria, for example.

(Slide.)

**As a university college the College of Medicine based research aims to fulfill the college's function of basically advancing learning while at the same time being quite sensitive to local needs.**

**(Slide.)**

**So within the college itself there are linkages relating to research with the Ministry of Health because the IRB, if you like -- the national one is based in the Ministry of Health headquarters, the so-called Health Sciences Research Committee, which has members from the College of Medicine Research Committee.**

**And during the last three years or so it was first felt necessary that the Health Sciences Research Committee decentralizes the IRB to the college itself so as to facilitate the processing of research proposals and there are linkages within the various departments within the college and also the sister institutions within the university.**

**But there are also linkages with institutions outside Malawi and notably at the Queen Elizabeth Central Hospital, also at College of Medicine. We have attached -- are working hand-in-hand with the college, the University of Liverpool in U.K., the Wellcome Trust Research Laboratories from U.K., and**

**also the two American organizations like Johns Hopkins and Michigan State University of the U.S.**

**(Slide.)**

**And basically those are the types of research: clinical, community-based and then a very small percentage purely scientific. Well, mostly it is that I have got to say.**

**(Slide.)**

**In terms of operational arrangement, funding for a lot of this research as I said earlier with the Ministry is part of the disease programs that are funded through multilateral arrangements. And then for the College of Medicine you have, you know, specific staff with specific interests submitting proposals to donors that they have contacts with and then, of course, when you have the international organizations they fund their researchers.**

**(Slide.)**

**I mentioned earlier on about the ethics review boards. There is the national one, the Health Sciences Research Committee based at the Ministry with members also from the College of Medicine and to speed up activities this was locally decentralized to the College of Medicine and basically this use of international guidelines, including the issues that we**

have discussed previously.

In terms of manpower resources usually it is the regular staff at the designated facilities, be they district hospitals or College of Medicine who undertake this. And then, of course, with the Ministry in the funded programs they have technical assistance from donor agencies and then, of course, there is the international institutions who use their own research staff who are sent to Malawi to do specific research.

And then as part of the capacity building program there is research associates who are locally recruited and are in training.

(Slide.)

It is certainly the wish of the various research committees that research results get disseminated as widely as possible. In terms of the Ministry based operational research activities, these are usually noted as translated -- these are usually translated as changes in the national policies regarding the management of the various diseases. Malaria is the one that comes to mind.

Malawi was one of the countries that first decided, for example, to use SP as a first line drug in the management of malaria when it became clear that

chloroquine was not working in the country.

In terms of the College of Medicine research it is now a standing situation that every year there is regular annual research dissemination conferences.

The only small problem that I see is that there is very little coordination perhaps the College and Ministry in terms of actually implementing the results of research, especially when these come out from the college research. Part of the problem, I am sure, is not sheer negligence but rather a funding issue I imagine.

(Slide.)

So the areas of concern that some of us see is that in Malawi research priorities seem to be determined by funding opportunities rather than the actual problems within the country and there is probably maybe limited consultation between the -- between the international research organizations and the Ministry, for example, in actually setting out priorities for research within the country.

And then in terms of research -- in terms of funding there is a kind of type of war if you like between the public sector and the better paying research projects so you will tend to get a lot of

your better staff moving into research projects more to the depletion of the national services.

And then, of course, another area of concern is what was mentioned earlier, I think, in regard to my colleague's presentation, is there is always this worry about the sustainability of the implementation of the successful results once the study period is over.

(Slide.)

However, we see that there are some opportunities despite those concerns that as long as there are these partnerships with international organizations there is always some opportunity for funding for research in our resource-strapped institutions.

And as part of the collaboration that we have there is some opportunity again for infrastructure development in terms of physical structure and service delivery which are there and some of these research staff also participate in the teaching of the undergraduates and then, of course, as part of the capacity building program some of these international based research do have -- who do make opportunities for training of local staff and again it is a plea at the bottom that if there is anything that could be

done almost willingly it would be the support to the local research committees or IRBs so that they are able to carry out their work better amongst which, of course, is the dissemination of the research results.

That is where my overheads end but I will add that I have circulated a one page paper which simply points out some of the ethics issues which, as I say, as a clinician I have tried to avoid.

And may I, before I end, thank everybody and members of the commission for giving me the opportunity to participate in this meeting from which I hope to learn a lot.

Thank you very much.

DR. SHAPIRO: Well, thank you and let me express the gratitude of the commission for your willingness to come so far to participate with us today. We are very grateful to you and very much in your debt.

Now let me turn to see if there are questions from committee members.

Arturo?

DR. BRITO: Yes, thank you both for your presentations. And I have a question actually for both of you that have presented thus far.

One aspect I have not heard and I make some

assumptions in my own mind as you are going through this about who the volunteers might be for research both in Haiti and Malawi.

I am curious how does -- how do the volunteers -- the demographics of the volunteers in terms of economic levels and their access to health care relate to their volunteerism for research projects in both your countries?

DR. MALENGA: If I am to answer for Malawi, Mr. Chairman, as I said a lot of our research is sort of clinical work and it is usually patients who come to the hospital and as Chris will vouch, in fact, our research set up offers better services so it is not even a matter of volunteering, you know, to participate in the research. I mean, they do not -- it really does not take a lot because they see this as a better service than would normally be offered.

DR. BRITO: Right.

DR. MALENGA: And, in fact, it is interesting you should say that we are conducting at the moment some research in the use of a combination of SP and another drug in the management of malaria.

And as part of the study we have included a questionnaire at the end of the one month that we are following our patients to try and find out why,

indeed, they joined and so far most of the results point to the fact that all the mothers that submitted their children to the research program were actually hopeful that they were going to get better management than they would have in the rest of the service available to them.

DR. BRITO: And is that made clear to the volunteers that there is a possibility they may not actually get better care because if you are doing true research you may not be giving --

DR. MALENGA: Well that, in fact, comes to my mind in relation to the placebo, you know, double blind placebo type of trial and that is a concept I notice we have problems really explaining and I do not know how we can do it and even the actual consent from that we are using -- I am not even sure it is very clear because it is a bit difficult to explain because I think there probably -- you know, the concept would be so difficult to perceive that it is not -- I do not think even explained enough -- much as, you know, attempts are made towards doing that.

DR. BRITO: Thank you.

DR. SHAPIRO: Is it also true in Haiti that the volunteers are very often patients in the hospital?

**DR. PAPE: In our situation health care in our facility is our entirely free. It is also free at government facilities but they do not provide good care there and if you compare the outcome of patients involved in research projects it is excellent compared to patients who are seen at government facilities or even at private physician facilities. So we strive to give the best available care for a population actually which is very poor.**

**DR. SHAPIRO: Thank you.**

**Next is Alta.**

**PROF. CHARO: Dr. Malenga, thank you very much. I would like to ask you perhaps to expand on the topic that you had mentioned was discussed previously with Dr. Pape and that was the expectations that the human subjects and the investigators have about the continuity of care following the study.**

**Dr. Pape had suggested that he will not work with sponsors that do not make some kind of commitment to make sure that the materials under study are somewhat available following the conclusion of the formal research.**

**Has that been your experience as well that studies are simply not done unless there is this commitment and if that has not been your experience**

could you perhaps talk to us a little bit about what does happen in this negotiation?

DR. MALENGA: Well, relating to HIV related studies that is true but in terms of malaria so far the kind of research that has been carried out is, indeed, to look for remedies that may eventually be affordable when that eventually is, is probably the difficult question and may be, indeed, either Ministry of Health has not, you know, seriously started questioning when that would be.

But on the face of it when you think of something like, you know, SP and combination of artesunate or something like that is something you feel maybe one day this will be done, and this is where I also personally now find there is probably a problem in the way the results of research are disseminated once they are known.

I think there should be a deliberate policy to involve policy makers or at least make them aware of these research results so that they can, indeed, make some kind of allowance in the purchasing of these drugs, you know, for the nation.

And so at the moment I think the problem is -- apart from, you know, being mainly financial but also one of not being aware of what is feasible --

what is feasible in the country, and I can also only blame the researchers for not probably making that very clear to the policy makers.

I am sure once the policy makers eventually know we will discover that -- if they, in fact, are the reasons for not implementing, you know, the results, which will probably be mainly financial.

But there is that, you know, loose linkage at the moment to sort of ensure that the results are put into practice on a much more long term basis.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I want to thank you for coming such a long way to share your thoughts with us and I guess first I was fascinated with the handout you gave out and was hoping you would say more about some of these ethical issues.

Maybe I could just ask you if you could highlight for us on this page what are the issues you think we need to pay attention to as we think about ethical issues in tropical medicine research. Of all of these, which are the ones you think deserve our most thoughtful attention?

DR. MALENGA: Well, if I may, indeed, under number one the issue of how much information to share

given the educational background of some of our patients. You really do not want to scare patients off because you want to tell them too much. After all, you know, they come, you know, trusting in your judgment.

You start asking questions or telling them to sign, you know, some papers and immediately, you know, they will look at them, some of them have actually withdrawn, you know, they were willing to participate, let's say, into the exercise and until you are asking them to sign a piece of paper then they start to wonder, you know, why you ask them to do that.

So these are some of the issues which I think are probably more related to the education or background than anything else.

And then the issue of sustainability is the one we have -- I have just -- we have just talked about but it is even more important maybe when -- if it is part of the consent and this is only part of the research activity that may not go on after the research itself is over, and if it is something that may have some negative, you know, effect on your service that you will end up eventually chasing away the very community that you are trying to get, you know, to come to your health services.

So again basically here I think the highlight is what is it and how much and how do you put it to participants in your research study whose understanding perhaps of some of the research concepts are not, you know, as much as, you know, you would expect them to be.

And then again, basically number two, the issue of a placebo controlled study in the management of malaria becomes a real ethical issue. I mean, you know that by not giving somebody the treatment that they deserve they could die and malaria can kill within a matter of seconds and there may not be that time to give them the rescue treatment.

How do you insist on, you know, use of placebo controlled trials for such a serious problem, for example? I mean, these are just some of, you know, the areas.

And maybe finally to just mention about the HIV related issues. Of course, the issue of the expenses -- expensive intervention when there is no long-term view for the therapy is not only applicable to HIV.

I probably was a big cagey when I was answering about malaria. I do remember that it is more than ten years ago when a drug like mefloquine,

for example, which is superior to quinine, which is superior to chloroquine was used in Malawi and found to be more effective and yet 10, 15, 20 years later it is not used.

So it is not just AZT and now what do you do. Those are just some of, you know, the issues indeed.

DR. SHAPIRO: Thank you very much.

Diane?

DR. SCOTT-JONES: Thank you, Dr. Malenga. This has been very, very helpful.

I would like to ask you three questions.

First, I was wondering if you could say something about the extent to which there are U.S. researchers conducting studies in your country? Could you say whether there are a few or many or do you have any statistics on that?

DR. MALENGA: A few. As I pointed out in the overhead there is mainly the two institutions that I am aware of but Chris may be able to correct me. He says three. I think he will give more details. There is the Johns Hopkins. There is the Michigan State University and --

DR. PLOWE: University of Maryland.

DR. MALENGA: There. So there is three institutions.

**DR. SCOTT-JONES: Okay.**

**DR. MALENGA: But all of them more or less crowded around the one hospital, Queen Elizabeth Central Hospital. So unless, Chris, I have sort of left out --**

**DR. PLOWE: I guess the CDC has had a presence there for a number of years.**

**DR. MALENGA: With the government mainly.**

**DR. PLOWE: Exactly. Based in the capital city and they go out and do field studies as well.**

**DR. SHAPIRO: I do not like to interfere but when you speak if you could get to the microphone because they are recording here, it would be helpful. You do not have to repeat that.**

**DR. SCOTT-JONES: So even though there are only a small number of institutions involved I was wondering about the steps that would be taken to get permission to start a project in your country.**

**You mentioned during your presentation that there is limited consultation with the clinicians or health care providers in your country.**

**DR. MALENGA: The Ministry.**

**DR. SCOTT-JONES: So what would be the steps? How would they go about getting permission to be in your country conducting the study?**

**DR. MALENGA: The first step would be to contact the Ministry of Health, of course, and this is what is normally done. And then the Ministry of Health, in general now, not simply the review board of the Ministry, simply to see whether they feel that indeed it would be a relevant study to the country. And then after that then you would have to go through the usual review by the ethical committee, et cetera, and that would be now initially to be centrally again at the Health Sciences Research Committee but this has been decentralized to the College Research Committee, which does have some representation from the Ministry of Health.**

**DR. SCOTT-JONES: Okay. And my final question has to do with training. You mentioned that there are some training opportunities that arise from the studies that are done there. Could you say a little bit more about that? For example, to what extent are there researchers in Malawi who do become trained, who do become involved in the design and implementation of the research that is done there?**

**DR. MALENGA: Well, for example, at the moment the Wellcome Trust, which is the institution actually that is recruiting a number of young Malawian doctors -- maybe I should say at this juncture that**

Malawi has had the College of Medicine only in the last 10 years or so and they have been having graduates in the last eight years.

So the Wellcome Trust is now recruiting some of these young doctors as researchers and as I am speaking there is three if not four who are in England doing their post-graduate training having started with the malaria research project and Wellcome Trust training.

DR. SCOTT-JONES: Thank you.

DR. SHAPIRO: Thank you. We are going to have just three or four more questions before we go on to our next panelist. We can come back, of course, later.

I have on the list right now next is Eric.

DR. CASSELL: One of the problems in the early years of IRBs in the United States was that the investigator might be very committed to getting a good population -- research populations, informed consent and so forth, and yet the staff is not nearly as committed. Short cuts in getting consent and not as rigidly adherent to the ethical principles that the research was laid out as.

I am sort of interested in whether you have the same kind of problem and how you deal with that

**both in Haiti and in Malawi.**

**In other words, the issue of staff on research projects and their commitment to informed consent and the other ethical principles, and how you deal with that.**

**DR. MALENGA: Well, I think the issue of enforcing the proper adherence to informed consent has actually been touched upon. The local research committee, for example, in Blantyre, if I give one specific example, this is the autopsy study that is part of the Malaria Research Project, for example.**

**The local research committee insists that it is only Malawian doctors who speak the same language as the patients are the ones who are going to ask for a post-mortem from, you know, a guardian of a subject that has died from malaria.**

**So I suppose that in a way -- I am not sure it sort of gets rid of the issue of translation, et cetera, but I think that is an attempt to make the process consistent, that the same message is adhered to, and then the cultural, you know, issues are taken into consideration. Those are some of the attempts that have been made, for example, in this particular example.**

**DR. SHAPIRO: Dr. Pape, do you have anything**

to add?

DR. PAPE: I do not think it was a problem when the consent form was short, one page. As it got longer and longer it is read and explained to the volunteer.

But do we really have an idea of what they fully understand? No. And this is why we have come up with another way of doing it which is having a test. Having the volunteer take a test before they provide the consent. And they have to be able to answer all the questions. If they fail they are re-counselled again and can take the test again.

So now I think that it is in a much better way than it was before.

DR. SHAPIRO: Alex?

PROF. CAPRON: Thank you, Dr. Malenga, for being here.

I wanted to pursue a couple of questions along the lines that Dr. Scott-Jones had raised with you.

In looking at international collaboration have you found a difference between collaborating with investigators from the University of Liverpool or the Wellcome Trust or other U.K. sponsors versus those with U.S. sponsors since we are particularly concerned

whether the U.S. regulations and procedures make it more difficult to carry out research than it ought to be?

DR. MALENGA: Maybe to answer your question directly, maybe too much at the clinical end, maybe towards the end of the whole process that it has been very difficult for me to see if there is any difference. But if I must answer from what I see, I do not notice that there is that much difference working with U.S. or British investigators.

After all, in fact, the Wellcome Trust and Malaria Research Project is co-sponsored by the two institutions.

PROF. CAPRON: I see. Along that line perhaps if it would not be a burden to you to inquire with your colleagues who perhaps have had the more direct contact if you would follow-up with our staff here any additional information you could provide might be very illuminating.

The second question relates to the point you have number one on informed consent and how informed the consent is. And I wondered there if I understood you correctly. You seem to suggest that the process of telling people about the research project in the way which U.S. or maybe U.K. expectations are as the

amount of information they have to be given and then signing the consent form will scare them off from participating.

Did I understand that correctly?

DR. MALENGA: Sometimes it has actually happened. You ask somebody -- you -- they understand and the minute you say please sign here then, oh, no, you know, they do not want -- it is difficult to know whether they are looking at in a legalistic manner or maybe it is fear of eventually being blamed by members of the, you know -- members of the family for accepting, you know, to enroll.

The actual reasons are rather obscure and this is why, as I say, as part of the current research that we are doing we want to inquire how people understand, you know, this process of informed consent. But there have certainly been examples when people have come along with you that far and it is the time for you to say please sign here or, you know, your thumb print here, then they have withdrawn.

It is not too often but it certainly happens from time-to-time.

PROF. CAPRON: Where -- if I can ask, where are you in the process of the research project you just described in terms of finding out from subjects

what they understand and what they may not?

DR. MALENGA: Very early on.

PROF. CAPRON: So you are not going to have results any time soon because it --

DR. MALENGA: Not yet.

PROF. CAPRON: -- seems to me a very worthwhile inquiry which could be very informative for your own research committees and perhaps for the IRBs because while it is obvious that one does not want to create false fears in people's minds -- on the other hand I wonder if you would agree that it is important for people to realize that the relationship to the researcher is somewhat different than the relationship to the physician in whose judgment they were otherwise trusting. I mean, it is a subject-researcher relationship even in the medical context and you would not want people to go into it not realizing that fact.

Would you agree with that?

DR. MALENGA: I do agree. But again in this case you are both a researcher and a clinician.

PROF. CAPRON: Yes. Thank you.

DR. SHAPIRO: Ruth?

DR. MACKLIN: Yes. I would like to thank you also and follow-up on a couple of points that you made.

I think I will stop for your answer after each of my brief questions.

First, you mentioned in the discussion of the malaria studies in your handout the randomized placebo controlled studies and life-threatening conditions.

And my question here is who imposes the placebo controlled design in those malaria studies? That is -- or to put it another way, even though as you stated here the scientific justification, you are questioning whether the scientific justification is sufficient to use placebo in a life-threatening condition.

Well, even in the Declaration of Helsinki, just to use one example, in the latest version the use of placebo is justified but not in conditions and circumstances where withholding a known effective treatment for a life-threatening condition would take place.

So this question is how does it come about and who designs or who imposes the placebo controlled design in the malaria study?

DR. MALENGA: This particular example actually was taken from a MOH center study that WHO -- in fact, it is WHO just to answer your who. It is WHO, who really recommended that this placebo

controlled trial be undertaken in the use of artesunate as the -- oral artesunate as an antimalarial in the peripheral health facilities.

DR. MACKLIN: Well, our colleagues at WHO should be reminded of the Declaration of Helsinki in this regard.

My second question is in the placebo controlled double blind studies where you mentioned that it is difficult to explain because of the complexity and you question whether or not the consent form or the consent process can adequately explain it, suppose it were possible to explain it with sufficient time and using appropriate terminology, do you have any -- we have heard from other researchers in some developing countries that if potential subjects were informed that they might be randomized to essentially a placebo control or an arm that would not provide an active medication they would refuse to enter the study?

Do you have any sense of whether the volunteers in your country would respond in that way?

DR. MALENGA: This is what we are trying to find out in this, you know, particular study. Although it is not completely placebo versus, you know, drug. In fact, it is SP plus placebo so there

**is already some active ingredient there but it is -- it is the idea of adding something else to a well-known drug that would have, you know, to convey to the participants.**

**So because they know there is already something that is useful, I think, probably would not cause the same problems but we still want to find out if they understand that.**

**DR. MACKLIN: Thank you. And one final question.**

**You spent some time talking about the dissemination of the research results and you mentioned some of the difficulty of failing to have that dissemination adequately go to the policy makers.**

**My question is whether there is or has been any attempt to disseminate the results of research to the participants, that is the people who are actual participants and to the community at large?**

**DR. MALENGA: The community, no, unfortunately. All the dissemination has been more or less to the researchers and clinicians but not to the community participants.**

**Although maybe some of the community based treatment studies have had some kind of feedback but not as much as one would hope it to be.**

**Thank you.**

**DR. SHAPIRO: I have got other people who want to speak here but we are going to have to adopt some rules to get ourselves on schedule here and I am going to propose the following:**

**I have Trish and Alta and Diane on the list. Please no compound questions. One question. Pick your most important question.**

**And then I would like to ask Dr. Plowe if he would be agreeable if we took a break and then went to your testimony. Would you be agreeable to that?**

**DR. PLOWE: Yes.**

**DR. SHAPIRO: Because that I think would -- the commission needs a break in a few minutes. I think it will serve us all very well but let's go to the last three people on the list now.**

**Trish?**

**PROF. BACKLAR: Thank you, Dr. Malenga, for your very sensitive and illuminating discussion.**

**I would like -- because your discussion showed such sensitivity to the subjects or the volunteers, I am wondering if you could describe a little bit about the experiences of the volunteers in the study that you have going on? I know I am allowed only one question but within this one question --**

(Laughter.)

PROF. BACKLAR: -- which is I see -- I know that you are currently involved in a study. I think it would be helpful to know as you describe the experiences of people who are in the study now, not just the consenting process, but how many people you have, how many in each arm, and are people dropping out, and what is their feeling about as they describe to you, as a clinician, as you observe them, how they are experiencing being in a research protocol.

DR. MALENGA: Thank you.

The particular study I am mentioning now is the one where we are using, as I say, artesunate and SP, and in three arms there is SP alone, SP and one dose of artesunate, and SP and three dosages of artesunate. The idea -- eventually we hope to recruit about 450 patients. We have done at least up to the time that I left about 80 patients and had seen less than 10 actually of those who had completed over a month.

And the kind of questions we were asking were, you know, if they understood the process and why they joined having understood the process, and the kind of question we were asking were did they join, for example, looking for answers like they were

expecting better care for their children. You know, I am working in a pediatric unit. Or was it -- were they taking special pride in participating in a scientific exercise or, you know, why.

And it seems so far the ones that answered and completed, you know, the whole month of the trial, they were more interested in actually getting better care for their children.

None of them specifically said they derived any, you know, pride in participating in a scientific research. Again it is too early to say yet but those are some of the answers we got.

DR. SHAPIRO: Thank you.

Alta, one question mark in your question.

PROF. CHARO: Dr. Pape, Dr. Malenga said that in her experience there is little difference between collaborating with the U.K. and U.S. researchers.

I understand that because of your joint appointment at Cornell your work is always subject to Cornell's oversight but could you comment on whether in your observation your Haitian colleagues without such U.S. ties have seen a difference working with non-U.S. sponsors versus U.S. sponsors in terms of the feasibility of getting through the process of approval or resolving conflicts in substantive standards?

**DR. PAPE: We have experienced, not me personally, working with Canadian or French agencies in particular, and it is much more simple. That in their process that involves ethical clearance with U.S. universities is so much different with the French and Canadians, and this is why they do not understand that when they work with us they have to go through that entire U.S. clearance process.**

**I cannot say anything working with the British, we never had.**

**DR. SHAPIRO: Thank you.**

**Diane?**

**DR. SCOTT-JONES: Dr. Malenga, I have a question to follow-up on one of your comments. You mentioned that some 10 to 15 years after malaria research that mefloquine still is not available to people in your country. Could you say a bit more about that. Have there been efforts in that regard and what does it look like for the future?**

**DR. MALENGA: Well, has there been efforts? Really I do not know. Again I think that boils down to how far did researchers carry the policy makers, you know, towards implementing the results of the research. Attempts may have been there but I think the other problem is one of, you know, financing for**

the Ministry itself really.

And I think this is a problem that probably researchers per se may not help very much but maybe if they were to play a role maybe could be one of advocacy through -- you know, like WHO is trying to use, you know, patent -- what is the word? -- patent, you know, to sort of get drugs less expensive than, you know, they would otherwise be.

So I think the problem is probably a bigger one that needs more discussion and probably right from the beginning that the research come out to see how, indeed, the Ministries can adopt the results of the research activities.

DR. SHAPIRO: Thank you very much.

We are going to take a break now. I hope, Dr. Malenga and Dr. Pape, you will be able to stay with us.

I know we are asking for more of your time than we promised so if your schedules take you away I will certainly understand but I hope you will be able to stay with us.

Chris, I want to thank you very much for be willing to wait a little extra time in order to talk with the commission. I appreciate it.

It is now about 20 to 11:00. I would like to

reassemble at five to 11:00. Let's take a 15 minute break.

Thank you.

(Whereupon, at 10:35 a.m., a break was taken.)

DR. SHAPIRO: I would like now to turn to Dr. Plowe from the University of Maryland. As was mentioned before, representing the American Society of Tropical Medicine and Hygiene and also his own tremendous experience working abroad in various kinds of projects.

Welcome.

I thank you very much once again for your patience and willingness to stay a little longer than we anticipated.

Let me just turn directly to you now.

**CHRISTOPHER PLOWE, M.D., M.P.H.**
**UNIVERSITY OF MARYLAND MEDICAL SCHOOL,**
**REPRESENTING THE AMERICAN SOCIETY OF TROPICAL MEDICINE AND HYGIENE**

DR. PLOWE: Okay. Well, thanks very much for asking me to come. Again I am here on behalf of the American Society of Tropical Medicine and Hygiene.

Terrie Taylor, who is also on the council of the society, worked very closely with me to prepare

this testimony.

(Slide.)

But rather than present the views of the society as a society what we have kind of done is taken a directed needle biopsy here getting the specific experiences of a couple of us who felt that our experiences would give you a fairly on the ground picture of the work we do and some of the issues that we face and the problems that we have encountered.

Since my colleague, Ogobara Doumbo, cannot be here today there may be a couple of points at which I will expand a little bit on something I was going to leave to him, although he could say it much better, and try to touch on one or two things that he might have mentioned.

So, again, this is a perspective from U.S. investigators who spent a lot of time overseas. Terrie is in Malawi for six months of the year and I am probably overseas about four months out of the year both in Mali, which is what I will focus on, our project there, as well as in Malawi where I work with the Malaria Project that you have already heard about from Dr. Malenga.

(Slide.)

Just a very little bit of background to

remind you that malaria is a parasite that is responsible for a huge amount of morbidity and mortality. Two to three million deaths a year and about 90 percent of those are in Africa and the vast majority in infants, young children, and in pregnant woman.

So up along -- up until the HIV epidemic it was really the biggest single killer in that part of the world and now HIV and TB are rivaling it if not surpassing it.

And it is getting worse these days in large part due to drug resistance. We do not have a vaccine and I think the U.S. interest in malaria research -- the specific interests are in protecting travelers and military although, of course, there is a great deal of interest in vaccines and other interventions for people in the endemic countries.

(Slide.)

So I am going to tell you about a project where we are developing a malaria vaccine testing site in Mali in West Africa. You can see the red country up on the right there. It looks like my picture of the escarpment -- Bandiagara escarpment is not going to show up very well.

This is a contract funded by the NIH. I am

**the principal investigator and Ogobara Doumbo is the Malian co-principal investigator.**

**The objectives are to conduct longitudinal studies in a site on malaria epidemiology, parasitology, entomology, meaning the mosquitos, in a community with a high burden from malaria.**

**One thing we are doing initially is to do a case control study where we are trying to identify risk factors and protective factors for severe malaria. A large component is training both Malian and American scientists and physicians. And in the relatively near future we hope to have malaria vaccine candidates and possibly other interventions that we can test at this site.**

**(Slide.)**

**So our site is up in the Dogon country in Mali. It is about eight hours from the capital city on a tarmac road and then another hour or so on a dirt road. The Dogon is the dominant ethnic group there but there are many other ethnic groups and many languages in the area.**

**The Dogon architecture is depicted in the upper photograph there. Again that is not coming through very well. But they -- some of the villages are right on the face of a cliff. It is a very harsh**

environment to live in.

The town of Bandiagara is actually a fairly large town with a population of 12,000 people and it is on the plateau up above the escarpment. There is very intense malaria transmission there and minimal modern -- maybe I should put that in quotes -- health care available. In general, in Mali, the government does not provide any medications or any supplies to sick people who show up at clinics or hospitals and there is a very strong presence of traditional medicine.

(Slide.)

And so this is our kind of nexus of partners, is the way I try to describe it, and the thickness of the line indicates sort of the strength of connection among the different groups.

As you can see our strongest connection as the U.S. researchers is with our Malian researchers and we naturally, you know, have a relatively weak connection at least as we started the project with the community of Bandiagara.

And had we not been -- had we come in as outside investigators and not been working with Malian researchers we would never have known that traditional healers even existed there, much less that if you want

**to get at the community the most powerful and important way to do that is with the traditional healers. Nothing would happen in that city, in that town, without them and we just simply would have had no access to them.**

**So our relationship with the Malian researchers has been absolutely critical and they, in turn, have strong relationships with the community directly because of prior work there, with the traditional medicine center, which works very closely with the traditional healers, and relatively weak relationships with the local doctors at the district hospital.**

**So if we had come in as outsiders our natural instinct would have been to go to the hospital, talk to the director of the hospital and try and set up a collaboration. Had we done that bypassing the healers the project would certainly have fallen flat.**

**(Slide.)**

**As I mentioned, the Malian team had been involved in the community for some years. Our PI, Professor Doumbo, as well as several members of the research team are actually from the Dogon country. And one of our senior investigators was the Director of the Malaria Control Program for that region and it**

turns out his uncle is the commandant, which is more or less the mayor of the town. So we had very good access to the community and ways of trying to understand what the decision making processes were there.

And the Malian research team had conducted very descriptive epidemiological and entomological studies in the early '90s. For those studies, as for all their studies, they followed local procedures for community informed consent and this is really a month's long process and I think this is one thing that Ogo would have dwelled on a bit, and I will try to summarize it briefly.

Basically, members of the research team, including the senior investigators, would go to the site, visit with the elders of the town or the village, lay out what they proposed to do, and it is done in a rather ceremonial fashion with an offering of kola nuts, the traditional sign of respect. Again, something that if we were to have walked into a village we would not have known what the protocol was and would not have brought kola nuts and I am sure would not have gotten very far.

And after they have kind of informed the elders they will leave and then they come back. The

elders may say, "Come back in a month and we will have another discussion."

And they come back in a month. At that point the information has been disseminated throughout the community, including through the women's community, which in some villages they actually have a women's group or sort of council. And feedback comes back and however many questions that have arisen.

And so the point of contact is always the elders and if you try to bypass them -- again there have been interventions where they try to get to the youth of the village but if you do not go through the elders your projects will not go anywhere.

And so they may then answer questions and they may say, "Come back again in a month." And this can go on for quite some time. And eventually there is essentially unanimous agreement among all members of the community and that agreement is articulated to you by the village elders.

So this process was gone through in Bandiagara. Malaria and all other diseases were treated by study clinicians as a part of this study and technicians, both at the hospital and at the traditional medicine center, were trained in the microscopic diagnosis of malaria so there was some

benefit, some lasting benefit to the community.

And at the end of the studies, as we always do, feedback was provided to the community in an open meeting.

(Slide.)

This is just a shot of a group of village elders in a different village just to give you a sense of, you know, who we are going to see and there is a couple of elders of the University of Maryland in the background there.

(Slide.)

And this is where the elders spend their time in a traditional Dogon village. That structure you notice has only got about three or four feet of space and the idea there is if you are having a discussion and somebody gets a bit exercised or they try to stand up they bump their head and calm back down and things can go on in an orderly fashion.

(Slide.)

And really participating with the community functions is a key part of being involved with the community. This was a sort of coronation of the new leader of the local hunting association in Bandiagara and we were told by our guide that we needed to come quickly and join this celebration that was going on

**and they brought us right in and kind of sat us in a position of honor and we sat there the entire afternoon and participated in the ceremony. I think it was very positively viewed by the community.**

**(Slide.)**

**So this particular project was built on studies that began a couple of years ago. This is a partnership between American and Malian investigators.**

**I have been working closely with the group there for seven years. We have spent substantial time on the ground, in the field, in Mali, out in the village, pricking fingers, enrolling kids, really a part of the team. So it is not where we kind of subcontract and walk away and the Malians do the work. We work very closely together.**

**The Malian investigators have been to the U.S. for all sorts of research and training, not just in the lab, but taking biostatistics courses and that sort of thing.**

**And through these years we have really developed a very strong and trusting relationship through conceiving and designing studies, publishing papers, et cetera.**

**Local approval and support both at the**

national level and again at the very local level have been critical for success of our studies. And as I mentioned, we found that traditional healers really hold the key for success or failure of any project involving malaria case management.

(Slide.)

I should mention that I have already sent a staff copy of this talk so I am sure they will be able to print that out and distribute it if you are interested so you will be able to get all this.

So in those early studies the study team arrived in Bandiagara and quickly set up a clinic treating uncomplicated malaria as part of an observational study of drug resistance but we wanted to move on and study severe malaria and so the Malian investigators sent out and word and gathered the traditional healers at the traditional medicine center to meet with the investigators.

Again we had to adhere very carefully to the local customs and protocols. The study aims and procedures were explained. It was a kind of a multi-step set of translations into several languages. Common aims were identified and agreement was reached. And the healers agreed to start referring children who had fever, seizures or coma to the research team.

(Slide.)

We learned a little bit about how people understood malaria there. There was one term that was identified for "cerebral malaria." This term is "Wabu." It referred to fever that was accompanied by seizures, altered consciousness or coma.

And what most people believed was that fever without neurological symptoms is malaria. There is a word for malaria. And that you treat that with chloroquine but Wabu is due to a bird crying at the same time that a child cries as the bird flies near a child and taking the child's spirit. So for that you go see the traditional healer and get herbal remedies and other interventions from the traditional healer.

(Slide.)

Five of the healers let the team look through their treatment records. They kept very careful treatment records. And what they found was that there was a 50 percent case fatality rate for Wabu as it was managed by the traditional healers and the healers acknowledged that these methods were failing and, you know, that there was a problem.

But also it was clear to the community that the methods used at the local district hospital were also not working well. For one thing they did not

have the capability at that point at the hospital to do microscopic diagnosis routinely. And, as I said, patients have to pay for all medications and supplies.

So you bring in a child with coma and the doctor evaluates them, he writes down on a prescription pad you need vials of quinine, you need needles, you need syringes, you need alcohol, you need the tubing, and if the family cannot afford to go to the pharmacy and buy every last article of medicine and supplies there is no point going to the hospital in the first place.

And largely because of those kinds of reasons late presentation and under treatment were common and, also, I think because people would go to the healers first and if they -- the kid did not get better after they were at the healer then they might refer them to the hospital when the disease had already progressed quite far.

So everybody, including the traditional healers and the local doctors, recognized that we needed better ways of managing Wabu or severe malaria.

(Slide.)

So we also reviewed the records at the district hospital and during the kind of peak malaria season of June through September only 11 cases of

severe malaria had been treated at the hospital.

During the same time period 218 cases in this community, 218 cases of Wabu, had been treated or had been identified in the records of just the five traditional healers, five of probably 25 or 30. So clearly the vast majority of cases of severe malaria were going to the healers.

One day after this meeting with the healers five cases came to our study team after two months with only 11 cases coming in for antimalarial drug therapy. And during that first season 55 cases of severe malaria were treated by the study team and in the next season 164 cases.

(Slide.)

So the way this would work is that the healers would bring the patients directly to the study facility. The clinicians were available 24 hours a day, seven days a week. And throughout the role of the healers in the process was recognized, respected and compensated.

And when the child was better they would be referred back to the healer to preserve continuity of care and the status of the healer so that the healer would then be the one to bring the child back to the family and say, "See, you know, you did the right

thing by bringing your kid to me because I knew what to do. I knew this was a kid who needed to go and see this team for this kind of treatment."

And in the second year of studies they did ask for a little bit of compensation. They asked for $36 a month to help maintain a garden with their -- all their traditional remedies. And even though that was not budgeted, we thought that was just something we could find in our budget to provide them.

(Slide.)

This just shows you the traditional medicine center which is right across the street from the hospital so it -- it works out very well.

(Slide.)

Now, of course, we have to also collaborate with the local doctors and there is a physician actually who runs the traditional medical center and also several doctors at the hospital, and they were included in all the plans and discussions.

We provided training in microscopic diagnosis and with the local doctors developed simplified appropriate case management plans that involved using effective but cheaper and shorter regimens that were actually going to be affordable even when we are not there or certainly more affordable when we are not

there or in children who show up to other facilities where the research is not going on.

At this point now we are sharing facilities with the physicians at the local hospital. We make essential medicines available not just for our study patients but for other patients as well and we are hoping that continued interaction and professional education is going to strength the capabilities of the physicians and other staff at the hospital.

It actually turns out that the presence of our team and this project contributed to the government's decision to renovate and expand the district hospital.

(Slide.)

So in this project what we found was that from local case fatality rates for what was most probably severe malaria, although again we are going on healers's records, was about 50 percent and that is about what it is known to be if you do not give antimalarial treatment.

In the national pediatric hospital in the capital city of Bamako the case fatality rate for severe malaria was about 16 percent. In our first year we saw fatality rates of nine percent and in our second year 1.2 percent. We think that is probably

**because people are coming in more quickly.**

**Feedback was provided to the community, to the health workers and the traditional healers, and everybody recognized that this was something that was really working and really made it very easy to continue research in this setting.**

**(Slide.)**

**A couple of ethical concerns did come up. One of the most concerning is that in this setting our team is really the only source of adequate care for this life-threatening condition. So the question arises do parents of sick children really feel they can decline to participate?**

**And there are some mitigating factors. For one thing what we are doing now is strictly observational studies. There are no experimental interventions. Clearly the benefits of getting the treatment outweigh the risks of an observational study.**

**And we are doing training and capacity development to leave a post-study legacy.**

**And, in fact, some children or some parents do decline and, in fact, we do go ahead and manage their severe malaria. We simply do not take blood for the studies and in one instance that my fellow told me**

about last week after the parent had declined the father came up afterwards and said could he be in the study after all because they were pleased with the care he had gotten.

I think we are going to have to be much more cautious and careful as we get into interventional studies. I am pretty comfortable with how we are working things now but if we are coming in with a vaccine study or a drug study clearly we are going to have to be very careful about individual informed consent.

And one thing that came out as we were discussing this was that if you are going to have clinical trials monitors going to sites like this you have got to have somebody who either can access what the local beliefs and decision making processes are or who can work with a local person who can help them get at that information because your routine clinical trial monitor would come to a place like this and just have no clue what was really going on and how people were viewing the study.

(Slide.)

Let me move on now to Malawi and these are some slides that Terrie Taylor helped put together.

And this actually is the same institution

that Dr. Malenga told you about.

The Malaria Project there specifically grew out of local priorities. The Malawi Ministry of Health had recognized pediatric malaria as a major problem and prioritized severe malaria as an important research area in the late -- mid to late '80s and encouraged investigators to pursue funding in that area.

(Slide.)

The investigators had been working in Malawi for quite some time. Malcolm Molyneux from Liverpool School of Tropical Medicine had been working as a clinician here for ten years before this research project started.

And Terrie Taylor from Michigan State University has been living in Malawi for half of the year for seven or eight years at least doing research as well as teaching.

Now the local collaborators -- you have got one exception to the rule in Dr. Malenga but, in fact, because, as she mentioned, the school -- the medical school in Malawi was only established a few years ago there was not a large cadre of Malawian physicians.

In fact, much of the faculty of the school is from other countries. So that the local collaborators

were far -- few and far between. Many of them are over extended and on many projects. They can perform an advisory role but, again with a few exceptions like Dr. Malenga, most of the research is directed by overseas investigators.

(Slide.)

It began modestly with just using the existing hospital wards with no extra staff and a couple of years later they kind of got a little side room for managing cases of severe malaria with a few staff. And currently they are building a new clinical research unit and the project employs 80 Malawian staff.

(Slide.)

The contributions that this project has been making have been at the hospital in terms of offering improved diagnostic service. Simply being able to diagnose malaria routinely at all hours of the day and night is not something that had been available before.

Clinical care for severe malaria and other conditions in this research unit. As Dr. Malenga said, people do get a higher quality of care in that unit than they can get in the general hospital.

And also with the new College of Medicine the

investigators contribute by doing undergraduate teaching, post-graduate training. There is an NIH training grant that has several Malawian trainees getting degrees and receiving training in the U.S.

(Slide.)

And when we get to community involvement -- in my example of Malawi, the community is really the community. But I think in this case in a big city the community, if you think about it, is really the hospital and the medical school as opposed to a particular neighborhood or a town.

And so community participation takes the form of patient care, teaching, serving on committees. Involvement of the community has been difficult, again because local clinicians are contributing to research when it is possible and they are kept informed, but with their overwhelming clinical duties and lack of resources it has been difficult to have a major involvement from Malawian investigators.

Staff compensation actually is an issue that Malenga mentioned, that people have more security and get pensions if they are out in the hospital community but those who work for the project get higher wages at the cost of some loss in security because if the grant evaporates so does their job.

(Slide.)

The oversight of the ethical review process in Malawi -- again you have heard a bit of this so I will move quickly here -- initially was on the national level with a very rigorous and thoughtful national health science research committee.

They did not approve all protocols and now has been moved down to an IRB at the College of Medicine. They meet more frequently. There is more dialogue with investigators. They are very careful to ensure informed consent and now there have been a couple of NIH projects. They have gotten their single project assurances from OPRR.

(Slide.)

SO now let me move on and give you some of our observations based on both of our experiences and starting with a couple of problems a the U.S. end of the ethical review process.

One example was that our IRB requested completely inappropriate language that was designed to limit University liability. And I hear people complain about this a lot. In our case when I explained the situation the University said, "Oh, okay. You can strike that paragraph."

And I think IRBs might be more amenable to

this sort of thing if you really let them know the circumstances in which you are working. Again they may never have set foot in the country but at least in my case I had a very responsive IRB when I went and talked to them.

Now single project assurances, as I am sure you know, are defined by projects based on the funding mechanism, not based on the protocols, the human subjects research protocols.

So we have had to get multiple SPA's for a single study protocol when there are multiple funding sources and we have also had to get a new SPA when the funding source changed for the same protocol. This is burdensome for all of us and it is really hard to explain to your collaborators in the IRB. "We have already reviewed this. We have already signed this paperwork. Why are we doing it again?"

And then on the other extreme a single SP is required for one project so we have a five year project that is going to have many different protocols and OPRR gave us our SPA based on review of a very low-risk observational study and there is not going to be any more review from OPRR for what could be vaccine studies four years from now. So the process does not really make sense to me.

(Slide.)

And then problems at the other end. I think if you do not go and present the study the local review process is really inscrutable for U.S. investigators. We do not really know what goes on and so having trust in your local partners is really critical.

And then something that Dr. Pape touched on is that some local IRBs request overhead or operational costs. And this intermingling of the ethics and the finances is problematic. Protocols can be delayed over monetary issues and not over any ethical concerns.

The issue comes up should we pay -- you know, they want 10 percent. So should it be 10 percent of the total grant budget including, you know, all the laboratory studies in the U.S. and technician salaries here or 10 percent of the in country budget?

And keep in mind that NIH does not pay over indirect costs to these subcontracting off shore institutions and WHO pays no overhead whatsoever to anybody. So what you end up doing is trying to bargain by offering to train personnel, provide equipment, provide services, or trying to somehow embed the equivalent of overhead in your budget and

deal with it that way.

(Slide.)

So some of our observations. I think a key one is the ethical issues and approaches are very different in different projects. Short-term versus long-term projects, for example. A short-term project, individuals should clearly benefit directly. Lasting community benefit may be more difficult to achieve.

In a long-term project the individual benefit may be less but there is much more of an opportunity to benefit the community.

And here again let me digress a little bit. One of the things that Professor Doumbo was going to talk about was how they do that and in every village where we have a research project going on in Mali there has been an attempt to get the community to mobilize and we provide or find seed money to build a dispensary or a clinic, often provide a local doctor, and so that when the project leaves you leave behind a clinic and a functioning doctor in a self-sustaining way.

Observational and interventional research is obviously quite different. Written individual consent, as you have heard from both of the previous

**speakers, may be inappropriate for some kinds of studies, for observational studies and especially in illiterate populations.**

**You can document in a written fashion that you got oral consent but the whole business of thumb printing or signing can be really problematic in some populations, not in all but certainly in some. And, as Dr. Malenga indicated, that -- even if they understand the study and want to participate, when it comes to actually putting pen to paper -- I have been told by several people, I do not understand it, but I have been told that in Mali in many settings if you have to sign a paper it means somebody is going to die.**

**And I have tried to figure out what they mean by that but whatever it is, it is serious and people just do not like the idea of signing a piece of paper.**

**I think nevertheless written individual consent is probably still going to be necessary for high risk studies.**

**And then in terms of the collaborations we are very lucky in Mali that there was a very strong well-established group of local collaborators in the medical school who had been there for 30 years versus coming into a setting where the medical school is only**

five or six years old.

And when there is no established cadre of local collaborators it can take many years to develop and train local scientists and that is something that the Malaria Project is now doing with support from NIH.

(Slide.)

The ethical issues and approaches also differ among different types of communities. In our project we were in a remote rural area where there was no health care system to speak of, a very traditional culture. In the local language there simply is not a word for "science or research." So, boy, try to back translate our consent forms from the Dogon language. I do not know what you would get.

The community is really defined by the village or the town. The community consent is really more relevant than individual consent here. Once you have got community consent it does happen that individuals are much less likely to decline to participate.

Whereas, in the Malaria Project in Malawi it is an urban setting, a very well established health care system, much higher literacy, and more sophisticated. Again the community is defined by the

**institution, the hospital or the medical school. So when you think of benefits to the community you need to think in that context.**

**And community consent at the national or institutional level is much farther removed from the individuals and, say, the real community.**

**(Slide.)**

**And we will end up with a few recommendations. First with respect to the U.S. oversight.**

**Detailed regulations and guidelines, no matter how comprehensive they are, they may just not encompass such different settings and different kinds of projects. What is appropriate for one kind of study is totally inappropriate for another kind of study or setting.**

**Nevertheless, if you have very general guidelines, it is clear it is going to be very difficult to implement and enforce them. So one potential solution that we thought we would put on the table is to have oversight of the ethical review process by an experienced and adequately resourced office.**

**And that evaluation of projects and the response to problems that come up could be made on a**

case by case basis following flexible guidelines rather than following a very specific and rigid set of rules. I think currently the OPRR simply does not have the people to do much more than what they do with the SPA process.

But it seemed to us reasonable to think that certification of foreign IRBs and foreign review processes could be based on guidelines and dealt with by people with expertise and judgment tailored to the specific situations instead of following a very rigid set of procedures.

And, finally, the single project assurance system, I think, needs to be reevaluated. I would think that it might be possible to develop a special version of the multiple project assurance for overseas institutions so that you could certify the IRB for a period of time or for a number of projects rather than have it be based on the funding mechanism.

(Slide.)

And then the issue of compensation that Dr. Pape raised. I think clearly it costs money to run the IRB and to perform their functions.

My recommendation, rather than 10 percent of the project budget -- I mean, our contract is something like $9 million over five years, so $900,000

for, you know, your IRB review would be a bit much. Maybe a standard payment per protocol review would be reasonable.

And, also, overhead and indirect costs to overseas institutions. I mean, just the issue of fairness. U.S. institutions can get 30 or 40 percent overhead, and even for studies that are done completely overseas, our institution takes eight percent overhead and the overseas institution where the work is going on gets nothing. It is not fair.

So it seems reasonable to allow overhead on the in-country budget, or make it explicitly allowable to have budget line items for overhead sorts of costs at the off shore research sites that can be payable directly to the central institution.

(Slide.)

And I will end by saying that I really think the key to doing ethical research in these settings is partnership with the local communities, meaning communities in all sense of the word, including the local community, the local investigators, and the scientific community there.

That close long-standing relationships between the Northern investigators and the local investigators and communities is critical. If you do

not have these relationships the processes for community decision making and informed consent are just not accessible to you as an outsider.

And if you do not have local collaborators you need to develop them, and it takes time.

And the training and capacity building really should be a part of projects in these settings and these provide you with mechanisms for building and strengthening the relationships with your collaborators and for leaving behind lasting benefits in the communities where you are working.

And, lastly, this is something again that Professor Doumbo would have talked about but -- and I will not dwell on it but just to mention that the granting agencies, I think, are beginning to and need to deal with the issue of realistic compensation for foreign investigators in their U.S. funded research projects.

Thank you.

DR. SHAPIRO: Well, once again thank you very much.

I know there will be questions. I have got a list already of questions people would like to ask you and, of course, we have our other guests here, too, if you want to direct any additional questions to them.

But, Jim, you are first.

**DISCUSSION WITH COMMISSIONERS**

DR. CHILDRESS: I would like to thank all three presenters for very helpful presentations that will really be important to us as we continue to think about how to proceed in this area.

This one I will address to Dr. Plowe, our last speaker, and then others may wish to comment on it, too, because throughout the morning there has been obviously a series of comments that suggest how difficult it is to draw a line between therapy and research in particular settings.

And you commented that one concern you have is that avoiding -- that you need to avoid coercion. You did not talk as much about the kind of information that needs to be disclosed in that sort of setting but I guess I am curious as you think about the process of consent, voluntary and informed, how -- what kinds of things do you feel it is important to do in order to make sure that this therapeutic misconception, the close connection for both the individual as the individual perceives it, and also the community, between therapeutic benefits and research. Ways in which you can tease that out and actually have voluntary informed consent by the individual.

**Any reflections you have would be helpful and then others too.**

**DR. PLOWE: Yes. I mean, I think it is difficult but I think you can convey a lot of the concepts that are important to convey. I mean, I have sat actually in the township clinic that we have outside Blantyre, Malawi, and watched informed consent take place with my laboratory assistant so he is not part of the clinical team and, hopefully, not biased whispering in my ear an English translation of the Chichawa conversation.**

**And remarkably the clinical officer was following, you know, very carefully the process. Comprehension, of course, is a whole different question. I think we have been lucky in the kinds of studies we have been doing in that we are not doing placebo controlled trials yet, for example, and so we have not had to grapple with some of those issues.**

**But with a lot of back and forth, you know, you can get across the idea that, yes, we are providing clinical care but we are going to take blood and we are going to take blood because we want to understand, you know, why the malaria parasite makes some people sick and other people are not sick when they have the parasite.**

So even if you are not using terms like "research or science," I think it is possible to work with your local collaborators who understand the culture to come up with creative ways of wording things and techniques for conveying the key elements of what you are doing so that people do understand.

DR. SHAPIRO: Trish?

PROF. BACKLAR: And I am actually going to pass.

DR. SHAPIRO: Okay. Bernie?

DR. LO: Thank you for a thoughtful presentation.

I want to ask you some questions about one of your last slides on partnership and I think we all have a very clear understanding of how you work so hard to achieve that partnership in the rural Mali setting, going to the community and so forth.

One question is, did you revise your project or protocols in response to those discussions? Was -- did they -- did the partnership extend to your getting input from the community elders and the community at large that led you to modify your research project?

And, secondly, how do you involve the community in the urban area? You talked about the hospital and clinic really being a community. How is

**it possible to involve potential subjects or their representatives in this partnership process in an urban setting as you were, for example, in the rural setting?**

**DR. PLOWE: The first question -- I do not think we modified the actual protocol based on input from the community but we certainly modified what we did and how we went about things. I mean, certainly, practical suggestions on, you know, how to approach people and how to inform people, and how to enroll people, how to conduct follow-up, all, you know, had input from local people at various levels.**

**And then the actual clinical protocols that we used for treating severe malaria were modified with input from the local physicians based on what was realistic in that setting and what they might be able to continue to do once we left with all of our research resources.**

**I guess in terms of involving the -- I mean, my slide said that the review process can be quite remote from the real community in the urban setting and, boy, I think that is tough in an urban setting in Africa. I mean, you could go out and look for a community representative but -- I mean, maybe Grace would like to address this.**

**I am not aware of a kind of community structure in the urban setting that you can tap into. It just seems so fragmented as opposed to the village where there is such a clear hierarchy and, you know, contact point and a procedure involved. I am kind of mystified by how you could -- other than just kind of asking someone almost at random from the community to be involved.**

**DR. SHAPIRO: Thank you.**

**Alta?**

**PROF. CHARO: Dr. Plowe, as I was listening to your discussion about the problem with the single project assurances and such, I found myself reflecting on the current interest domestically in an accreditation process for IRBs in the United States and potentially even for individual investigators that would allow for more abbreviated procedures for those people that have been demonstrated to have the capacity to handle the rules and understand the concerns.**

**Are you suggesting something on that order that would supplant the existing regime of rules and, if you are in any respect, would you focus your attention at the level of Ministries of Health or at the level of the individual IRBs given that the**

countries can vary in size as greatly as Nigeria to Togo?

DR. PLOWE: I think I do have something like that in mind. I do not really know how the MPA process works. I have not really been involved with that. But it seems like some kind of standing recognition of the IRB as being properly constituted and composed that is not just sort of random -- I mean, it just depends on how many grants go in and how many SPA's and how many times you make sure the IRB is still composed the same way.

So, yes, some kind of certification process perhaps analogous to MPA's, perhaps some entirely new mechanism.

Remind me what the second part of your question was.

PROF. CHARO: Focus being at the level of individual IRBs or at the government to government level.

DR. PLOWE: Right. I think it would be tough to do it at the Ministry of Health level because how involved the Ministry is in the research and how tuned in the people in the Ministry are can vary hugely from country to country.

And in some countries like Malawi where it is

a relatively small country and I think everybody knows what everybody else is doing pretty well, it might work but I would think you would want to go directly to the IRB.

I mean, in the case of Mali, the people involved in the research at the university level are much more sophisticated and responsive and I think you would get a lot farther with them than you would with the Ministry.

DR. SHAPIRO: Thank you.

Arturo?

DR. BRITO: I, too, want to thank you for that very informative presentation. I was most struck by the sense I got about the collaboration going on in these studies.

I have two questions. One of them relates to what Jim asked about the therapeutic misconception idea that you partially answered by stating that you are not doing placebo trials at this time or you have not been.

I was curious about the trial in Mali that you described. I am not real clear on what the design of that project was and I got a sense on some slight -- well, not sense -- on some of the slides they used the word "treatment" to refer to research protocols

was used and that in itself is a therapeutic misconception because true research does not necessarily provide treatment.

So I would like a little more clarity on what the design of that project was and then I will ask the second question.

DR. PLOWE: Yes. The project I was referring to was a case control study of severe malaria. So what we are doing is we are enrolling kids with severe malaria and then going out and finding a case of uncomplicated malaria as a control and just this year began enrolling healthy controls as well. So matched controls.

And the only other experimental thing we are doing is drawing blood on the kids so we can compare risk and protective factors for severe malaria. There is nothing experimental about the treatment they get. They all get good standard treatment for malaria and whatever else they have.

DR. BRITO: So, therefore, the outcomes are generally going to be good in terms of the treatment and --

DR. PLOWE: Right.

DR. BRITO: Okay.

DR. PLOWE: We are actually not studying the

outcome. We are simply looking at what walks in the door and then can we identify risk and protective factors for that phenomenon that we observe, and then we just give them the best treatment we can and achieve the best outcome we can.

DR. BRITO: Okay. And then I was also struck by the graph that you had up there of the different relationships that you had, and at first I was a little bit worried about the strongest relationship was not with the traditional healers but with the intermediaries.

And this is something I have thought about quite a bit on other issues that have come up is what -- what is the culture of those -- the researchers, the Malian researchers?

Are they more -- is their culture more closely related maybe to Western culture or is it closer to traditional cultures, and what are their potential gains by being involved in these research projects? Or are they truly bicultural and truly think about both? I got the sense they do, but I would like a little more explanation on that.

DR. PLOWE: Yes. In this particular case, and it is a very different story in other places I have been in East Africa, say, where they have been

very much more Westernized.

But in this particular case I think they are truly bicultural to the extent that some investigators have more than one wife in traditional Malian style and maintain a big compound in the countryside, you know, with all the relatives and, you know, sending kids to -- nieces and nephews to school.

And our collaborators are very close to the community and, as I said, two of the senior investigators are actually from that community. So they are very able to see both worlds and actually a very good example of that is our anthropologist.

He is training in Montreal. He is getting his second Ph.D. in anthropology but he has also trained with two Marabous, two traditional healers, so he is kind of double certified both in traditional medicine and in anthropology.

He is a fascinating guy to talk to because he really understands the traditional culture and believes in it, you know, has dreams and interprets them and that sort of thing but also is very sophisticated in Western ideas as well.

DR. BRITO: Thank you.

DR. PLOWE: And in terms of benefits they get out of it, my graduate student got into malaria

**research after he had already become a successful pharmacist with his own business because of a younger brother who had died of malaria. I mean that is his story. He had a very personal involvement.**

**And I think many of the investigators in the endemic countries have a very, kind of, personal drive to do something good for their communities and for their field.**

**There are many other benefits, you know, recognition, publications, grants, salaries, et cetera.**

**DR. BRITO: Okay. Thank you.**

**DR. SHAPIRO: Diane?**

**DR. SCOTT-JONES: I also want to thank you for your presentation. It was very helpful.**

**I have a question about your thoughts about Dr. Malenga's comment earlier that mefloquine still is not available widely or available at all some 10 to 15 years after the research.**

**I understand that what you are doing is in a sense descriptive, that you are not testing any treatment, but what are your thoughts about the ethical obligation to leave some benefit to the country in which the research is done on a treatment?**

**DR. PLOWE: Yes. I think I would have**

**questions about doing a study in Malawi on mefloquine, as a specific example, knowing that that is going to remain a very expensive drug. I mean, it is available in Malawi if you have the money to buy it but it is not the drug that is out there in the clinics.**

**I think Malawi is a special case because they decided to switch from chloroquine to this other drug, SP, and that at the time was a very effective drug and a good public health choice.**

**But another example is from other countries in Africa. SP is beginning to fail and there is another alternative drug that is similar but has many advantages and treats the parasites that are resistant to SP and the research has been going on for a number of years.**

**And one of my colleagues in East Africa had been doing research on this and he got so concerned that the process was taking too long with the industrial sponsor and the WHO that he broke ranks and went and found a drug manufacturer in Kenya and is now setting up the formulation of the drug to sell it in Kenya because he just thought it was unethical to wait any longer.**

**And, you know, I do not want to blame industry because, you know, the scientists who work in**

industry are our advocates and they are pushing, you know, as hard as they can to get as many resources as possible to get these drugs and interventions out there and as cheaply as possible but, you know, within their institutions they are dealing with the accountants and other executives who are maybe more resistant. There are good people in industry who are really advocating trying to get drugs out there cheaply.

**DR. SHAPIRO:** Thank you. This Eric here, Eric?

**DR. MESLIN:** Chris, just very quickly. You had mentioned in your remarks that one of the consent issues was liability and an issue came up and you presented information that convinced the U.S. IRB to drop language.

Was that the standard regulatory language about compensation for injury which essentially says if there is a compensation program we will let you know, if there is not a compensation program we will let you know, or was it something more explicit that you asked be dropped because it was not appropriate?

**DR. PLOWE:** I do not remember the exact wording but it was something along the lines and a phrase where, you know, the University of Maryland is

**going to treat you if something happens, you know, and we are not going to Medevac somebody all the way from Bandiagara to the University of Maryland. You know, if we say that, you know, we will take care of medical problems, you know, locally or something but it was something along those lines.**

**DR. SHAPIRO: Thank you.**

**Eric Cassell?**

**DR. CASSELL: At one point you -- in your closing slide you discussed the relationship of community consent and individual consent, and that is a matter that interests us a great deal.**

**And I would like you, if you could, to make clearer what the word -- I mean, how that works and what it means because if we see it from the United States' perspective we tend to see it as hierarchy overwhelming unsuspecting individuals who will then be taken advantage of, but seen from a different cultural perspective it is very different.**

**And I would like you to make that clear if you could, please.**

**DR. PLOWE: Yes. I tried to touch on that a little bit with describing that kind of month's long process that goes on, but to my understanding of it from my Malian colleagues, it is a process that**

includes discussion with everybody in the community.

So even if the point of contact is the elder, it is not the elders sitting in a room by themselves making a decision and then imposing it on the community, it is an ongoing discussion at multiple levels with multiple iterations and chances for questions from anybody who wants to ask questions, including the younger people in the community, and then they bring their concerns and questions back to the elders or it comes up in a public meeting with everybody in the community and the elders then articulate it as the mouthpiece for the community back to the investigators.

And it is clearly a process without which in our settings we could not do the work but that does not mean that we get community consent and do not get individual consent. It simply means we recognize we have to get community consent to do anything and then once we have got that we still go through the process of getting individual consent.

DR. CASSELL: And that procedure that you discussed with the questions back and forth, and so forth, that does not just apply to the research setting, does it? In other words, that is a common procedure in the community to solve the community's

problems?

DR. PLOWE: That is how they make decisions in the community, and what I am saying is that I would not have any idea what that process was if I were not closely partnering with Malian researchers who did understand that process.

DR. SHAPIRO: Thank you.

Steve?

MR. HOLTZMAN: This is somewhat of a follow-up to Diane's question to Dr. Plowe but it really would go to all of you. It has to do with a situation that certainly I find my company runs into. We're much like you, Dr. Plowe. We do very early stage research into factors having to do with susceptibility and resistance. Our goal, and I am not sure what your's is, is to use that information then to develop drugs.

One can find yourself going into a community to gather that kind of information, and the question is asked, will those drugs be made available, and the first point is we do not even know if there is going to be a drug. Second off, the probability is that if we develop something and put it into human beings there is a higher probability of it failing than becoming a drug. And, lastly, it is 15 years off.

**And so what struck me is that, at least in your research, what you looked for effectively was a conferring of indirect benefit to the local community as it were a positive payback to the community here and now in terms of treatment, in terms of care, in terms of training.**

**And then a curious movement takes place in our minds where we start to worry about coercion. As soon as one talks about these indirect benefits, be they money or something other than the drug substance itself, it is coercion potentially. Yet, of course, it seems that a promise of making the drug available could also be a form of coercion.**

**So I am just curious as to how when you are dealing in communities such as all three of you deal with and you are approached by investigators who want to work with it, and there is a low probability of the benefit of the drug getting there, whether this raises the same kind of moral dilemma if there is an alternative benefit that seems to arise in the minds of those of us sitting on the outside looking at it?**

**DR. PLOWE: I had not thought of it in those terms but, you know, coming back to the mefloquine question. Maybe it would be reasonable to test an intervention like that that realistically is unlikely**

to be available to that community in the short-term if in the course of the study you are benefitting the community in other ways.

I mean, most of what we are doing right now is, you know, basic pathophysiological stuff that may or may not ever lead to intervention. The hope is that it will, as with all basic science. So to make it fair to the community we do provide these ancillary benefits not directly related to the research questions we are testing.

DR. SHAPIRO: Thank you.

Larry?

DR. MIIKE: A question for all three of you.

It is clear that in order to do research you either need an established local presence or you build the capacity for it. What is happening to the review process at that same time? Is it left up to ad hoc processes to develop a parallel IRB structure, for example, in these institutions? Or is there any effort -- a planned effort to develop a capacity of the IRB process at the same time that the research capacity is being built?

DR. PLOWE: In my experience, wherever I have worked, there has always been a committee of some sort

that reviews research either at the national level, as it was in Malawi before, or perhaps the institutional level, and then when you come in with an NIH funded project and start developing your site, in order to begin you need to have an SPA.

So you talk to your investigators who then go to the university chancellor or whomever is -- your Ministry of Health, whoever is responsible, and negotiate with them to get the committee constituted in a way that satisfies the OPRR requirements.

So that is essentially the extent of it but it has got to happen at the outset or else you cannot start spending money overseas if you do not have your SPA.

DR. MIIKE: But then you are in a situation where you walk into an environment that already had an established review process. I am more interested in how did it get there and is it by planning or is it just because, oh, we need a review process because we are going to do research and then it goes about -- it gets developed in an ad hoc way?

DR. PLOWE: Maybe I will ask my colleagues to address how it has worked in their settings.

DR. PAPE: In our situation in Haiti it had to be created because there was no institutional IRB

anywhere and, as I mentioned, the National IRB took a long time to create and it is only last year that it has been put in place. Therefore, research projects must be reviewed in that context and IRB are set up to answer specific questions that research projects may have.

DR. MIIKE: But that relates to your question about, you would like to see a percentage of funds or some kind of mechanism to use so that you can develop that capacity rather than leaving it to sort of develop on its own. That was the basis for your recommendation?

DR. PAPE: Yes. Clearly I think that if you really want to have these recommendations implemented there has to be some way to provide support for the local people to implement them. Otherwise, you know, you could be improving consent forms in your mind as much as you want but it will not be done. The best way to do it is to improve the situation at a local level.

DR. SHAPIRO: Thank you.

Ruth, you had a question?

DR. MACKLIN: Yes. I do not recall whether it was when you were discussion Mali or Malawi but at one point you said that the local review process was

inscrutable and that one had to trust the local process, the local researchers and process. Could you just elaborate on that a bit? I mean, what is it that was inscrutable? And here I have in mind Dr. Pape's recommendations that the researchers and that the review bodies communicate with one another and they visit one another and have some kind of communication.

So, I mean, you were there as a researcher. What was inscrutable and could there have been any better communication?

DR. PLOWE: My concern initially was that I did not know if the IRB was really going to review projects or there was going to be a kind of rubber stamp that would do whatever the investigator asked them to do. And over time those concerns were alleviated by the IRB coming back with objections or questions or, you know, in the case of Malawi simply not approving a protocol despite every effort by the investigators to convince them that it was okay to go forth.

But it is simply that -- especially where I do not speak the language I just do not know how it works and if it works the way it is supposed to work. I mean, the only way you can be sure it does is by believing your collaborators when they tell you that

it is.

DR. MACKLIN: You did mention the -- I guess the inscrutability was a function of your not knowing the language basically, in a way.

DR. PLOWE: Well, but I do not go to the meetings either.

DR. MACKLIN: Right.

DR. PLOWE: So I am not observing how it is actually working.

DR. MACKLIN: Did I hear you say that they did not approve one project and, if so, did you know why?

DR. PLOWE: Yes. Actually Grace may know more. This was a -- there is an autopsy study going on to understand why children die of severe malaria. And that actually -- even though it was reviewed in Malawi, it was not reviewed here and did not need an SPA because dead people are not human subjects.

But it was meant to be paired with a clinical study of a drug to treat severe malaria and they kind of went in together at the same time and the Malawian National Committee felt that doing a study where you are testing an intervention for a disease and then doing a study where you benefit -- your study benefits if somebody dies -- was an inherent conflict of

interest and that there might be bias to, you know, not treat people as well or something like that. So they nixed the clinical trial but let the autopsy study go ahead.

DR. SHAPIRO: Thank you.

Trish, then Alex, then Rhetaugh, and then I think we will take a break.

PROF. BACKLAR: Thank you, Dr. Plowe, for your presentation.

I must say there were parts of it that I thought that we should borrow to use as an exemplar for our report on research in this country, not just in international and under developed countries.

There was something -- it is -- I have a question that is in two parts. One thing that you and Dr. Malenga both mentioned was that clinicians who work in the country are -- benefit more by working in the research protocols because it is higher paid.

And I am wondering if that causes some kind of tension from drawing clinicians to work in research protocols and how their care -- their care -- ordinary care would proceed in such cases. How many clinicians, for instance, would there be available in a small country with -- as you describe it?

DR. PLOWE: Why don't I answer for Mali and

then maybe Dr. Malenga wants to make a comment about Malawi.

PROF. BACKLAR: Yes.

DR. PLOWE: In Mali they have had a medical school for 30 years and they turn out far more graduates than they can find work for. So there is a huge surplus of trained physicians. So the fact that we are able to employ some of them as physicians instead of, you know, restaurant owners is a good thing for the country.

PROF. BACKLAR: Okay.

DR. MALENGA: Well, Malawi is obviously a younger institution and the problem is certainly there but probably not just for physicians. This applies to nursing staff as well.

PROF. BACKLAR: Right.

DR. MALENGA: I mean, at Queen Elizabeth Central hospital now you have nurses resigning or retiring prematurely from government service, you know, to join the university project.

The nice thing, though, about it all is that, okay, you do not lose the nurses from service. They are just transferring from one unit to the other, but within the same hospital, so all in all I suppose you could say there is no actual loss as such but

**certainly the move is there from, you know, government to university institution both for clinicians as well as nursing staff, and probably more for nursing staff in terms of Queen Elizabeth Center hospital, at the moment, given the smaller numbers of the others.**

**PROF. BACKLAR: The other part of the question is for all three of you, it is that I noticed, other than Dr. Pape, there was really no question or you did not bring up any of the issues to do with assessing people's capacity to be in a protocol.**

**And, Dr. Pape, you referred to this questionnaire that you had, and I am not certain that that actually was for an assessment of capacity because you said that if somebody sort of failed it the first time they could retake it. And I would be a little suspicious of people retaking something that was assessing their capacity in that way of understanding something about the protocol.**

**DR. PAPE: We feel that there are questions that are so important, because in the questionnaire we have focused on the most important ethical concerns that a volunteer may have. Therefore, we have included questions that we feel are essential for them to answer. So if a volunteer missed one question**

because before he gets to pass that test he has three counselling sessions at different time periods that deal with different questions.

So it is quite possible that he may have misunderstood one or two of those questions and, therefore, we feel that if he is willing to participate he should be given a chance because this is a process that goes before he provides informed consent. We feel that he should fully understand what he gets involved in before he signs or provides the informed consent.

So we do not see any problem with him being re-counselled about one or two questions that he may have had difficulties with.

DR. PLOWE: And I think this is another example of something that may make a lot of sense in one setting and one kind of study and not make any sense at all in another setting and another kind of study.

You know, at the Center for Vaccine Development for our domestic vaccine trials, detailed testing is always done on all volunteers and. In fact, for malaria vaccine trials they have to know the malaria life cycle better than many medical students do and pass this test to be in the study.

But to then go out into a rural village in Africa and try and, you know, administer a test just strikes me as something that would be pretty tough to execute.

DR. SHAPIRO: Thank you.

Alex?

PROF. CAPRON: Just a comment on the last.

The notion of trying to ascertain that volunteers are informed decision makers independent of a consent process strikes me as something that is very relevant and I am glad to know that you follow it in a domestic as well as in an international setting, and I think it should get more attention from us.

What I wanted to do was reflect on what I had heard from all three of you and ask if you can help with a problem that I am left with.

I am very sympathetic on a case by case basis in hearing the kind of trust relationships that you have built up and your wish that you had even better avenues of developing that trust between IRBs at institutions in the United States and in international projects, and between federal regulators. As Dr. Plowe suggested, it would be good to deal with a well-resourced and experienced office.

The problem I have is in knowing how to

**implement that when any particular research project in Malawi or Mali or Haiti may be connected to two or three different institutions in the United States, and additional institutions in France or in Canada, or in Great Britain.**

**And then finally, the question of whether in that wish for this well experienced office, what one is wishing for are people who will basically trust you, people who will ask you some reasonable questions but who will in their own judgment size you up, size up the project, and so forth.**

**And then I am left with the question that Ruth put to you, Dr. Plowe, which is if the process locally is somewhat inscrutable to you, then in your expectation that the IRB office or the OPRR office or whatever it would be in the United States will go along with the process of local approval, you are saying, in effect, that they should trust you to have basically picked a group of collaborators locally who you can rely on to have gone through a good local process, and in any particular instance once you get to know all of those steps you can feel confident.**

**I fully believe that the situations that you are describing would meet the kind of scrutiny that we would like to have applied but in developing a system**

how do you expect -- how would you help us to describe such a system in a way which the American people, to the extent that they want to rely on these regulations and guidelines to ensure that support from the United States is not going to projects, which when brought out into the light of day will cause people to say, "How did that ever get approved?"

I mean, how can you be doing that? And look to the office and say, "How did you ever allow that to go on?"

Is there any regularized mechanism that would cover all this, because the idea of all the different IRBs traveling around the world, interacting with all of their counterparts elsewhere. And the idea that someone will have an adequate judgment in a well-resourced OPRR office somewhere that -- I am just not sure that that is going to play out and I wonder if you have any way of helping me with what I see as a problem in wanting to follow the lead that you have suggested but being skeptical as to whether or not as a generalized matter applicable to researchers, not only of your quality but perhaps people who are less scrupulous, we could feel equal assurance that it is going to work.

DR. PLOWE: I do not think I meant to imply

that what I was hoping for would be an OPRR that would just sort of take me at my word and trust me that, you know, we are doing things okay. I think what I was hoping for was more flexibility and then I come back to the SPA example.

So that if it does not make sense to have four different SPA documents come into OPRR for the same protocol to have the flexibility to say, okay, we have got the SPA for this protocol, we do not need another one from this university, and because of this, this grant -- I mean, that is the kind of judgment and case by case decision that would be nice to have the flexibility to make. And I guess the experience and confidence to make judgment calls like that like many government offices do.

I think -- that is -- it is a long detailed and tough question. I think I would have to sit down and think about how you could actually formulate an office that would function the way that we are envisioning but it certainly was not that, you know, just leave us alone, let us do our job, and take our word for it that the process is okay, but to have a standard process.

And again coming back to the example of maybe if you have a site overseas where they are doing

federally funded research, to have an annual certification of that IRB that would say that they are properly constituted and, therefore, qualified to approve this and any other projects that come in, in the next 12 months, that have been approved by the U.S. IRBs.

Because the OPRR does not review the protocol. They simply look at the constitution of the IRB and if it does not have the right members then that is all there is to it.

So that this kind of rigorous standardized process is not particularly meaningful in terms of really reviewing what is going on. All it does is make sure you have got one of this kind of person and one of that kind of person on the IRB.

DR. PAPE: Well, I view things very simply instead of looking at them in a complex way. I see that there are really two concerns. The first one is informed consent. Are we really sure that the person who is going to participate in that study fully understands the advantages, consequences, et cetera, et cetera.

And you can write the longest consent form in the world, it is not going to ensure that for this country or any other country. So this is why I think

that having a test, and a test we have done it for the rural areas. It has to be -- the questionnaire has to be as complex as the study is. If it is a simple study it could be five or six questions. So this is the first one.

The second one is who is going to make sure that there is compliance with those regulations? You are here and you have no way of monitoring something in Haiti or in Mali or in Malawi. So you have to trust your counterpart in that country.

And the best way to do that is to make sure that they are trained, that they obey by certain rules, and that you work with them and that there is a working relationship. The same way there is a relationship between the researcher and the potential volunteer, that the two IRBs know what each other is doing.

So to me I think that eventually we will get there but I see it very simply and I think it will work this way.

DR. SHAPIRO: Thank you very much.

The last question, Rhetaugh?

DR. DUMAS: I would like to add my appreciation to all of you for coming and sharing such an enlightening presentation with us.

I have concerns about research resources which is a common theme for all of you. And I am wondering whether it makes any difference whether there is joint sponsorship with the country -- countries that are participating or not.

And then I had another -- I have another question. In cases where there are several United States institutions doing research in a particular locale, is there collaboration among those investigators and those institutions here?

Do you want to start with the one about research resources? Does it make a difference whether or not there is joint sponsorship as to whether or not you have the resources that you need to have and whether there is resources available for -- to help the local people?

DR. PAPE: Well, we have had various projects supported by various universities. It is true that it brings more resources but it makes the ethical process much more complex because you have to submit to different committees and, you know, they have different rules and regulations, et cetera. But it is true that it brings more expertise and more possibility for training in particular.

DR. PLOWE: It is hard for me to imagine in

Mali, which is one of the five poorest countries in the world, convincing the government that they should spend their incredibly limited resources on research in kind of cosponsorship with the NIH given that perception of how kind of rich we are compared to the hospital and the other government institutions.

But having said that, in a sense we are cosponsoring in terms of, you know, them deciding that they would renovate the hospital where we are working, in part, because it is becoming a research center.

And, similarly, this is something that Professor Doumbo could have articulated but they are working directly with the National Malaria Control Program so the National Malaria Control Program pays for the bed net study or bed net interventions and that sort of thing with a lot of input from applied research and provision of expertise. So there is partnership but certainly not really sponsorship -- local sponsorship of the research projects themselves.

DR. SHAPIRO: Well, let me thank all our panelists very much for being here today and echo the many sentiments of my colleagues here of our gratitude to you for being here and, needless to say, for the work you have done over the years in the field.

We will break now and reassemble about an

**hour from now, which will be a quarter after 1:00. I would ask commission members to really try to be back because that is when our public comment session is and I think it is important for us to be here for that public comment.**

**There should be -- we only have one person signed up right now. There may be others at that time but I really ask you all to be back here one hour from now.**

**Thank you again very much.**

**(Whereupon, at 12:15 p.m., a luncheon break was taken.)**

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

**PUBLIC COMMENT**

**DR. SHAPIRO: Colleagues, if we could reassemble and begin our meeting this afternoon.**

**Is Mr. Corey Kinna, K-i-n-n-a, here?**

**Mr. Kinna had signed up. From the Thurmont United Methodist Church had signed up and now is our public comment period. So I just want to make sure that we make provision if he is here.**

**Is there anyone else here who would like to address the commission at this time?**

**All right. If not, we will move on with our agenda.**

**Before we turn to -- let's -- our discussion this afternoon, essentially of aspects of the International Research Project, Chapters 3 and 4, let me turn to Alex, who has a -- I think a motion or a request that he would like to make.**

**MOTION BY MR. CAPRON**

**PROF. CAPRON: Following along our discussion this morning growing out of the charter provision in the 1999 version of the NBAC charter that we specifically identify the federal department, agency or other entity to which particular recommendations are directed and request a response within 180 days of**

**the recommendation, and given the report that we have had that our report on research involving human biological materials has not generated any apparent response or action;**

**I move that we request that the Department of Health and Human Services, the Department of Energy, the Department of Defense, the Department of Veterans Affairs, the National Aeronautics and Space Administration, the Department of -- excuse me. The -- I have lost my list for a second -- the National Science Foundation respond to our report and recommendations.**

**And I looked through the report -- that is the end of the motion. If I may offer a comment on it.**

**Some of our recommendations, of course, are addressed particularly to IRBs and it was encouraging to hear from our Executive Director that he has had responses from a number of IRBs indicating how helpful the report has been and they are taking steps to implement it in their local institutions.**

**It seemed to me, however, that the thrust of what we were doing vis-a-vis the federal regulations was to request a clarification from OPRR and the other federal agencies that this -- that these**

interpretations of the obligations under the regulations were consistent with our conclusions.

There is also, of course, the recommendation number 23 urging that medical privacy laws under state and federal legislation and regulations seek to protect patient confidentiality in a way that will insure appropriate access to biological materials and have them treated in a way which is comparable to the development of protection for other medical records.

It seemed to me that with the current process which the Department of Health and Human Services is now engaged around its own set of privacy protection rules, this is a particularly appropriate time and if there is going to be recommendations for further legislation in response to that that we would ask in particular that the federal position, whether spearheaded by the Department of Health and Human Services or by the President's Science and Technology Council, respond to that recommendation as well.

DR. SHAPIRO: Thank you and it seems like an entirely appropriate thing for us to be doing at this stage.

Is there any objection to proceeding in that fashion?

If not, we will do so. Thank you very much

for raising the issue in that fashion.

Okay. Let's now return to our agenda, which deals now -- we will turn -- I think, Ruth, we want to turn first to chapter 4 but let me turn the chair over to you for now.

**ETHICAL ISSUES IN INTERNATIONAL RESEARCH (Continued)**

**DISCUSSION WITH COMMISSIONERS**

**RUTH MACKLIN, Ph.D., ALICE PAGE, J.D., M.P.H.**

**OBLIGATIONS TO SUBJECTS, COMMUNITIES, AND COUNTRIES IN WHICH RESEARCH IS CONDUCTED (DRAFT OF CHAPTER 4)**

DR. MACKLIN: Okay. Chapter 4 is at tab -- it is hard to remember what these chapters are -- tab 2C. And, again, I will just remind you of what I said before.

It is only 12 pages here and let me indicate what is coming.

Alice Page has been working very hard and very successfully on a long paper that excerpts of which will become part of this.

That is, remember at the last meeting we heard a variety of testimonies about prior agreements, what agreements have been forged with WHO, what its practices are in this regard, and Alice has been using

those presentations and additional documents that we have received from the presenters in addition to her having conducted a wealth of research.

So the way this chapter will be fleshed out in addition to these 12 pages will be largely, if not entirely, taken from that paper. It is not quite ready yet so we did not want to put it into the chapter or the briefing book in an unfinished form.

What you do have, though, are our -- well, tentative subject to your modifications and approval, some recommendations with justification.

The way we thought it might be most useful to discuss this and the next -- the other chapter, which precedes it in the order -- is to pose the following questions:

What, if anything, is missing? Now with the understanding that we have the part -- Alice's part that we know is missing that I have now just indicated will be part of this chapter.

What -- from the factual information provided and the justifications for the recommendations, what is missing that ought to be in here?

What is in here that is either superfluous, gratuitous or in some way ought not be in here?

And what suggestions do you have for

**additions, modifications, alterations or possibly violent disagreement with what is here?**

**So those -- that is the set of questions that we would like you to address in the discussion of this chapter.**

**DR. SHAPIRO: Okay. Now just for point of clarification before I turn to members of the commission, you are -- those questions apply to any and all material in the chapter?**

**DR. MACKLIN: Yes.**

**DR. SHAPIRO: Okay. Thank you very much.**

**Alta, and then Alex.**

**PROF. CHARO: I am going to take up your offer with regard to the first category, which is things that might be added that are not yet present.**

**Let me just kind of go through my list very quickly here because it is just reflected on my notes.**

**In the discussion about obligations once a therapy has been shown -- once an investigational drug or intervention is shown to work was very helpful but there was never a point at which one contemplated that it might not work and that there might be obligations to populations when a study has been shown -- has shown something is noneffective -- ineffective. And that was something that I thought could be added.**

When it came to obligations with regard to -- let's see, it is on page 6 here -- whether or not there is an obligation to continue to provide staffing and equipment and such, I did want to know that at least in my very limited experience working in resource poor countries, often it is difficult to maintain relationships with the suppliers for parts and equipment and drug supplies. And even just leaving *in situ* some kind of ties or facilitation of ties to those suppliers might help.

DR. MACKLIN: Excuse me. Can I just ask a --

PROF. CHARO: Sure.

DR. MACKLIN: Are you saying that we should acknowledge the point that it is difficult to maintain ties and then what is the positive -- the recommendation then?

PROF. CHARO: That it might be possible to help facilitate some ongoing relationship with the suppliers. Often the sponsoring researchers are the ones who are providing a fair amount of equipment and are bringing it in with them. They have their own independent relationships with suppliers, including things as simple as spare parts.

And to leave in place some kind of relationship might make it possible for the host

country investigators to -- and clinical physicians to take fullest possible advantage of what is left in place.

More globally, I found as I was going through the chapter that I began to mentally test the discussion and the recommendations against the situation domestically in the United States and realized I would have to go through kind of point by point and try to identify where these debates do or do not mirror the domestic debates and where the recommendations are proposing obligations that do not necessarily apply when we have rules here in the United States. And if it were not too burdensome to ask that you go back through it and highlight those very factors.

So where the debates are mirrored but the recommendations differ from the domestic policy, it would be valuable to explain why.

And I think that one can on occasion say that the obligations should be different and it leads me to the last thing I was going to mention.

Although this chapter is discussing simultaneously research that is financed by the Federal Government through grants and also private sector research performed by those who are subject to

**federal regulations for other reasons, it did seem to me that at least when you are talking about federally financed research that there is an argument to be made that there is an enhanced obligation to human subjects.**

**It is an argument. I am not saying it is true. But an enhanced obligation because it is particularly egregious to see governments abuse citizens, whether of their own countries or others, and it is one of the reasons why some of the classic horror stories that we recite are so horrible. It is that it is not individuals who fell down on the job. It is whole governmental institutions that are devoted to a certain level of responsibility that fell down on the job.**

**And to that extent it may provide a justification for some recommendations where there is an enhanced obligation to provide, for example, ongoing services, wrap around care, et cetera, that might not be present in all circumstances, even domestically.**

**And that kind of concludes the stuff that I thought was missing, not missing so much as could be valuably added.**

**By way of closing I will also note that I**

assume that there is going to be perhaps some further discussion about the possibility of trying to be more specific on the notion of “reasonably available” since after the rehearsal of the difficulties with it we wind up using the same language in our recommendation.

I am hoping we will have an opportunity here to see if we can possibly come up with anything more specific than the very language that people are still debating.

DR. SHAPIRO: Thank you.

Let me suggest the mode of operating here this afternoon because I think a lot of us have some issues.

Why don't we as we go around talking about it, why doesn't each person pick out to begin with their first one or two things they think are most important, and then we will come back around --

PROF. CHARO: Sorry.

DR. SHAPIRO: -- with all due respect to Alta, and then we will come back around and there will be plenty of time for everybody to participate.

Alex?

PROF. CAPRON: Well, taking that advice I want to start by thanking Alice and Ruth. The whole

mode of proceeding on this report seems to me, given the difficulty of the subject, to offer us the best chance of coming up with something good by forcing us to look at what a chapter might look like earlier in the process than we have some other times where we have had these very long discussions and it has been months or years before we have had things on paper.

This has been very helpful.

As to the present draft what that did to me, for me, was to crystallize the central problem and following Harold's suggestion I want to just raise one central problem. I cannot tell what we are doing here as an ethical exercise.

Are we talking about something which we believe is ethically obligatory or are we talking about a set of aspirations for individuals who want to behave in a virtuous fashion?

The reason I have -- it reads as though it is the former as though these are ethical conclusions that are what ought to happen.

The difficulty I have with that, and it is partly to follow along Alta's strategy of saying what is different about this situation than if this were research occurring in the United States is that after the first recommendation, which has to do with

**disclosing what is up to people, the general sense is you have to do all these things sort of regardless of what you agreed.**

**That is to say -- put it a different way -- that an agreement that did not promise to provide reasonable after care and do all these different kinds of things where the only issues that we are grappling with is just to how many people. Is it to the entire continent? To a country? To a community? To the individuals who are in the research project?**

**I do not know where that comes from in the end. In other words, the statement that it would -- is this a statement that it would be unethical for a researcher -- with full disclosure of what is up -- to come in and say:**

**"I am going to do a research project in which I am looking at X. At the end of that research project I hope I have learned something. This is not research which is directly intended to benefit you. You might get some benefit from it but I am not going to promise you anything when I am done. That is the way I behave at home. I recruit a bunch of subjects. I do some research. I do not have any further obligation to them unless I have injured them in the process. I may have some, but even there I can agree**

with them that I am not going to provide them, that they are on their own, whatever health care they are entitled to under insurance or government programs or whatever, that is it. I am permitted to do that and that is what I am going to do here."

We seem to say that once you cross international boundaries and do that it would be wrong to have such an agreement, that the sponsor should not do it, the IRB should not allow it. I want to know from where we get that.

Is it the notion that people are in such a constrained situation that their own willingness to agree to such terms is unconscionable, that we therefore should say that they have to be protected from their own impulse to do that? In other words, the desire to be -- to get anything out of the research projects.

We heard today as we have heard before that just being in a research project offers so many benefits to people that they find it attractive. So this is -- to me this is the central issue and it lies behind all the more technical questions that we have to resolve as to which I will get back in the queue to come on my particular comments on them but I hope that we as a commission before we start talking about

**additional things can talk about that because I still feel unresolved but I am very grateful.**

**This sounds as though this is a global criticism of the chapter but I am very grateful that in reading through something which was written, "Alex, some day in the not too distant future you will be asked to sign this," that I found myself saying, "Now, how would I defend to a skeptic the conclusions here and would I be defending them on the basis that this is really ethically obligatory because it would be wrong to allow anyone to agree to other terms?"**

**DR. SHAPIRO: Ruth, you may want to respond to that now or not.**

**PROF. CAPRON: And this is not -- but my point, Harold, is this is not just addressed to Ruth.**

**DR. SHAPIRO: Right, I understand.**

**PROF. CAPRON: This is really to all of us.**

**DR. SHAPIRO: But I want to add something to that, whether you are going to respond now or not. And that is one of the -- I think it is either the same or similar -- or associated notion that Alex raised.**

**As I read through this chapter and thought about justice as reciprocity, which is a principle that comes in here, it seemed to focus on one level of**

compensation, one type of compensation, namely compensation providing care, for example. And that is certainly a perfectly legitimate form of compensation but I could think of many other forms of compensation.

And I was uncertain really in that same spirit that you raised that what was so special about the form of compensation that was being focused on here. That is just a subset of the question that you are asking.

And, Ruth, I do not want to ask you to respond now if you want to just hear more questions but I want to give you an opportunity if you would like, and I do not mean to hold you --

DR. MACKLIN: What I would like to do is give a very brief response because it is going to invite more discussion and more debate and the need for more clarification, so let me be very brief just so we do not lose this thread and, of course, we have to come back to it and provide more of a justification.

One -- the -- one question that Alex posed in this forum is what is different about doing research in a resource poor country than doing it here and if the researcher says, "Why should I do it any differently there from doing it here," goes back to two premises.

**The response has to go back to two premises. The first is that the -- and again we find this -- you may want to reject this principle but it is in the -- a lot of international guidelines and that is that research that is conducted anywhere should have some promise of eventual benefit to the people who -- on whom the research is conducted. Otherwise it could be a form of exploitation.**

**Now when you say, "Well, they have agreed to it," I mean it -- that -- the analogy there is all you would need for the ethics of research in this country would be people's informed consent to be participants. Whatever the risks and benefits, whatever their chance of getting any other benefit, whatever else may follow. But we know there are more obligations that surround research, in general, than simply the consent.**

**So the -- starting with at least one premise that research must be related to the health needs of the country and may have at least a prospect of benefitting them, since these countries are so poor they are never going to be able to afford it unless some of these are undertaken as obligations. That is one picture.**

**Now Len Glantz said last week and maybe --**

last month and maybe we have to get some documentation for this, is he cannot think of any example of research that is conducted in this country where the class of people who are -- from whom the research subjects are drawn do not receive eventual benefit from it.

Whether it is in the form of insurance, direct insurance -- I mean, this is separate from people's access to health care in a way but whether it is from private insurance, public insurance, Medicaid or Medicare, this country is wealthy enough, there are insurance schemes in place, and even though there are different levels and layers of access to different kinds of treatment by and large there is not an entire class of people who are experimental subjects who never receive -- as a class of people who never receive any of the benefits and could never possibly either afford them or have them provided by the government or by insurers.

Now that is exactly the difference with these other countries because the entire population except for the very wealthy cannot afford it, there is no insurance, there are -- they use the public health system and the public health system in those countries cannot afford the products that are the ones that are

being tested.

So one has to, I suppose -- and maybe we need more of this -- specify what are the differences between doing research in a wealthy country involving the population where there is access to health care, although it is far from perfect, and the differences in those countries where there is practically no access to any of these products?

DR. SHAPIRO: Okay. There are a lot of people that want to speak but I am going to even go out of order since Eric seems so desperately anxious to ask a question.

DR. CASSELL: Anxious. Anxiety, right.

DR. SHAPIRO: Anxiety. I am working as a physician here now.

DR. CASSELL: Ruth, that is a good argument that people should consider when they come to making the rules for their country and agreeing to things with the sponsor but it does not address Alex's question, and that question is more central. What are we doing?

Let's suppose that we took recommendations. We now say, "If you do research this is the way you must do it." In which case we are back to a kind of understanding that would neglect what we heard this

morning. For example, the very fact that we are talking about the researchers and sponsors leaves somebody out.

We have already heard this morning and we already began to know last night if we had not known before that there is always the host involved and the host may be neither the researcher nor the sponsor, and that the host has a say in these matters.

Now have recommendations -- that is what we are -- I mean, we have recommendations about it. There are things we want the host to pay attention to that this country has to offer and so forth.

So I think we have to answer Alex's first question first before we get into the issues of, well, what is addressed in that recommendation, which I happen to disagree with but that is not the point. The point is the first thing.

DR. SHAPIRO: Okay. Bernie?

Eric, do you want to put your -- thank you.

You are next, Jim.

DR. LO: To follow up on Alex's question, which I think really is an important point, I think we are talking about different sorts of things that researchers and sponsors and hosts might owe the subjects. On the one hand we are talking about

clinical care that is not otherwise available and you have to provide because otherwise it is kind of coercive to offer it only in a research context and then to cut it off.

It seems to me that could very well be different than what happens after the trial and down the road. Will the drug become available? And I am not sure we should be sweeping it all together and saying because we owe something based on these abstract notions of justice, you owe them this, this and this in these different sort of situations.

I would be much happier if we sort of tried to be much more specific about saying why -- what are the reasons we think that in the course immediately after the trial or if someone -- like the case we heard about this morning of the family did not want to be in the trial but could not get care for Wabu any other way that you should provide even nonparticpants in the community basic sort of care that everyone agrees is effective.

That seems to me -- the reasons you would want to do that are somewhat different than the reasons you might want to say you have an obligation to try and negotiate access to a drug if proven effective.

**Given all the things we heard last meeting about lots of different ways to do it, lots of uncertainties, you know, if you negotiate a discount or a licensing agreement you still do not guarantee access because --**

**[Phone ringing.]**

**DR. LO: Who wins the lottery this time?**

**DR. SHAPIRO: They got another number, Eric.**

**(Laughter.)**

**PROF. CAPRON: That is because he turned his other one off.**

**DR. SHAPIRO: Yes, that is right.**

**DR. LO: It is for you, Eric.**

**DR. SHAPIRO: Why don't we continue, Bernie?**

**DR. LO: So I think that, you know, there is -- there is some things that you could say to an investigator you really have control over and it seems to me there are other things having to do with the long-term accessibility to the drug that you can only ask them to do so much.**

**And, you know, the problem with something like reasonable accessibility is that I do not know what that means when it comes to an actual situation and we heard a lot of things last time about different strategies that seem to be a promise in different**

clinical situations, different countries, different diseases.

And I just think that we run the risk of being very sweeping here and sort of not being sensitive to the real differences in the types of research in the countries we are dealing with.

DR. SHAPIRO: Thank you.

Jim?

DR. CHILDRESS: In some ways relating to the point that Alex made and the invitation he issued to address some of the conceptual normative issues at work in this chapter, I like the general direction very much. Let me draw a distinction -- not working with the language of ideal versus obligation but rather say between an obligation to someone and an obligation to do X, Y or Z.

I think one of the things I like about this chapter and the direction it is going is to say that there is an obligation, a continuing one, to subjects and others as a result of this principle of reciprocity or justice reciprocity that operates.

But then much of the rest of the chapter tries to go out specifying what is entailed by that obligation by talking about obligations to do X, Y or Z.

**Now I guess the major question I would have at that point is how we decide that something really is a specific obligation to do X or Y versus what is left up for negotiation and it seems to me this is the kind of tension that is present in the chapter.**

**So how long the obligation extends is a matter of negotiation. Whether it includes family members as well as the patient/subject is a matter of negotiation and I guess we need something clear if we are going to use -- whether we use the ideal versus obligation or obligation to versus obligation to do X, Y or Z, whatever framework we use here I think we are going to need to be a bit clearer about how that works through and then what really is left up for negotiation.**

**And so I would raise then two possible matters that could be included here in terms of continuing obligation just to sort of challenge us and the writers for the next draft -- and by the way I echo Alex's strong praise for the work that has been provided.**

**Dr. Pape said this morning that there is an obligation to treat diseases diagnosed during the study. Now we did not come back and talk about that but that was one of -- that was on his slide and it**

was something that was stated as an obligation to do.

Is that the sort of thing that there is a continuing obligation? Diagnosis of a particular disease during the study and what are the obligations of the researcher/clinicians in that regard?

And then -- and one that raises serious questions in our own context, what is the obligation to treat research related injuries that persist past the study, disability, for example.

And so those are some of the -- two -- at least two examples of something we might consider in terms of the obligations that might continue after the study.

DR. SHAPIRO: Thank you.

Steve?

MR. HOLTZMAN: I think this follows on Jim's, goes to Alex's, as well as your comment, Harold, about alternative forms of compensation, which is something I was trying to raise this morning in the context of particularly research where there is not a drug article, and one of my comments on this, is this specifically about drug trials or is it about research per se?

Is it about human subjects research per se? Is it about in developing nations or in all nations,

**which goes to your question about the ability to consent?**

**With Jim I would not phrase it so much are we being normative obligatory versus hortatory. I would say we probably could all agree with Ruth's observation that it is obligatory not to be exploitative. One ought not exploit people. But then the question is, in any given particular case is it exploitation. That is another way to phrase it.**

**And we seem to be pushed in these recommendations and in the literature that has evolved over the years to there having to be an intrinsic relationship between the research and the outcome of the research or the benefit.**

**And I think the question is does that necessarily have to be the case? Is it exploitative? Is it coercive to offer an alternative benefit in lieu of the access, say, to the drug?**

**And I think that is what we are getting at and it also, therefore, comes to the issue of the accessibility -- how you are defining the class of people and what does it mean for a benefit to be available or a different kind of benefit, and that may be distinct among how you are defining that class of people.**

**Ruth's point was, well, if I define the class as the U.S.A. citizens, all right, it is generally available to them in some sense, right. If my study is of hypertension in Blacks where most of them will, as it turns out, not have access to the benefit, or if it is of a drug which is a lifestyle drug where it will not, in fact, be compensated for by insurance, all right, the test subjects will not as a class, in general, get it.**

**So I think that there is a couple of different questions there about the overall conceptual structure of what constitutes exploitation, which I think again we all would agree that there should not be exploitation.**

**DR. SHAPIRO: Ruth?**

**DR. MACKLIN: Steve's comment, and I agree with the factual -- the observation of fact -- forces us, again as has been raised frequently here, what are the obligations in this country as well.**

**Now just because we do not do X here does not mean we ought not do X. So it is not going to be an argument that will -- it is not an ethical argument that says we do not do X here when otherwise we might argue we should be doing X here, so why should we do it over there.**

So when we see that kind of situation, and if this is actually an accurate picture of the study of hypertension in African Americans who then do not have access to it, then that is an example.

I do not know if I would call it exploitation. Not every wrong is exploitation, but it is clearly an example of an injustice in studying something, knowing that there is a remedy, if not a cure at least something that could be beneficial and not providing it. So it is a good example, but it may do the opposite of what you are implying.

MR. HOLTZMAN: No, I did not mean to imply the is and ought, what is here versus -- because I think it drives you to ask some more fundamental questions about, for example, the trade off.

I mean, why is it exploitation if someone comes to me and says, "You are never going to have access to this drug but we want you to participate in this study and in exchange for that we are going to build a manufacturing plant in your community that will have jobs available to people."

Why is it that we make this intrinsic relationship between the benefit and the participation? And there is a -- which you do. It is a guiding assumption here and Harold has raised that

question. All right.

And I think what -- and Alex's reflection is the fact that we do not see that necessary connection in this country. We seem to be calling for it elsewhere and it really should drive you back to the question is that the right connection in the first place.

DR. SHAPIRO: Okay. A lot of people who want to speak.

Alta?

PROF. CHARO: I would like to add another factor that may or may not fit comfortably within a discussion that calls itself ethics and that is the issue of international relations.

The reason why research -- medical research particularly with human beings, has been singled out over the years as being so problematic is because there is an emotional dynamic at the center of it. Medical personnel are perceived as being people who are caring for you and suddenly in research they are not necessarily caring for you as their top priority.

So that a relationship that is built on a trust is one that is now amenable to a sensation of betrayal. All right. And if you look at the most classic examples of scandals in the U.S. and I think

again of Tuskegee, we see the enhancement of that sense of betrayal when the government is part of it because, of course, the government comes and says we are here to be your advocate, your protector.

And we have seen around the country now with the scandals over police procedural problems in Philly and Los Angeles and others, the difficulty that is created when the people who are supposed to be your protectors turn out not to be your protectors and, indeed, are the source of your distress. Where do you go?

We do not expect that every individual in the world will treat us well but we do expect ideally that the institutions and the professionals that are set up to care for us will, in fact, respond with care.

So when you have this nexus of government and doctors I think you create a situation that goes beyond the usual rules about rational actors making autonomous choices because there is an emotional dynamic that cannot be escaped.

Now when you move it to the international level I think speaking politically we have got a question before us.

If the United States Government wants to present itself to the rest of the world and, in

particular, to the areas of the world that are still resource poor, in the kind of benign countenance with which government presents itself domestically to its citizens here and doctors present themselves to patients here, right, if it wants to be perceived as benevolent and benign it has to take on the obligation to avoid creation of distress, even distress that might be justified by autonomous rational choices under libertarian theories because the creation of that distress under whatever circumstance will feel like a betrayal.

If you want the trust you have to accept the enhanced obligation in order to avoid creating a sense of betrayal.

We do not have to take on the task of wanting to be viewed as benevolent and benign, but I think that if you look across the health related programs that the U.S. has embarked upon most of them really do have that as their goal. Certainly some of them are politically oriented towards providing assistance for certain countries for reasons having nothing to do with health.

Certainly those of us that have worked a little bit with AID are familiar with unfortunate examples in the past of the intertwining of the health

care programs with other kinds of national security concerns. I am not naive.

But most of the programs really are created by and implemented by people who are genuinely committed to providing assistance from the most benevolent of positions. And I think that very decision creates an enhanced obligation that you may not have realized you take upon yourself because you are inviting trust, and people then are at risk of feeling betrayed.

I do not know that that is an ethics argument, Alex, but it certainly is part of the reason why I have been more cautious in this area than I am in others and why I think that, in fact, in the domestic area I have been as cautious as I have in the context of other reports dealing with vulnerable populations.

DR. SHAPIRO: Thank you.

Rhetaugh?

DR. DUMAS: Alta's comments have helped me a lot because I have been really torn in relation to this issue and hearing that comment it makes a lot more sense, the obligations, than they did previously.

So thank you, Alta. I will continue to think about it but that makes a lot of sense to me.

**DR. SHAPIRO: Larry?**

**DR. MIIKE: I think I will talk a little bit longer than I usually do, but the question about what are we trying to do in this study here. We have already discussed and I think we all agree that, sure, we are going to treat overseas differently than domestic. Why are we sitting here otherwise?**

**But I think our most -- our difficulty is going to be what do we expect out of this chapter, out of the direction that we are going, and what do we expect in terms of the consequences of what we then propose.**

**I think as in all our other studies our greatest difficulty is going to be between what I would characterize as the generalists among us versus the specific -- whatever. You know what I mean. The very detailed people among us.**

**And I think that is going to be particularly important this time around because I think that the best that we can expect from reports such as our's, where we can be characterized as well meaning idealists, is that we set a direction for the ethical principles and which way we want to go in changing the ethics of the research overseas.**

**Because I think if we get too specific in**

what we mean by some of these kinds of things we will be the very ones that researchers and people in these countries are going to say we are being too patronizing. If we get into too much detail over what we mean in any of these specific areas we are going to run into the danger of being well-meaning people but misguided as far as they are concerned.

So I think that the best thing we can hope for is that we enhance the issue about the ethics in terms of the patient side because the researchers can fend for themselves and our charge is really from the research side.

And I think that the best that we can do is to make enough of a forceful and acceptable and reasonable statement so what we suggest is a default position, which is you start from this premise and if you deviate from it you should have very good reasons for doing that, and that would be on a case by case basis.

Whatever we say about there is an obligation, you and I well know that there is no hope that we can say that that is what you have got to do or else there is no such research going on.

So I think it is more a question of if the force of our argument moves people along certain

directions, but then we still have to do that balancing act because I think if we get too specific in too many of these areas then we just face the danger of doing exactly what people do not want us to do and which other people have been criticized for.

DR. SHAPIRO: Thank you.

Arturo?

DR. BRITO: I had several things to say but I am going to just focus on one point here. The general sense I had on this, and I want to thank Alex for summarizing it so eloquently the way he did, some of the feelings I had reading this, but one of the general sense I had while reading this, is it is a little bit on the paternalistic bordering on patronizing.

And -- because a true collaborative process involves at least two parties and here we are talking about a developing country and an industrialized country collaborating on a research project and if at the very onset it is disclosed what it is that will or will not be provided, which may mean absolutely nothing after the research is done, should not that be assuming that there is no human rights violations or international law violations. Should not that be up to the host country and eventually the individuals

from the host country to make that decision?

So we have to be very careful regardless what it is we decide on the specifics, is not to be -- not to write this in a way that is a little bit on the paternalistic side because I think we would get just as much criticism from that end.

DR. SHAPIRO: Ruth?

DR. MACKLIN: Yes. It is dismaying to be called paternalistic but let --

(Laughter.)

DR. MACKLIN: -- let me say this: The problem with preparing a report is that you have to start somewhere and this chapter comes before the next chapter. The next chapter is going to deal with the collaborative process and you are perfectly right -- I mean, I do not question for a moment the importance of a negotiation and a process by which you have equal full collaborators.

What this is meant to -- what this chapter and the question of obligations is meant to address is what do the rich owe the poor. Okay. Now some people say they do not owe them anything. That is the way the world is and it is unfair. Okay. We are trying to make an ethical argument.

Maybe we are not succeeding yet, Alex.

**But we are trying to make an ethical argument that there is an obligation of some sort that the rich owe the poor.**

**Now notice there is no consequence in here. We are saying, what do people owe other people. We are not yet saying or have not said in here, at least, that if you are not prepared to honor these obligations then we, the rich people, will not do the research in your country or that the research ought not be done.**

**So far it is silent on that and I think we have to await the remainder of this chapter where we talk about the negotiation process and what should go on.**

**But I think your point, if this appears paternalistic now, we need to insert a caveat at some point that says that the actual negotiations between the collaborating partners, and what we want to urge is a full collaboration, is something that comes in the next chapter.**

**Now who is doing this collaboration? Quite clearly the Minsters of Health might have something to do with it and as we heard this morning in Dr. Pape's eloquent discussion of how IRBs should be working together and there should not be the imperialism.**

Maybe it is not only paternalism but also imperialism of the U.S. IRB or really the U.S. system saying here is what you have got to stick in the consent form and here is what you have to do.

So we hope to a -- we not only hope to, we intend to address the process of collaboration and the equality of the partners in the next chapter but I take your point, if this now looks like it is saying if we do not -- you are -- we are going -- this is what we think we are going to do and you do not have a chance of saying do the research anyway, even if we do not give you anything in return, but it is well taken.

DR. BRITO: Harold, can I quickly respond? It is not a response to that. I just -- I do not want to seem like an ingrate to Ruth for the amount of work she has put in and I think it is a great -- it is a great help to us to do this all ahead of time so we can look at these issues. And I did not mean to imply that it all seemed paternalistic.

I guess the way I want to say it is that the disclosure -- maybe there can be more focus on the importance of disclosure ahead of time before the research projects began is a better way to put it.

Thank you.

DR. SHAPIRO: Let me just say I have a number

of others who want to speak, Trish, Bernie, Steve and Rhetaugh, all on this, but I think what I have to say now is directly relevant to this.

One of the issues, Ruth, I kept coming back to in my mind as I went through the material here is trying to decide in my own mind whether the obligation I was concerned with arose out of the feeling of, as you said a moment ago, what do the rich owe the poor.

And to me that is a critically important issue, but a separate issue in my own mind because if the rich owe the poor anything there is all kinds of ways to discharge that obligation and we have to be clear what it is we are trying to solve here. That is a general problem of the international distribution of income. Is that a problem we are trying to solve? Or what is it that we are trying to solve? And it just -- it is maybe my own deficiency. I was not able to really straighten that clearly out in my mind.

And then there is -- Alta has raised the issue of there might be foreign policy concerns in here, that is that we might want to project an image abroad of some kind of benevolence or something. I have forgotten.

Excuse me, I have forgotten how you described

it, Alta.

And that is a perfectly legitimate objective, too, but it is yet a separate objective. And I think one of the tricky things here is to keep these parsed out in a way that enables one to know clearly in any particular situation whether you are meeting an objective that is intrinsic in the research project itself, for example, or you are trying to make up for some international distribution problems you do not like, or if you are trying to project a foreign policy stance, all of which are legitimate things to worry about.

But the question will be whether we will want to load them on to this particular subject or not, and I think that is something that is an open issue.

But anyway, Trish?

PROF. BACKLAR: I was struck by a comment that you -- a section on page 5, lines 25 to 27, which actually answer what Arturo is requesting. You say here, in a departure from the way research in developing countries has been carried out in the past, a true partnership should be forged rather than approach in which the industrialized country's sponsors dictate the terms of the research.

I feel almost as if you took that and put

that right very close to the beginning you would start the whole way of looking at this in which when one is looking at one's obligations in a kind of procedural fashion that would give you some help to get it out in a way where you are respecting those host countries and understanding the differences between what we have in this country and what we owe elsewhere.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I want to try and get back to a question you raised, Harold, about what is it we are trying to solve. It gets back to Alex's question and Jim's question about what is the grounds for these obligations.

And it seems to me we have heard things from a number of the physician researchers that really went back to this inability to sort out their role as researcher from their role as physician. And I think we hear over and over again that I would have a lot of trouble doing a study where they were not going to get the contraception for 15 years, they were not going to get the malaria drug for 15 years.

And it seems to me that what is different here from the domestic situation is the relationship between the researcher and the subject. We heard that

many of these researchers feel that if they are truly responsible they do a lot of basic care for their subjects. They are the only source of health care. They feel they must provide it otherwise they are sort of being coercive.

And it seems to me they are feeling -- one of the things I think they are trying to say is that they feel if they have done research, proved it is effective, and then sort of have to pack up and move out and have no way of sort of continuing what they have done, they feel personally that somehow the relationship they formed with their subjects, which is really not quite the scientist-participant relationship, it is more of a doctor-patient relationship, that personal interaction that in their minds at least has created some obligation, whether that is an ethically defensible position or it is just an emotional reaction, I think we need to sort out, but it seems to me that would take us -- steer us away from the income redistribution problems, the sort of political image the country is trying to project, which are all issues that are not just research issues. They are really issues that are much, much broader.

I think another thing I would suggest is that

in trying to sort this out we try and think of case examples. I mean, I take Larry's point that, you know, we cannot get too specific because we would be wrong and people will understandably accuse us of sort of, you know, trying to impose things when they do not fit.

But these -- this chapter is marvelously clear and logical but it seems to me it is lacking sort of the cases, the examples that generate for these researchers, and I would bet for a lot of the subjects and a lot of the people living in a country, a sense of betrayal or lack of trust.

You know, we were in the study, we were not even told it was effective, we found out from reading the New York Times it was effective, and now 15 years later we still do not have the drug, and they are asking us to be in other studies. And that somehow feels like betrayal or mistrust or something.

But I think if we put some examples in we might be able to better capture what it is that sort of generates the sense of obligation and then we can analyze whether it is ethically something we are willing to hang our hats on.

DR. SHAPIRO: Thank you.

Steve?

**MR. HOLTZMAN: If we had written a recommendation that said -- let me find some language -- sponsors and researchers have an obligation to get informed consent from participants, I think we would be very clear we would mean it is obligatory that there be informed consent. Otherwise this research ought not take place, there should not be government sponsorship of it, et cetera, et cetera.**

**So I took this chapter and the recommendations as putting in front of us parameters of that form and the suggestion that international research ought not be undertaken or sponsored by the U.S. government unless the following conditions are met.**

**All right. In other words, justice as reciprocity or whatever you want to call it demands of research the following. Otherwise it ought not be sponsored, and that kind of logic and reasoning might be of the form that Alta introduced.**

**To the extent that that is the way we are going to read it, then in terms of Arturo's point about the negotiation, this defines the frame in which the negotiation takes place. These are not up for grabs. The specific form or for how long you get the drug, et cetera, et cetera. All right.**

So I think that comes back to Alex's point at the beginning, is we need to decide is that what we mean. Are we putting the bar here? All right. And then we can get into other discussions about whether it is for the private sector as well.

I think we are going to have to be very clear then on what kind of human subject research. Is it specifically only drug trials? Are we talking about -- you said rich to the poor. I did not see here where it said to developing nations. You know, is it equally applicable if we are talking about Germany?

We need to get into the cases because a lot of this can make sense if the paradigm case in mind is something like contraception or AIDS drugs in a Third World country.

But if you are talking about things which are not as dire as that where the risk is very, very low, and do we really have the same examples, same thoughts in mind, or were those alternative benefits that can arise. There is a great danger in generalizing from the most dramatic cases.

So I am not saying it is wrong. I think it has been very well done and crystallizing that in front of us, at least for me, is to start to think through the cases.

**DR. SHAPIRO: Yes?**

**DR. MACKLIN: Let me just ask --**

**DR. SHAPIRO: Ruth?**

**DR. MACKLIN: -- about that. It is interesting that the researchers who have come before us -- I mean, we could be talking about epidemiologic research and then there is not any product or there is not anything else to bring.**

**We have to bring bed nets back into this, okay, because that is something, you know -- but what we have heard, I mean the researchers who have presented to us at all of the meetings have been talking about AIDS, malaria and tuberculosis. Now those fall into the examples you just gave. One might -- arguably even more dire than contraceptives.**

**So these are the examples we are hearing and this is a lot of the research that is being conducted. I mean, they are not doing research on cures for the common cold in Malawi.**

**MR. HOLTZMAN: Right. And so the fundamental question I have about this report, which I asked from the beginning, is it about international research, that is any and all research conducted on human subjects sponsored by someone who is labeled U.S. of any nature, or is it about such drugs in**

developing countries, and specifically by the government.

Because if it is the former, all right, what we have heard about represents, I would estimate, less than one percent of the research that goes on in international research in human subjects. Why are we focused on it? What is our report about?

DR. MACKLIN: What is the rest of it? I mean, I do not have a grasp empirically or factually on -- what was the percentage you just gave?

MR. HOLTZMAN: What is the United States Government budget for clinical trials and compare it to the pharmaceutical industry's clinical trial budget? It is minuscule. I mean, I have asked this question a number of times. How many human subjects research -- people are undergoing international -- in an international context research, all right, by the government, by the private sector, what is the proportionality? All right. What are we talking about? What is the subject of this report?

DR. MACKLIN: Let me just ask again. I am not sure -- I mean, you have said two different things. One is the percentage -- the budget and the percentage of the budget that is the government or industry. The other is the type of research. I mean,

**I do not know.**

**Maybe we will get this information but I have no idea what -- what we have heard and what the researchers who -- the people who have come and whom we invited have spoken about is research in these areas of serious problems -- health burdens in theses countries. I really do not know what other research U.S. researchers, be it drug company or NIH, are doing in the other countries.**

**And the conclusions about what you owe people afterwards -- I mean, quite clearly if it is epidemiologic research then there is no product in the lucid sense of product. If it is something else like developing interventions for safer sex, well then there is not a physical product but it is an outcome that presumably should be able to be sustained.**

**DR. SHAPIRO: Rhetaugh?**

**PROF. CAPRON: Wait, wait. Can we get an answer?**

**DR. SHAPIRO: I think that is what Rhetaugh wants to speak to.**

**PROF. CAPRON: Oh.**

**DR. DUMAS: I am not going to comment on the previous question and I did not know whether Alta wanted to answer that question or not about the**

proportion of studies.

PROF. CHARO: I will talk later. I am happy to wait my turn. It is no problem.

DR. DUMAS: Okay. Well, my concern is -- and I think it piggy backs on what Harold said earlier -- that inherent in this report and in our discussions are a number of very critical issues that we all care a great deal about. International relations, the inequitable distribution of wealth and resources, et cetera, et cetera.

The question in my mind is do we expect the research enterprise to address these issues in the international projects, and I think it is unfair to expect that these issues can be successfully dealt with through the research enterprise, and I would think that there is a place for information, knowledge and sensitivity to all of these issues but whether or not the investigators, the collaborators are to be expected to deal in great detail with these issues is something that continues to worry me.

DR. SHAPIRO: Okay.

Jim?

DR. CHILDRESS: I think Steve is right to press the question and I do not think I have an answer to it but I really do think as a group we will have to

**resolve it in terms basically of the responsible agents we are talking about here in the context of international research.**

**But on his point about obligation -- how did you state it? Obligation to get informed consent from subjects or not enroll them or not go forward with the trial. At most even in our own society that is a prima facia obligation because there are lots of ways which we specify it, we get third party permission, when we cannot get consent, we have emergency research, et cetera. So we can always specify it. We also balance it against other kinds of things.**

**So even if we were to set it out as a prima facia obligation in terms of reciprocity, and there are ways in which we would have to work on it a lot more, and that is why I think the starting point here is really great in terms of the notion of reciprocity.**

**But because we start with reciprocity I guess I was surprised when Ruth said what we are really concerned with, in effect, was obligation of the rich to the poor. I do not think so in the context of reciprocity in research as I think this chapter already nicely specifies that in terms of this particular kind of relationship.**

**And then what we also have to do there is to**

take into account the particular contours of that relationship, as Bernie has suggested, because there are certain features of it in particular context that may help us understand what reciprocity involves a lot more than simply thinking about it as an abstract principle.

DR. SHAPIRO: I want to say something but I will not.

Alta, you are next.

PROF. CHARO: I guess this continues the reaction to Steve's comments. You know I appreciate the fact that speaking as a legal matter there is a distinction between the pharmaceutical companies as private sector companies and the U.S. Government, but I think the distinction is not as strong in reality as it might seem according to certain rules and I do not know that I would want to divide the world that cleanly for two reasons.

One, and I will leave -- I mean, certainly Dr. Pape and Dr. Malenga and others can speak to this more authoritatively, I suspect many people who are the subjects of research do not make these distinctions.

So to the extent that a sense of betrayal is considered to be a harm that we take into account, I

do not think it really matters who is the sponsor.

The second is that realistically when it comes to major industries there is a very close working relationship with the government. The pharmaceutical industry ran into difficulties with the South African Government over questions about property rights with regard to AZT. It was not worked out privately.

We found ourselves with Vice President Gore leading up the U.S. delegation to negotiate among parties looking for some kind of solution. In other words, the government became a collaborator in the form of mediation looking for solutions and there was both a carrot and a bit of a stick going on there.

So I think that we have to treat large scale entities that go forth into the world with this degree of close partnership with the U.S. Government as being necessarily subject to the same kinds of concerns we have for formally government sponsored research.

I think the problems that are created when people feel themselves to have been misused, whether or not they technically meet the definition of having been exploited, will be the same and we need to decide really whether or not we care about those problems enough to want to make the burden on the sponsoring

companies and countries substantial when they go in to do research in these areas.

DR. SHAPIRO: Thank you.

Carol?

DR. GREIDER: I wanted to ask Steve a question, which I think there was something that was not quite resolved in the exchange that went on here.

What I heard you saying to Ruth is that in your opinion the kinds of trials that we have been discussing here is only a very small percentage of the kinds of international research that goes on and we should decide at the outset what we are going to cover in this report before we start writing it, and I absolutely agree with that.

And then I think I heard you say that there is a lot of other research that is not covered here. Ruth's response was she has only heard from those people that we have invited but if you only invite certain people you only hear from them.

So I want to give you a chance to follow up because I would like to know what you know and how we might get that information so that we can decide what we are going to cover in the report.

MR. HOLTZMAN: So let me start actually -- if, Alta, you thought I was saying there should be a

distinction between private sector versus nonprivate sector, I was not.

I mean, I have taken as one of the premises of our operation, because I have been hearing it from the beginning of this commission, that we feel that there is an issue that the Common Rule and ethical obligations seem to differentially apply to who is the sponsor. Whereas there is still a human being who is the subject and there is something fundamentally wrong about that.

One of the things that struck me as we embarked upon looking at the question of international research, all right, is that my hunch was that the overwhelming number of subjects exposed to human subjects research in an international context with U.S. sponsorship, all right, that the overwhelming number of those will be as a result of pharmaceutical sponsorship companies so that this was a perfect context to look at that question.

Or that we -- you could not look at this question -- I think Alta made -- it was the elephant with its nose under the tent or I have got the wrong -- camel with the nose or whatever. The elephant in the room that no one is noticing.

So, Ruth, my point about budgets, which is a

way of looking at number of subjects, is just go look at the clinical budgets of the pharmaceutical industry, go look at the clinical budget of the NIH and the entire Federal Government, ask how much is spent on clinical studies off shore.

And my gut says -- and I have asked staff for these numbers -- it pales -- the government's number of subjects that are being exposed to human subjects research outside the U.S. with U.S. sponsorship by the government pales in insignificance.

So what is our report about? Is it international research on human subjects or is it about government sponsored trials of AIDS and TB drugs in Third World countries?

You are going to draw very, very different conclusions because your paradigm cases are going to be very different. We are writing recommendations with the latter in mind and yet they do not say with respect to developing nations where it is a life-saving drug, et cetera, et cetera, we are saying any research sponsor has an obligation that can provide the benefit free of charge to the participants -- to the subjects if they can benefit from it.

That really says that if I sponsor a trial of a cholesterol lowering drug in Germany, all right, I

have to participate -- I have to make sure that I provide the intervention free of charge to the participating subjects if they can benefit from it.

Just we need to be clear what we are writing about.

DR. SHAPIRO: I will have something to say about that in moment and at least give you my opinion about that but let me turn first to Alex and then Diane, and then I have a few comments to make, and then I want to turn back to Ruth and see where she would like to direct our attention herself, but first, Alex.

PROF. CAPRON: I think Steve has been right to emphasize this. I found myself thinking as I was reading these chapters that we needed in the introduction to say that we had begun this examination broadly concerned about difficulties that the U.S. regulatory structure poses for people doing research abroad when they have U.S. affiliations which require them to obey the U.S. regulations because of those affiliations.

And that we had then decided to focus in on the subset of issues that arise most acutely in situations in which the research is taking place in resource poor nations.

**And that is what I had assumed that we had moved to, Steve. Not because in percentage terms it was the most significant, and if we do not differentiate government sponsored and privately sponsored it still is a significant chunk.**

**It is much more than the one percent you talk about even if a lot of research is done with subjects in Western Europe by U.S. based companies or international/multinational companies that have a U.S. aspect to them.**

**It seems to me, Ruth, though, that what I would conclude if I were in your situation having heard this discussion is that we are inclined to talk in terms of obligations or presumptive obligations, not in terms of supererogatory duties that a virtuous government or a virtuous research sponsor or a virtuous researcher would follow.**

**I think that is fair, that most people who have spoken up have said that. We come face to face with this question of paternalism and I think what we have to acknowledge is the IRB system and the Common Rule are paternalistic.**

**They basically do say it is not legitimate in regulation -- in research that is subject to any of these forms of regulation to have certain**

relationships in which people are asked to do things which are regarded by objective observers as being too risky under the circumstances where it must be somehow they are either not understanding or they are under some form of coercion because the rational balance does not lead in that direction even if a researcher would think, gee, I might learn something that would be worth learning, damn the costs.

We have -- I have heard now two rationales and they are -- they seem to me different and I would -- I hope that in the next draft you can explore them.

One draws directly off of that and it is the rationale that Alta gave and that I think you also gave at one point.

And that is just as we say that the more powerful physician/researcher should not be allowed to do certain things which are, in effect, exploitative of even a consenting subject, and we set certain limits on that.

So, too, the more powerful nation, the richer nation should not be allowed to exploit, and this is that sense that Alta says, you know, there should be some sense of benevolence in this -- and beneficence in this relationship.

And as we carry over from the medical

**relationship to the research relationship -- I mean, there is nothing inherent that says researchers should be beneficent. There is something that says that physicians should be.**

**And as we have carried that over so, too, we are carrying it over in the international context. And I think that explanation would have to be given quite fully and it would be particularly important there to follow along the last comment that Alta made.**

**Why does that apply as much to companies as it does to governments?**

**And here it would probably get us into some of the kinds of things that Harold knows a lot about, about regulated industries.**

**I mean, there used to be some notion of the burden being imposed consistent with a fair return on investment that a very rich company that is making a lot of money off of something has a bigger obligation than a company which -- where the burden you want to impose will not be able to run its operation in the whole way public utilities were run. A fair return on their investment.**

**This is a very dicey thing when we get into pharmaceutical companies and so forth because there are huge arguments about whether they have a very high**

**return on investment or a reasonable one given the risk that they take.**

**So this gets us into some troubled waters but that would be, I think, something we might have to explore.**

**The other rationale that I have heard is different and I think that the comments that both Harold and Bernie made are very relevant here.**

**Beginning with the notion that it is unethical to conduct research which with its inherent risks will not produce a concomitant benefit, we have added on two further statements.**

**One is benefit to whom, benefit to the people who are either in the research, or who are members of the group from whom the research subjects were selected. So it becomes unethical not to produce a benefit to this group and the second is a benefit of the particular type that the research is producing, and that leads us into the real difficulty what about, as you say, epidemiological research, basic research and failed clinical studies. Failed in the sense that they have not produced something that the sponsor can use by way of product but maybe not failed as science.**

**If they have been well designed they have**

shown that this intervention being tested against the null hypothesis was not better than null or than existing treatment.

And yet that is good knowledge that will teach the sponsor or some other sponsor coming along and using that knowledge maybe later on to get a product and so we have real -- I think we have a real issue in that expansion from the basic principle with which we would all agree that it is unethical to expose any subject to research for a project that will not produce benefit, to then say that necessarily follows logically the benefit to that group or to that individual who was in the subject of the type -- not that he got some payment, which he can use to feed his family or whatever, not that the country benefitted from the infrastructure that was built up, but that they are going to benefit in the particular way of getting access to the products of the research.

And I think that really requires much more justification than it has now in this chapter.

I hope that is helpful to you.

DR. SHAPIRO: Ruth, did you want to say something?

DR. MACKLIN: Yes. I think this is the point to notice the following, because people made some

comments here about the use of the term "obligation" and the distinction between being beneficent and having an obligation or supererogatory or virtuous, et cetera, and also whether if you fail in the obligation then it means the research should not be done.

So let's look specifically at the places where obligation is stated here because the discussion has this usual global quality about the chapter without perhaps attention to some of the specific words.

So the first recommendation is on page 1, chapter 4 here, at line 19 and this simply is the obligation to disclose. Okay.

PROF. CAPRON: There is no debate about that.

DR. MACKLIN: No quarrel, no deal, no problem. Okay.

The second recommendation is on page 3 -- at the top of page 2 -- where, indeed, following what Alex just said there is a very specific, and actually Jim said it earlier, a specific obligation to do X and to whom X is owed. Very specific.

"Researchers and sponsors have an obligation to continue to provide the beneficial intervention

**free of charge to the participating subjects if they can benefit from it."**

**Now the model here -- this is where there is some attempt to say something about that in the text. The model here is people are sick, you are doing this intervention, you actually come up with a successful product even if it is randomized and some people get the usual thing or maybe some even get a placebo, and then the research is finished. You reach the endpoint of the research and it is finished, pack up, go home, take the drugs away, and leave these people still sick.**

**Okay. Here the argument is there is an obligation not to pack up and go home and leave these sick people sick after you have provided them with a beneficial intervention from which they have benefitted and then go away.**

**So that is that obligation and I mean if people want to argue against it and say nothing is wrong with that then let's hear the argument but that is what this obligation is.**

**DR. GREIDER: What is the beneficial?**

**DR. MACKLIN: The product that is being studied. Okay. In other words, you are studying --**

**DR. GREIDER: You do not know if it is**

**beneficial.**

**DR. MACKLIN: No. At the end -- no, if it is beneficial you do not know that until the conclusion of the research. Right. A successful product. They have an obligation to continue to provide the beneficial intervention. I mean, this is the presumption that there is some benefit.**

**PROF. CAPRON: Okay. Ruth, is this -- I mean, put this way, is it the psychological starkness of walking away from someone who for the last year has done well on your drug?**

**DR. MACKLIN: No. It is making them worse off after the research than they were in the research.**

**PROF. CAPRON: In the research but not before the research.**

**DR. MACKLIN: That is right. Not before the research.**

**PROF. CAPRON: And as between --**

**DR. MACKLIN: This draws on Ruth Faden's presentation if you remember.**

**PROF. CAPRON: Right.**

**DR. MACKLIN: And which we try to use her arguments here to say that the obligation is not simply to make people -- it is not just the**

**psychological thing here. You make people better off for a while.**

**PROF. CAPRON: Right.**

**DR. MACKLIN: Okay. And then you take away what made them better. You are making them worse off than they were during the research. Now maybe we have to argue more what is the relevant comparison before the research or during the research.**

**PROF. CAPRON: I mean, I think when we talked about this before I sort of turned on its head the usual statement of a Jewish ethical principle that it is wrong to end even one moment of one life by direct action because every moment was precious and I said what if you thought here that you have said to these people you have a miserable condition that is going to kill you. We are able to give you another month or year of life. After that is over your miserable condition will kill you but we have given you -- each one of those moments of that year of life we gave you is infinitely precious.**

**We have given you something of infinite value. What more can we give you beyond that infinite value?**

**Now that seems to me a moral argument. It may be one -- I mean, to me -- when I said psychological,**

I meant it. It would seem to me very hard if I were the physician who was on a daily basis giving someone a pill, which if they did not have, I would watch them wither and die before my eyes. I would have a hard time to stop giving them that pill but if --

DR. MACKLIN: I do not know about that.

PROF. CAPRON: -- but, Ruth, but later in this chapter you have a situation in which you talk about the people who are in the previous treatment which did not work but who gave as much of themselves and were left no better off at the end of the trial because it did not work and they are in the next village over, and now you have got something that works, why isn't your obligation now to run over to that village and give them the intervention that you have now found works?

DR. MACKLIN: I put that stuff in this chapter because you raised it at the last meeting.

PROF. CAPRON: Well, I -- but it is not --

DR. MACKLIN: That is why it is here.

(Laughter.)

PROF. CAPRON: It is there but its intellectual consequences are not grappled with.

DR. MACKLIN: Okay. All right.

PROF. CAPRON: I mean, I want to know why

**that obligation to a villager who has had this infinite benefit of a year of greater life is not in a way less than the person in the first village who participated in equal good faith and has, you know, struggled and just about died, and now you could run to that village with the drug from the successful trial and save that person's life for a year. Why isn't your obligation to that person even more? They never got any benefit.**

**Just the way we would say your obligation to the person who was getting the placebo the whole time. I mean, our usual assumption is, if you have been on a placebo arm of a trial we owe you somehow. If we found something that is going to work, we give it to you now because you made the equal sacrifice and did not get anything out of it.**

**DR. MACKLIN: So what is probably needed here is an --**

**PROF. CAPRON: It is a real dilemma. I do not have an easy answer.**

**DR. MACKLIN: What is probably needed here is some kind of -- what is probably needed is some further elucidation and grappling with this issue but it seems to me, if you will just let us look at the next recommendation, again which talks about an**

**obligation --**

**PROF. CAPRON: Right.**

**DR. MACKLIN: -- on the bottom of page 3, top of 4. Okay. We are moving outwardly in each one of these. Okay. We got the clear present obligation and then we have the one to the subjects who have benefited. Now it is needed again for those who participated in a trial for a limited time after the conclusion of the trial.**

**Now the limited time was meant here both to be realistic and I suppose appropriate in saying obligations do not last forever. They do not last for an infinite time and I do not know about this infinite --**

**PROF. CAPRON: Just to be -- for clarity sake, you are talking about -- the limited time was you do not need it today but if in the next X years you needed it, we will come back and give it to you.**

**DR. MACKLIN: Something like that, yes.**

**PROF. CAPRON: That is just a scenario.**

**DR. MACKLIN: That is it, yes. That is the scenario.**

**PROF. CAPRON: I am just trying to clarify.**

**DR. MACKLIN: In other words, they get malaria. They are in the malaria trial.**

**PROF. CAPRON: Right.**

**DR. MACKLIN: Okay.**

**PROF. CAPRON: They are cleared up but it reoccurs.**

**DR. MACKLIN: And it is cleared up and then they get it again, and I do not know that much about malaria but they get it again. Okay. And the question is, they have been in that trial for a limited time.**

**Now the limitation --**

**PROF. CAPRON: So this is a subset of the first one without the immediate sort of -- I was calling the psychological punch. When you walk away from them they look healthy but a year from now they might need you again.**

**DR. MACKLIN: No, no. The first group was not going to be healthy. They are going to get sick again.**

**PROF. CAPRON: No, no, the first group is the sick group.**

**DR. SHAPIRO: Okay.**

**PROF. CAPRON: The second group is the one -- the difference is that you are walking away.**

**DR. MACKLIN: Right.**

**PROF. CAPRON: You can leave them healthy.**

**The question is when they get sick again in a year do you have to come back. So it is a subset of the same moral principle.**

**DR. MACKLIN: Okay. I think what I was hoping to do --**

**PROF. CAPRON: Harold is going to get --**

**DR. MACKLIN: -- what I was hoping to do is failing and it is failing because Alex responds and I respond to him.**

**Let me just say what I was hoping to do in pointing to the specific recommendations. Okay.**

**The discussion sounded like the obligation was to provide all kinds of stuff to the country or to lots of people in the country but, in fact, the obligations are quite limited when you look at what the recommendations say the obligations are until we come to the most troubling one of all and that uses the -- still uses this vague language or the unhelpful language of reasonable availability, and that is the recommendation on page 11.**

**And that is where we move from a direct obligation to use Jim's terms. Where we move from an obligation to do X or Y or Z to an obligation to negotiate and have this discussion in advance. And then the whole discussion that will follow that, is**

**the discussion of prior agreements.**

**So I had the sense that the discussion that took place in the last 45 minutes was kind of indicting these obligations as being too sweeping, too global, promising too much at the end of research. Whereas, in fact, there is some very limited -- there are limitations put on every one of the other obligations until we get to the last one and that is an obligation to negotiate.**

**DR. SHAPIRO: I have a number of commissioners who want to speak. Let me say a word before Diane. I have Diane, Arturo, Eric and Steve on my list at least as of right now.**

**Let me say a word about this coverage issue that keeps coming up in one form or another and at least -- not try to resolve the issue but at least share my concept of what I thought we were getting at here regarding which research we covered, is it just clinical trials, clinical trials of certain diseases and so on and so forth.**

**My view is that the topic that one begins with is international research. It includes everything. Then we may have good reasons -- and we ought to state them -- to eliminate certain classes of things and we just ought to really state them early on**

so we make sure we know what we are talking about.

But I think that it should be as broad as we feel we can handle and should include research.

To give you an idea of what I mean, let's suppose you consider the following divisions as research in resource rich or resource poor countries, that is Germany and Canada, or other poorer countries.

In my own mind, and I am not trying to -- this is not the commission's judgment. In my own mind I can eliminate quickly in my head all the research going on in resource rich countries because I have, my own view, a very simple solution to that issue and we can get it out of the way. That is just my perspective and we can talk about that later.

However, when we get to resource poor countries a whole -- a much more complex set of issues come into play and maybe that is where we want to focus our attention. That is my view since I think the other one is so easy to solve but that is an open issue.

So we ought to really find a way to clarify for ourselves perhaps by the next time we meet just what it is we are covering. I think my own view is that we can cover quite a lot and we can eliminate quite a lot quite successfully without just ducking

and that is really deal with it because I think a lot of it is quite easy to deal with but there are some very hard questions left over.

I also think that, Arturo, to turn to your point about -- or other people's point about paternalism. I mean, if there were not a certain amount of paternalism there would be nothing for us to discuss here, frankly.

And so that I think I accept your point that we cannot behave like we know everything and no one else knows anything. I mean, that is a very bad situation but a certain amount of paternalism I think is adherent in the fact that we even care about what goes on somewhere else and we are just not letting someone else take care of it but we care how we behave elsewhere or how we export our dollars with certain kinds of commitments and so on.

So I think that the -- there is a hard issue, which is what level is appropriate. I mean, I think your point is well taken in that respect.

Finally, I think when we come to obligations, I have a sense that at one stage or another, and I do not think perhaps this is a subject at all for this afternoon, we are going to have to decide whether a transfer of resources or fulfilling an obligation

through the provision of health is something different than meeting that obligation in some other way.

And I do not -- and that is not a topic for this afternoon, but I think we are going to have to deal with that in some way before we can really resolve finally some of the issues that come up in these recommendations.

But let me go now to the list that is here.

Diane, you are next on the list.

DR. SCOTT-JONES: The first question that I wanted to raise is one that Harold has just addressed and one that Alex mentioned too, when he was talking and that is what the real topic of this report is.

And, as I recall, from previous meetings, I thought that we had discussed that and decided that this report is focused on international research that is of a specific kind and in their first page of chapter 3, Ruth and Alice say it is research where an industrialized country sponsors or conducts research in a resource poor country.

I thought that that was our focus and if it is not, I think the report probably does need to be changed quite a bit but I thought we had agreed some time ago that that was our focus.

The second point that I wanted to make has to

do with the motivation of U.S. researchers when they go to a resource poor country.

From the presentations this morning about malaria, a couple of reasons that were brought up were, you know, to protect U.S. travelers or to protect the U.S. military but it seems to me that at least part of the motivation is benevolence.

It is that U.S. researchers want to study a disease like malaria where it occurs because it would not be reasonable to study it in this country. There would not be the incidence of it and so forth.

So if one is studying malaria one goes to the countries where malaria is prominent or prevalent and it seems to me then that you are then entering a different context for conducting research than the context that exists when -- if one were conducting a study, a basic research study here. It seems to me that one then does have these various obligations that are discussed in this research.

Otherwise, why would one go to that country in the first place when malaria is not a serious problem in the U.S. for U.S. citizens?

It seems to me that you have already -- in going there in the first place -- undertaken a different set of obligations. If not, then the only

motivation is to predict the small number of U.S. travelers who need mefloquine or the U.S. military and that seems to me just not a way to interact with people in a resource poor country.

So I think we need to examine the motivation of U.S. researchers for choosing to study a disease in a resource poor country.

DR. SHAPIRO: Thank you.

Arturo?

DR. BRITO: I am going to just make one more comment about the paternalistic comment I made before. I am going to put it to rest. But if Eric is my witness here, I had the lines that Trish mentioned on page 5 about the true partnership being forged highlighted and I thought that was a very good point here.

My whole point about the whole thing is to try to focus more energy into this partnership and the disclosure part of it, not to say that there is not going to be paternalism and that there is not going to be obligations that we are going to agree to. I will just put that to rest.

The one comment I have about what were the obligations, the second and third recommendations about obligations, the one thing that made me a little

bit uneasy on the general term here, is that if we are only going to provide -- and we are assuming -- I was assuming here we are talking about resource poor countries where we are doing this research and significant research such as malaria, TB, AIDS, et cetera, is that it makes me a little bit uneasy that if we are only obligated to provide the care to participating subjects, then at what point does this become a bit on the coercive side or undue inducement, et cetera.

And I know in chapter 3 there is -- it is somewhat addressed in here but I just want to mention that. I think that is something we should think about.

DR. SHAPIRO: Thank you.

Eric?

DR. CASSELL: I will pass.

DR. SHAPIRO: Thank you.

Steve?

Excuse me. Trish, did you have a quick question?

PROF. BACKLAR: I think part of the problem with this discussion is that we are discussing chapter 4 without discussing chapter 3 first and what is preceding it. Some of chapter 3 we had read before.

**It still is very useful to look at that first and then go to chapter 4.**

**DR. SHAPIRO: We will be getting there in a moment.**

**Steve?**

**MR. HOLTZMAN: I want to thank Ruth for pointing out the difference between the different recommendations. The first two really go to obligations owed to the particular subject as an individual. And so I think the question we need to tackle there is twofold.**

**Again it comes back -- if you are really looking at these people as individuals, why would we distinguish the international from the noninternational case because you have really isolated them as individuals. Is there something special there or not?**

**And then the second goes to the question, not is this enough or too little or too much, which is how you took the question, Ruth. Rather it is the logical form of the compensation.**

**DR. MACKLIN: Which?**

**MR. HOLTZMAN: It is about the logical form of, as it were, the compensation, that it has to take the form of the drug itself. All right.**

When Alex was talking about the psychological impact -- instead of psychological because people will say we only saw psychological, I think it goes to the whole issue of meaning and that relationship that Alta was talking about. All right. But I think one can raise the question whether it has to take that logical form or not.

And so I think it is important for us to look at the individual versus the other ones about where you do leave scope for better design of discussion of what is the best form of compensation, number one.

And then, number two, the logical form.

And I had another point but I forgot it.

DR. SHAPIRO: It will come back.

Other questions from members of the commission on this?

Carol?

DR. GREIDER: I just wanted to respond to what Diane said about why would people go to resource poor countries to do research. And just to add to the kinds of scenarios that you put forth, you can also imagine that there may be a disease that is widespread throughout the world, and that developing some sort of a treatment for that disease, even though it is not endemic in the United States, may be a good market for

which to market some sort of a treatment.

So we are not necessarily just thinking about the United States treating the United States citizens. One could be thinking about -- I do not know if malaria is a good case but some disease that is worldwide a serious problem for which you could have a good market to sell drugs to treat.

DR. SHAPIRO: Tom?

DR. MURRAY: Yes. I hope I am -- I fear I may be complicating rather than simplifying matters but since these comments are inspired partly by what Steve just said and by some things that Alta said earlier.

And that is, I believe a great deal of the complication in this issue is because, in fact, the relationship between investigator and -- particularly investigator and subject, but also sponsor and host community or country, is not a traditional relationship of contract. It is not a relationship of wage labor.

It is a different order of relationship. That is how we have understood the ethics of human subjects research for some decades. And efforts to sort of literally cash it out in terms of how can I compensate the subject, never worked very well because

we are talking about some sort of -- it is a relationship based on things like honor and trust rather than contract and straight forward wage compensation.

And that is maybe one reason why we think that the drug, if it is an effective drug, to deprive them suddenly of that thing which has been keeping them alive and keeping them healthy -- even if we gave them the money cost, you know, or that plus 50 percent more, would not be right. It would not be right because it is that relationship.

I also think that -- and I hope I will be corrected if I misunderstand that -- that we really are focused on avoiding exploitation.

I mean, that is the -- at least theme that has been in my head the whole time. And that these various principles and these arguments are all ways of understanding how, in specifics, we can avoid being in a position of exploiting some persons who are less wealthy, powerful, et cetera.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Carol's comment brought back my thought and that is -- I always push for us thinking about different cases. It is an old line from Lichtenstein, a one sided diet of examples leads

to bad philosophical disease.

So take malaria. There is no big market for drugs for malaria in the United States. So the reason you go there, is that is where the disease is and it is to treat those people and it is -- that is why pharmaceutical companies do not sponsor that research. It is not a big market.

That is very different than the case where you say I have got a potential -- an interesting drug for the Western market. It is a very risky drug. Let me go find some undeveloped people and buy them off and test it on them. And that is very different again -- and I can think of an example I was recently exposed to for a bone healing drug for fractures.

You know, -- It is widely applicable. People break their legs everywhere in the world. It just so happens they found that because there are a lot of men riding motorcycles and mopeds in certain places in Northern Africa, you can really accrue a lot of subjects very, very quickly there.

It is not a toxic drug. You are not doing it because you could not do it elsewhere. It is just purely the accrual rates. I think it is unlikely that, if approved, that drug will be widely available in those countries because it will be very expensive.

Is that, therefore, wrong? Are they being exploited in the same way as when you had in your mind the paradigm case of a drug you would never think of testing on a white male subject so go find someone else to test it on?

DR. SHAPIRO: Thank you.

Alex, and then I am going to turn to Ruth to see if she has anything she would like to specifically ask us, and after that we are going to take a break.

Alex?

PROF. CAPRON: Three quick comments. First in response to you, Harold. I think it may be possible for us to dispose of the nondeveloping nation issues quickly, but when we began the report, we were thinking simply about what barriers exist to research conducted across national borders from U.S. regulations that are largely unintended problems.

Not where we say, well, these are standards which of course make sense but -- and, as I recall, we heard from Tom Puglisi early on that there was only one institution outside the United States that had a multiproject assurance.

In other words, none of the other ones had ever met whatever standards, and it was in part

because they did not adopt the Belmont Report or their adherence to this or that was unclear. And that seems to me something that we, therefore -- not at a big moral level but at the level of what we thought we were going to write this report about --

DR. SHAPIRO: Good point.

PROF. CAPRON: -- cannot dismiss.

Now we may end up saying in an introduction we thought we were going to write about that but it turned out that, as we looked at it, the more ethically troubling sets of issues come when rich nations, including the U.S., work abroad particularly in clinical trials but perhaps in other kinds of research, too.

The second point is maybe, Steve, if we look at the two recommendations on page three that have to do with obligations to individuals, and if we frame them with the following introduction:

In circumstances where the majority of the population from whom subjects are going to be drawn or the overwhelming majority will not have access then blah, blah, blah because that does distinguish it. As Ruth says -- I mean, it may well be that Viagra was tested on a lot of people who now do not have any entitlement to Viagra under their insurance plans

because they regard it as a -- I do not know if it is a recreational drug or --

(Laughter.)

PROF. CAPRON: -- but it is not for most --

DR. SHAPIRO: Do not go there, Alex.

PROF. CAPRON: -- but for most of them it is not regarded as medically --

MR. HOLTZMAN: Do you have a conflict on this one, Alex?

PROF. CAPRON: No. Thank you.

(Laughter.)

PROF. CAPRON: Overall our belief is that, between our public and private programs, if a drug is developed in most U.S. testing centers, the population, even if it were a poorer than average population that was going to a university center, which may be a county hospital or a public hospital or a city hospital, are still likely to get access if a new modality comes along and is therapeutically useful. It is probably going to be made available to them and that may distinguish it. That is equally true and probably more true in most of the developed world that has better health care plans than we do.

But in the underdeveloped world, if the

government of Malawi could not supply this drug which we heard about for malaria even though it was developed there, then you are in a situation where these obligations come into play.

Now I am not arguing whether they are correct obligations but it is a way of framing the difference that may be useful.

The third thing is something new which I have not spoken of before and I just wanted to ask that you give some attention to the bottom of page 8. You give a specific example.

You say, "For example, if a vaccine trial is conducted in Uganda, all of East Africa is too large an area, whereas only the trial participants or local community in which the trial takes place is too small an area to be ethically defensible."

Again I come back to the notion of -- I mean, where does the particular ethic come from? If we were talking about a privately sponsored trial in another context, we would ask what is the ability of the sponsor to bear this burden?

And, for example, if I can give you an analogy, in the area of punitive damages, the argument about punitive damages, is not that they are tied at all to the need of the person who has been injured.

**They are quite separate from any compensatory damages.**

**They are supposedly going to be keyed to the wealth of the injurer so that, if a very rich company does some bad thing, and a not very rich company does the same bad thing, the jury is allowed to measure punitive damages on a level which will be punitive. In other words, that will get their attention and you have to be much more punitive to a very rich company to have any effect.**

**Well, the same -- not on the punitive level, but the same thought would seem to me to be part of the notion of ethically defensible. It would not seem to me if you are talking about a small biotech company that, you know, maybe has never turned a profit to say that they have an obligation to include all of Uganda as opposed to the village in which the research trial might be -- might not be ethically defensible because the burden would be too extreme.**

**Conversely, if it is Novartis, or some big global company, maybe they could take on all of Uganda because the profits that they will be drawing on are much greater.**

**So it seems to me we have to explain when its ethically defensible. I mean, what is the origin of**

**the measurement of what is ethically defensible? Is it the ability to pay? Is it the burden that would be imposed?**

**DR. SHAPIRO: That is an interesting question. I did not have the analogy, which I thought kind of interesting, that you proposed. I had not thought of that at all but I was concerned -- I did not understand where that phrase came from, but we can get to that another time.**

**Ruth, is there anything you would like to specifically ask us on this or --**

**PROF. CAPRON: I have heard more than enough.**

**DR. SHAPIRO: Well, I know you have heard more than you want to hear but I mean that is a separate issue. I am not asking that question.**

**DR. MACKLIN: Well, let me say one thing -- I want to clarify something. Although this report is largely, and these chapters are primarily, about obligations of industrialized countries and rich sponsors to resource poor countries, it is not -- the entire report is not and will not only be about that.**

**One problem has arisen here in that we started our deliberations and discussions with chapter 2. We did chapter 3. We are on to chapter 4. We never had a chapter 1.**

Chapter 1 is going to set up the problem and now is the time to write it so before we meet again you will see chapter 1. And chapter 1 will say among other things -- I mean, it will give a little history and a little background -- among other things, it will say the reasons for the focus on the resource poor countries and how that is primarily what the subject matter of chapters 3 and 4 are about. When we get to chapter 5, it will not only be about that because of what we heard from Dr. Pape this morning when he commented about what the French and the Canadians think about the imperialism of the U.S. in that if they are one of the sponsors they have to follow the U.S. rules.

So the next chapter, which you will see, not at the next meeting in April but the subsequent meeting, will be about the collaboration and enhancing collaboration.

When we talk about resource poor countries, we will raise the questions that Arturo raised and consider the point of not being paternalistic and having a full collaboration.

When we talk about other developed or industrialized countries, we have to look at a situation where OPRR, or whoever the powers that be,

will not accept something that comes even from another country that is very well represented in Stu's chart, for example, as complying with a whole lot of very important regulations.

So we will be talking about the relationship or the collaboration with other -- with industrialized countries but it will not be the same issues that have been dealt with.

Harold asked what I would like to ask from the commission.

I think from the first meeting we have heard calls and appropriate calls for examples of this, that or the other thing.

You have got here a philosopher, bioethicist and a lawyer, M.P.H., working on this without the kinds of examples of the sort that Steve gave, and a couple of here that are from our presenters -- people who have given testimony, and which we will then try to incorporate or seek to incorporate.

And what we would like to ask from the commissioners is where relevant, because I am sure you know of examples or have examples -- where you are asking for cases or examples, it would be extremely useful to us if you could -- you do not have to do research but, just as Steve gave a couple of examples,

plug them in so that -- and write it so that we get it accurately and do not, you know, goof, so that we have examples by way of illustration where needed and desired.

In other places people are calling for arguments and one of these people is my friend and colleague, Alex Capron, who periodically asks for an argument or challenges an argument, presents a response and a very good response in a dialogue that probably could be and should be written down so that we can test it. Okay.

So what I would like to see -- I mean, it is in the transcript. Yes. Would you be prepared if we give you the transcript --

PROF. CAPRON: I will be happy to.

DR. MACKLIN: -- to take out the "ur's and um's" and --

PROF. CAPRON: There never are any.

DR. MACKLIN: -- sharpen --

(Laughter.)

DR. MACKLIN: Well, you could use a little punctuation in there then.

(Laughter.)

DR. MACKLIN: But to sharpen the arguments, and in a way that is directly responsive so that we

can then do an “on this hand” and “on the other hand”, and be able then to take some of the points that are made here that may get lost. I mean, we do look at the transcript and try to do it but it would be helpful if the authors of the arguments could help us.

DR. SHAPIRO: Well, we will -- each of us, I hope, then take the obligation to do that. And for those of us that do have experience with being able to provide categories of cases that you think are illustrative, that would be very helpful. I think that is our obligation to do that. And I encourage you to just send them in to Ruth, or to Eric, or myself, anyone, so we can put that together.

Okay. Let's take a break for about 15 minutes now and then we will reassemble and look at the chapter 3.

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

## CHOOSING A STUDY DESIGN: ETHICAL AND METHODOLOGICAL CONSIDERATIONS (DRAFT OF CHAPTER 3)

DR. SHAPIRO: All right. I would like to go to the last item on our agenda today. We will adjourn no later than 5:00 o'clock. That is the absolute outer limits. As I have said on so many other days that does not mean we have an obligation to remain

here until 5:00 o'clock if we happen to run out of things that are worthwhile saying.

Let me deal with chapter 3.

Ruth, is there anything you would like to say before I turn to the commissioners to see if they have any questions?

DR. MACKLIN: No.

(Laughter.)

DR. SHAPIRO: That is said so full of hope. All right. Let me turn to issues that may be on the commissioners' minds.

Any questions anybody has?

Bernie?

DR. LO: I can testify to Ruth and Alice's organizational skills. They sent me an e-mail a week ago asking me to comment in writing on several questions I had raised. Luckily, I went on vacation so I ducked that one so they got me this morning.

I also just want to thank them for sort of laying out the issues so clearly and logically, and lucidly. I think it is really helping us think through some difficult issues.

And what I want to do is offer some big picture items and to save Ruth the trouble of repeating what she said before the break.

Yes, I will in response to my own questions about getting specific cases, try and think up some specific cases to flesh this out and see how this might work out in different circumstances.

It struck me as I read it through that this really read like a chapter in an epidemiology clinical research methods textbook. I would like to encourage us to put more attention to ethical issues into the chapter, which I think can actually fit very nicely.

I have had ongoing concerns about this new language we adopted of effective -- and I actually forget what the second modifier is.

DR. MACKLIN: Established.

DR. LO: Established and effective. The two "E's." What that actually means and it obviously does not carry some of the baggage that the CIOMS Helsinki language has but it, you know, may not be specific enough.

To me there are issues of how do you conclude that an intervention is effective. So what level of evidence do you need?

People have, you know, very different standards for what constitutes consistent -- compelling or convincing evidence of effectiveness and it is actually a -- there are nice discussions in the

epidemiology literature that actually include ethical issues in terms of how certain you have to be, -- where is the burden of proof and issues that I think really fall under the ethics domain. We should try and highlight that.

There is a risk that people will read this to be a technical decision where, in fact, it is really a very value ladened decision, and I would actually argue that we should try and say that this is not something that a bunch of epidemiology "wonks" should decide. It really should involve the community, potential participants, the host country, et cetera.

I also think it would be good to introduce the concept of equipoise in the chapter and use it. One of the things that is striking, it seems to me, about this debate is how readily people who disagree with someone else start pointing fingers and saying, "You are unethical."

And I think there is a notion, I think, embodied in equipoise that there are reasonable disagreements and, in fact, they are healthy and, in fact, are the justification for doing certain kinds of randomized trials and that we need to give some indication of how you distinguish reasonable disagreements from ethically unacceptable protocols.

I think again the sort of ethical philosophical concepts can help.

And, finally, I think that we obviously -- this is again an echo of what we saw in chapter 4. There are a lot of very tough substantive issues which I think we want to try and get at -- with some specific cases but also in the absence of being able to settle those once and for all, sort of procedural solutions are going to become very important.

I think we need to ask questions like who decides, what procedures are we going to set up for deciding when something is effective or not.

So I think those are the sorts of general directions I would like to see us head. I think it is very useful to have all this laid out so clearly but at times I lost the ethical issues because there was so much attention to different sort of research epidemiology considerations.

And if there is a way of condensing that, or moving some of it to an appendix and really focusing more on our charge, which I think is to highlight the ethical issues to help people start to think them through.

DR. SHAPIRO: Thank you.

Eric?

**DR. CASSELL: I want to pick up on neglected e-mails I have written. But today's testimony makes clear once again that whatever we write here, we are really writing a template for the development of ethical procedures for protection of human subjects in countries, in which at the present time, there is not a structure to do that. There are not IRBs. There are not trained investigators. There are not people committed to the ideas and so forth.**

**So that it is very -- I think it is important that whatever we do begins to lay down the method by which we think that will happen, and the example I used was our own development here and how people -- it took time for people to get committed to this.**

**You know, we can set up something and the stricter and more hard-nosed it is, the less chance it has of making itself felt in the host country.**

**On the other hand, the more the host country participates in the whole process, the more chance that in ten years, in fact, good research will be done that is ethical.**

**And I think we have to be explicit about how we think that is going to come about. How we think people will learn the procedure that was learned in this country over the past 25 years.**

**DR. SHAPIRO: Thank you.**

**Other comments?**

**PROF. CAPRON: Yes.**

**DR. SHAPIRO: Alex?**

**PROF. CAPRON: Yes. Eric, the notion that what we are talking about is evolutionary and we are trying to set precepts that will lead to change I agree with, but I think what we have heard repeatedly today, and on previous occasions, were that in many of these countries structures have been created and people are committed to the protection of subjects.**

**The issues arise mostly out of cultural differences. For example, the notion of community consent and what that difference would imply. The example that we heard today from Malawi of signing forms and what that implies and so forth.**

**But I think it would be a mistake if I understood what you were saying to say that the report is written for the situation in which there is no infrastructure and --**

**DR. CASSELL: Oh, no, that is not my meaning at all.**

**PROF. CAPRON: Okay.**

**DR. CASSELL: Actually what you said -- highlights what I do mean. When we use the concept of**

person in this culture, we are talking about a very different meaning than when the word "person" is used in other cultures with much stronger community base or the word "culture" is used in -- "person" is used in a -- just to make it simpler, as it used in upper class Britain. I mean, there are different things.

What we want to end up with is ethical research, which is based in the cultures in which it then takes place, and it is that kind of development that has to take place there. We would not come up with the developments that make that possible because we do not know enough about it, but if we encourage the participation at every step of the local authority or the host country then, in fact, we do make that happen.

And, for example, if we say so and so it is obligated, I think any time we mention it, we always have to know that there is a sponsor, there are participants in the research, there is a host country, these are all active parts of the process, and that they all have to be present at each time.

DR. SHAPIRO: Thank you.

Alta?

PROF. CHARO: First, I want to just say that I was going to move to a different point so I do not

**want to cut off anybody that might want to respond on this.**

**I was wondering, looking at this chapter, on page 36 there is, I think, a very central conclusion and recommendation about the obligation to provide members of a control group with an established effective treatment.**

**And I wanted to make sure that I understood what this would mean in the context of one of the paradigm cases, which is the Uganda AIDS trials, the AZT trials that started this whole debate in the medical journals. As I recall, when Bob Levine testified in January he cited a host of reasons for not giving the established effective treatment to the control group.**

**Some of those had to do with the inability to sustain that treatment *in situ* following the end of the trial.**

**Other reasons he cited included difficulty in providing that even in the course of a study and in his assertion that it would have required a change in -- I think he was citing specifically breast feeding habits that might have been overall to the detriment of the health of infants of mothers who were enrolled.**

**And I wanted to just -- in light of the**

**complexity of the objections to providing established effective treatment in that trial, I would like to just make sure I understand exactly what this conclusion means by testing it against that and maybe some other cases -- to make it easy to decide whether to sign on or not.**

**My inclination is to say yes but -- because I have always been the very protective one but I want to make sure I understand what I am saying yes to.**

**DR. SHAPIRO: Yes, go ahead, Ruth.**

**DR. MACKLIN: Yes. We could discuss that here. I think there is -- we have made a deliberate decision not to revisit those trials because it was so contentious because people on both sides never gave an inch, even at the end, and people drove in their stakes in their defense of something and could not move to the middle.**

**It would make this report more controversial than it already is to revisit -- let me just finish.**

**PROF. CHARO: I just want to clarify. I was not suggesting that you write it in here. I was suggesting we use it for discussion purposes, not to use it in the text.**

**DR. MACKLIN: All right. That is why it was not used in the text.**

**Now there are two ways to go with this. I do not know how long to spend on it but one way is to look at Bob Levine's comments, each of which has a response, and the other is to address it more generally.**

**Let me try the first just to look at it because there is a response to each of these and because we heard from Levine and not directly from the opponent in that debate. We did not get the response.**

**On the breast feeding issue, it happens to be true of absolutely any intervention to prevent maternal to child transmission, whether it is placebo controlled, short course, long course, established effective, 076 or whatever that the ability -- whether it is within the trial or following a trial, to reduce maternal to child transmission is going to be affected by whether the population is breast feeding.**

**So that is a red herring with regard to any particular design. It applies with every design and it applies following the completion of the design. There is that point.**

**On the question of whether or not using the established effective treatment in the control arm will ever be provided after the trial, the question is, no, it will not but so what. The intervention**

being tested is the one that will be provided after.

So the obligation to do research that is relevant to the country and not to testing that will never be used, if that is an objection, the objection does not apply because, in fact, what will be used is the short course. So, I mean, there are other arguments for that.

So to use the established effective treatment in a control arm does not require us to be able to provide that after the trial just so long as you are testing something within the trial that will be provided. That is the answer to that part.

As far as the ability to provide it during the trial, well, of course, all the equipment and the infrastructure and everything else is brought in for the purpose of the trial so it is possible to provide it. Not if you are going to do the trial in a rural area where they only have midwives and they do not have hospitals, you know, with all that equipment.

But if the question is let's test this on the relevant population, namely women who live here, and see whether or not the short course will work and work to whatever comparison with the established effective treatment, that could be done in the tertiary care center.

So there is a response to each one of those objections. There is not a response or -- I mean, if the other response is made, namely -- or the other objection that it will take longer and you have to enroll very many more people and, therefore, it will be a longer time before you will ever be able to provide the short course effective treatment.

The sad fact, as Len Glantz pointed out, is even in those places where there was no established effective treatment, the shorter trial that cost less to do and presumably was going to bring the benefit sooner, still has not been implemented in several of the countries where the trial took place. In Cote d'Avoir in South Africa.

So there are responses to each one of those. We are going to use this example as we did here in chapter -- which chapter? Chapter 3 or chapter 4 -- by way of brief illustration and we will discuss it in greater length in the introductory chapter.

But to try to come down on one side or the other, you are going to lose credibility in this report with half of the people. So we want to say that problem prompted this but we do not want to go into it more.

Now I do not know if that is fully

satisfactory now but that is at least a response to what you said Bob said.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Ruth, staying on this recommendation, it seems to me there were two different kinds of arguments that arose in the AIDS case but I think are generic. And the first had to do with whether or not you had to provide an effective -- an established effective treatment if the provision of such would make it impossible to actually get a meaningful result.

Now there was great dispute about whether or not a placebo was necessary for the scientific validity but putting it aside, the specifics of that case, should we read this conclusion, this recommendation, as saying one must provide the effective -- the established effective treatment even if the result of that would be to invalidate the study.

You know, you are saying --

DR. MACKLIN: Don't we say in here somewhere that this depends on the research question and how you formulate the research question? That is the very lengthy discussion of the superiority design and the inferiority design that would give rise depending on

which question you ask.

So surely if you are asking whether the short course regimen is better than nothing, you are not going to be able to answer that question if you use the established effective treatment in the control arm.

So as Lagakos pointed out, a different research question that would call for a different design would enable you to use the established effective treatment, get an answer to a different yet still meaningful research question.

So I thought that was addressed in there. Is it addressed, Elisa? Maybe we can point out where it is in here. Okay. This is the chapter here.

MR. HOLTZMAN: No, I think it is important to make that clear because that was a large part of the argument. Where the ships passed in the night was because there was a disagreement over whether or not you would have gotten a valid result with that other question. Okay. So I think that is -- but to the second --

DR. MACKLIN: It was not clear --

MR. HOLTZMAN: Right. Okay.

The second is coming back to Alta, which is the other part of the discussion. Again putting aside

**the Levine specifics, really your argument goes to essentially the principle of beneficence. Bottom line on the page before that at 35 you conclude that beneficence demands the provision of an established effective treatment. Isn't that a fair way to characterize the argument?**

**DR. MACKLIN: Yes.**

**MR. HOLTZMAN: Okay. So I think that perhaps one -- if one feels that that is not sufficient, one should present in writing to you the arguments.**

**(Laughter.)**

**MR. HOLTZMAN: Which I will do.**

**DR. SHAPIRO: You are getting the idea, Steve. You are getting the idea.**

**DR. MACKLIN: Excuse me. When you say not sufficient, sufficient for what? We are using here the principle of beneficence as applied to research, which is to maximize possible benefits and minimize possible harms. That is the principle.**

**And the application is, given a research design that provides to the control arm the established effective treatment, rather than a placebo, you are maximizing the possible benefits.**

**Now you are going to give a written reply. I am eager to see what it will be.**

**MR. HOLTZMAN: Yes. It is the other side of it. I agree that beneficence demands that. The question is whether beneficence is the relevant principle.**

**DR. SHAPIRO: Okay. Carol and then Bernie.**

**DR. GREIDER: Well, I am also interested in what this might say so maybe we will hear it at some point. I also had some questions about this conclusion and recommendation.**

**DR. SHAPIRO: Which one are you referring to now?**

**DR. GREIDER: On page 36.**

**DR. SHAPIRO: 36.**

**DR. GREIDER: The same one that we have been discussing.**

**DR. SHAPIRO: Okay.**

**DR. GREIDER: On page 27 you lay out an argument -- page 27, line 13 -- suggesting that there may be other considerations, and this one example, is political considerations for how a study might benefit a country. But there may be other reasons besides the actual science that is going on about whether there will be any benefit to be brought to people in the first place.**

**And it seems to me that by bringing that up,**

then the argument that takes place on pages 34 and 35 about beneficence -- that whole argument about practicalities and political realities is completely ignored.

And I felt like there was a disconnect between reading on page 27 and then reading further to page 34 that there may be real reasons why a population might benefit from something where there is a placebo controlled trial for practical reasons.

I am just wondering if there could be some linking of the arguments that are made in the earlier part of the chapter to the conclusion, because I did not get to the same conclusion having read the same chapter. I was surprised to see this conclusion having read what I had read.

DR. MACKLIN: Here, I suppose, one has to talk about the distinction between a political consideration leading to a conclusion and an ethical consideration and what should trump what. I mean, perhaps. But there is the political consideration that is mentioned here.

I see what you are pointing to but I think here is where we need to -- we need to -- gently, I suppose -- say that what people take in advance to be political -- politically expeditious may not turn out

to be so.

And again the point is that if the Ministers of Health or the policy makers or whatever, said you could show that this short course is better than nothing and, therefore, then we will commit the resources to provide it, that is a political consideration that may lead to the short course regimen.

But then you -- if you are talking about practical realities and not just about politics you have to look back and say what, in fact, was done in these countries.

If that was a consideration and that was the promise on which the design rested, did anyone come through with that promise sufficiently to say, "Well, now, we got the results. There is a significant difference. We now have the obligation to provide this for our people because we let these researchers in here and we supported them and we made this promise."

So I think what we need to do is somehow link this political consideration with the actual outcomes and indicate what --

DR. GREIDER: I am thinking more about the practical. I am thinking about it in terms of some

**practicalities that, in fact -- you know, no one in the country has access to the established effective treatment as you have --**

**DR. MACKLIN: That is right, but that was --**

**DR. GREIDER: -- brought up here.**

**DR. MACKLIN: -- that was not what they were going to get. What they were supposed to get at the end was the new experimental regimen that was cheaper and presumably affordable. But if they were not even given that, when the research design that was adopted was based on this presumed political consideration, then that cannot be a justification for accepting.**

**All right. Bernie is going to respond to this.**

**DR. LO: Yes. Let me try and follow this line of discussion.**

**I think what is bothering you about the bold face on page 36 is that, it gets more and more absolute and less and less a sense that there is a dilemma at stake.**

**You know, I think it is right to say that beneficence is one of the fundamental principles of research ethics. It is not the only one and so we have got to allow some situations in which there are countervailing considerations that are very powerful,**

and beneficence does not just mean providing an established effective treatment in the control group.

Well, it does not just mean what you give for a control group, but, also, it has implications for the scientific and clinical implications of the findings.

And I think, you know, one of the issues that has come up is that, if a randomized clinical trial comparing placebo to an active agent shows an advantage for the active agent, there is no question that if the study is valid and well done, that that is an effective agent.

When you do an equivalence trial, depending on what the results show, it may be uninterpretable and you could -- it seems to me it is not unreasonable to imagine a situation where a host country, scientists, group of scientists, responsible government officials and community representatives if you could find them, say, "That is not the way we want to commit our resources. We would much rather not do the equivalence trial. We would rather do this other trial and we have thought it out."

So I think with the recommendation we need some -- I mean, if Jim Childress were here, he would

somehow get us talking about prima facie. obligations. Generally there is an obligation, but I think to make it sound absolute that you always have to do it, I think, is a problem.

Carol also raised a point about the political implications, and you gave the response, but if you look at these placebo controlled clinical trials, the people do not end up getting the drugs.

It seems to me that the problem is there may or may not have been a decision that it was wrong to do a placebo controlled trial but I think the real problem was they did not do this prior negotiation about what happens after the trial is over, depending on what the results show.

And it seems to me that if you had that in place as we are going to get, you know, in the next draft, then I think that would probably take care of a problem that you did not get.

I mean, you can turn it around the other way and say, "In the equivalence trials, where has that been shown to really --" where -- is the fact that it was an equivalence trial as opposed to a placebo controlled superiority trial, make it more likely that you are going to get the thing -- I do not think so.

I think we are confusing two important but

very separate issues and I think we should try and keep the -- getting access to the proven intervention after the trial separate from how you set up the trial in the first place.

Ruth, you made the point that you could always change the research question so that the equivalence trial will answer the research question. The problem is, that may not be the research question that is of primary interest.

And I could imagine, again, a host country and all the different stakeholders there saying, "Do not tell us what is the most important question." We saw this with the AIDS community. "Do not tell us that this is the most important question for us. We want to tell you what the agenda and priorities are."

So, again, we can come out sounding very -- what was the term we are supposed to use now? Parentalistic. We can be parentalistic --

(Laughter.)

DR. SHAPIRO: Alta is pushing this vocabulary.

DR. LO: Okay. If we say that, you know, we will tell you -- we so like this equivalence trial, that we are going to tell you what the research question is that you ought to be asking because we can

answer it with this tool. I think, you know, that is sort of flipping.

It seems to me the research question comes first and then you figure out is there an ethically acceptable way to answer it. And if there is not, then you have a tough choice as to whether you answer another question that you are not as interested in.

DR. SHAPIRO: Thank you.

Alex?

PROF. CAPRON: If Steve or others want to stay on this point I will defer.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: It is following up to Bernie.

Ruth did not give you a direct answer but if you look on page 35, starting at line 28 with the word "assuming," you see effectively the way Ruth wrote it, that there is a prima facia obligation that only kicks in if it assumes that the host country, et cetera, et cetera. Read it.

So I think it would be fair to say maybe that should be more strongly clarified, but I think that language is there. For what it is worth, I would like to see it.

I will take the responsibility of

articulating the position that says, okay, it is a different kind of argument, which is, it seems just bloody irrelevant to provide the standard -- the established effective treatment when they are not going to ever get it.

And that it is almost -- the argument would go, one is assuaging one's conscience in using these people in research and giving them this nice better treatment, even though afterwards it is going to be irrelevant to their life situation.

That would be the kind of argument that would take on the beneficence argument from a different kind of --

DR. MACKLIN: But, Steve, is the placebo relevant to their life situation?

MR. HOLTZMAN: Yes, because the placebo is what is the standard of care in the country. That is the argument, Ruth. I will flesh it out but that would be the argument.

The other question you should think about is, if the short course fails, do you have an obligation to give the established effective treatment to everyone in the trial thereafter? Because in chapter 4 you recommended, if the short course succeeded that you did have to give it to them. So it is worth

thinking about.

DR. SHAPIRO: Okay. Let me go back to Alex. Is this all on the same --

PROF. CHARO: It is all the same.

DR. SHAPIRO: All right. Let's take on this issue if it does not go too long.

Who else would like to talk about this particular issue?

Alta, Carol and Diane.

PROF. CHARO: Thank you, Alex. I appreciate it.

I wanted to build a little bit on the suggestion that it is possible to discuss this in a way that allows for situations that are too complicated to capture with a simple rule through -- I think people have been calling it a prima facia rule. I call it the presumptions.

I want very much to have a very strong presumption that established effective treatment is the appropriate control and to make it very clear that to deviate from that requires some kind of special justification. Which is a somewhat more flexible rule.

The only fear, of course, is that it becomes the loophole through which you can drive an army of

trucks.

I disagree with Steve.

DR. SHAPIRO: Convoy of trucks.

PROF. CHARO: A convoy of trucks. Thank you.

I mean, I disagree with Steve about the irrelevancy here because I think the issue is discussed -- as I presented it before, it had to do with the notion of betrayal and on that score the placebo is a feeling of betrayal.

But more to the point, after this very well presented array of experimental styles, what has been shown is, that there are ways to approach the question of interest in a staged fashion that minimizes perhaps the number of people, whoever have to be exposed to the starkest kind of protocol. For example, the double blinded placebo control to test efficacy versus nothing.

There is going to be the established effective, experimental and natural history triple armed study. There are going to be dose response studies in certain -- I mean, there are ways that you can stage things where you begin to get a sense of how well the experimental intervention is working.

And then as a final check, to make sure that what you have not been seeing is an effect having to

do with the population right there that has been influencing the results on all the arms.

When you finally have to do the placebo, you can probably do it with far smaller numbers because you do not need to have statistical significance of the same degree in order to confirm what you have been approaching in a staged fashion.

In other words, I think there is a way to integrate all of the material before with ways to show that it should be difficult but not impossible for IRBs to come to the conclusion, and investigators to come to the conclusion, that they absolutely have to forego the established and effective treatment arm. Right?

DR. SHAPIRO: Yes. In that context I think flexibility is really quite essential because, just to take the example you gave, Alta, the importance of time affects whether staging is a useful strategy or not and that would differ -- but I agree in general. Anyhow, let me go to the people who are on my list. Carol and Diane?

Bernie, you are on the list.

DR. GREIDER: I like the idea of incorporating some flexibility into the recommendations and I think that Bernie really

articulated what my -- the trouble that I have with this conclusion as it currently reads, and that is that it dictates the science by saying that you have to provide the established effective treatment because there may be some scientific questions where you cannot then use a different kind of trial and you might not get anything valid out of it.

So I really -- I like the idea of incorporating some flexibility in here.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I just wanted to clarify, Steve, what you were saying before. And the argument that you were saying you are going to present, is that ultimately going to be an argument for not doing the research or an argument for doing the research and not providing an established effective treatment to the participants?

I was not clear what you were arguing.

MR. HOLTZMAN: I think that the paradigm case with which this whole concept comes about, starts with the notion that there is an effective treatment available to people in the normal course of events, such that, if you then put them in a research context, it would be unethical to subject them to a risk of harm which they would otherwise not be subject to.

When it is now extended into a context in which the ordinary course of events would not have them get the effective treatment,the question then becomes whether or not there is a special obligation to make it available to them because they are in the research context.

The argument that is made here, is that, because of the research ethics and the principle of beneficence, in order to be able to be ethically allowable to ask them to participate in the research, this is a requirement. A question that I think is reasonable to ask is that the requirement of asking them into research, because there is a departure from the paradigm case in which that requirement arose, which is that you do not subject people to harms that they would not otherwise be subject to.

That is the question I am asking. That is the argument that needs to be made. It can be rebutted and people with reasonable beliefs can disagree about that. But simply throwing it out, the way this seems to have done by starting with 1A, which I think was a -- anyway, that is all I am saying, Diane.

DR. SHAPIRO: Bernie?

DR. LO: One of the things that is very

**difficult about these discussions is that we never go back and sort of see how things evolve over time. So I want to take you back to different points in time. Right after the AZT, the ACTG 186 trial, the U.S. trial that showed that full course AZT is effective in preventing maternal to fetal transmission.**

**Would you say that it was established everywhere in the world or just in countries like the U.S.? Was it unethical, in other words, to do the first Thai study that was trying to do a shorter course compared to placebo? Or would we say, no, it was already established because you could do it in the U.S.?**

**There were considerations about different viral loads, -- you know, other delivery issues.**

**The next question is after the Thai study was done, so short course in Thailand is better than placebo, that is in a nonbreast feeding population. Okay. Do those -- is any form of AZT, short course or long course, established therapy in a breast feeding population?**

**You know, Peter Lurie said, "We will say absolutely. It is unethical not to give them some AZT because you know it works."**

**Other people would say you do not know that.**

That we know that HIV is transmitted. You could wipe out all the effective benefit by the breastfeeding and you could be subjecting moms and babies to risk.

It turned out one of the African studies showed that the combination of AZT and 3TC actually causes very rare fatal mitochondrial encephalopathy in the kids. Now you would not have known that if you had just assumed that this was effective therapy.

So I think that now in retrospect because we know that the placebo study was done, no one -- you cannot scientifically say that it is an open question whether antiretroviral therapy in a breast feeding population works. It clearly works in a variety of Sub-Sahara and African situations.

But can you have said that before that study was completed? And as different studies started coming in, there probably was a time when studies should have been stopped earlier based on the results of other studies.

So what makes this difficult is that we have information now that was not available, and I think, you know, what bothers me is that it is so easy to point fingers in retrospect.

I think what we want to say is this sort of discussion should have taken place before the study

was designed, before it was implemented at the first DSMB meeting, assuming there is a DSMB meeting, and not only after the results were published.

And I do not know if we really want to go much beyond that, which then gets us in the position of trying to say, you know, what is a legitimate scientific disagreement and what is blatantly unethical conduct. But I think we have information now, that was not necessarily available to people planning the study or conducting the study, and that is what makes this so treacherous.

This phrase "effective and established" bothers me because, I would like to see us, not in the publication, but just think through for ourselves, can we agree at what point, long course or short course AZT was established and effective in Sub-Sahara in Africa.

DR. SHAPIRO: As I understand, one of the things you are saying, Bernie -- I just want to clarify it for myself so I can think it through more carefully -- is that if you are going to use a term like "established and effective," deciding whether it is effective is an extremely sophisticated, subtle and very often demanding thing, over which reasonable people could disagree at various points in time.

**DR. LO: And which has a lot of values that has much to do with considerations of risk and uncertainty and priorities as is a matter of statistics.**

**DR. SHAPIRO: Yes.**

**DR. LO: I think my main point is that I want to see that discussion as broad as possible, and involving as many stakeholders in the host country as possible.**

**That is probably more important than trying to sort out the exact conditions under which something is really unethical versus just sort of ethically troublesome.**

**DR. SHAPIRO: Larry?**

**DR. MIIKE: First, I want to apologize to Alex for stretching this discussion before he can get on to his topic but it seems that in previous meetings I thought we had come to a conclusion that there would be certain principles that we would stick to and even if it meant the research could not be done in a country.**

**We seem to be backing off on that. Maybe this is not the appropriate example but I thought we had forcefully said that. We may still be looking for whatever we would back up on that.**

But I just wanted to remind the group that we had made a decision and this particular discussion says, well, you know, now it seems to me it is sort of like the research design will influence whether we will -- what our ethical principle is going to be, to put it starkly, and that bothers me a bit.

Because we are also approaching that from another side which is the suggestion by Ruth and Alice that we dispense with standard of care and move to some other criteria. I, for one, would not want to go back to the standard of care definition for reasons that have been stated.

And then, third of all, in countering the what I thought we had agreed on in the past, which was that there might be some principles that we feel so strongly about that, even if it meant no research, that is tough in a particular country. Is our discussion that what we are saying here is not absolute? It is sort of like what I call the default or prima facia or assumption.

But I look at that from a purely practical angle. I do not think anything that we say here can have that rigorousness and that absoluteness in terms of what would be going on in these countries.

Again I would state that it is the force with

which we say where the ethical direction should be heading from the report that we have rather than trying to impose an absolute which I know would always fail in doing it.

So I think we are sort of talking around and around and around because we had made a decision that we would like some specific suggestions rather than waiting towards the end and so we are getting into these specific conclusions without the context of the whole report as Ruth has said many times.

So I guess that is the tradeoff that we have had. Now we are discussing specific things but we are lacking the context. Whereas before we had the context and nothing specific.

DR. SHAPIRO: Alex?

PROF. CAPRON: Well, if Alta had a convoy of trucks, I have a gaggle of questions.

On this question that we have just been talking about, I want to raise a different aspect of what I recall from some of our earlier discussion, and ask whether it has a place here, and whether it is here and I do not see it.

I had thought -- and this is particularly relevant, I think, to what Steve is going to write up -- that one of the arguments that was raised was not a

beneficence argument but a deterrence against exploitation argument, which is not the same thing.

And the argument was that, we did not want to have a situation in which facing large research costs someone says, "I will go and do the study in the place where the underlying level of care is the lowest and, therefore, I have to do the least."

And the insistence that, no, you would have to bring in the effective established treatment to that situation, removes the incentive to look for the poorest country or the least level of care in selecting where you are going to do your studies.

Now that is a deterrence argument.

It, of course, plays into the question of why it would be unethical, even with consent, to do the study in this country once the effective level of care has been established in a certain place. And that goes back, Arturo, to the paternalism argument.

I mean, we say even if a group of women could be persuaded that this other treatment might turn out to be just as good and be a lot less burdensome as well as a lot cheaper, we could not allow it to be studied here somehow. I am not sure whether that is an accurate statement but I gather that was the perception at the time.

So I hope that somehow that can get back into the discussion around page 35 and thereafter.

DR. MACKLIN: Can I just ask --

PROF. CAPRON: Yes, please.

DR. MACKLIN: -- Alex --

PROF. CAPRON: Maybe -- is it there?

DR. MACKLIN: No. Let me just ask if that -- if this is the appropriate place -- and what I mean is this chapter is entitled "Choosing a research design." What you raise is a critically important question.

We have discussed it. It is going to come into this report but I do not think the context here is the right place for it. In other words, it is not the choice of research design. It is the choice of a country. I mean, when you are saying it is an incentive --

PROF. CAPRON: Well -- but I gather it is at this point on page -- where we say the principle beneficence, blah, blah, blah, entails an obligation to provide an established effective treatment.

I mean, it seems to me at least a cross reference to the notion that establishing that standard removes what would otherwise be an incentive to do the study in the country where you would have to provide the least.

**I mean, part of it is the choice of doing it abroad, rather than here, and I gather part of that argument is a research design which asks people to give up an effective treatment for a life-threatening disease, in favor of an unproven treatment, which on its face is designed to be no better than what they are getting now but may be cheaper or less burdensome. In this context it would have been a particular problem.**

**And I just think if that is explored in another chapter, fine. I just think this is a place to cross reference it.**

**It becomes more of an issue, Ruth, if Steve brings his language in here because his language would say there is no obligation as I understand it. Then you would have to say, "Well, wait a second. Once you remove the obligation aren't you back on to the risk of people selectively designing studies?"**

**To me it is part of the design. Okay.**

**The second question -- and this is for the whole group -- was anyone else bothered by the ordering of the material?**

**Maybe there were points from pages four or five, whenever it is you get into the actual design part of things, through to page 23 or 25 where there**

**are occasions to talk about standard of care or occasions to talk about established effective treatment.**

**But what I got at the beginning of the chapter there is this, "Well, we are not going to use this," and it is presented as though this is the language we have chosen, but there is an ethical argument behind that language.**

**And, by the way, I like your very brief but I thought quite satisfactory, discussion of why we do not want to use the phrase "standard of care." I thought that would really handle the issue nicely.**

**But then I am sort of waiting for some discussion of it and instead I am taken with all these details about research design, all very important and worthwhile, and underrated probably in the overall literature on ethics, and then finally I get back to the point at which these other issues become pertinent.**

**And I thought maybe since you probably do not want to put all the ethics in the front, maybe you want to put the discussion of the terminology closer to the point where you start using the terminology.**

**If I am wrong and that other language is used in places I just missed in the intervening -- the**

middle part of the sandwich, fine. But I thought that if other people are bothered by that, you might take that into account.

Point number three. On page 24 -- there is just one small thing you talk about and it is this issue that we were talking about in the other chapter. You talk about the -- line 14, 13 and 14 and then the point A on line 15, among the chief considerations are: (A) The research is responsive to the health needs of the host country.

This is a subtle question but I wonder if what we mean is the health needs of the population. The difference being that the health needs of the population are something which scientists, medical scientists, can make some conclusions about.

The health needs of the host country is a political judgment it seems to me. Now we may mean political judgment, but it seemed to me that, in terms of scientific benefit, and this is really a statement of the basic ethical consideration that there be benefit, you were really more talking about the health needs of the population.

That it is wrong to go to a group of people and study them in a way which has nothing to do with their collective health needs at all and it is one of

**the arguments about, you know, not doing certain kinds of cosmetic research on prisoners that they used to do and putting cosmetics in their eyes like they were rabbits or something because they were not going to get any benefit from it or whatever.**

**Point number three -- and anybody who wants to say, "Wait a second --" they want to discuss that, I will shut up and we will have a discussion on the point.**

**But point number three, on pages 32 and then again on the point that is on page 34, 33, 34, you have these statements about the voluntariness issue as it relates to the inducement that is offered.**

**Let's look at the one that is on page 33, the conclusion on 33, 34. The offer to provide members of a control group with an established effective treatment that is unavailable outside the trial does not constitute, flat statement, does not constitute an undue inducement to participate in the trial and is, therefore, ethically acceptable.**

**I believe that that depends on what are the risks of the trial. I mean, I can imagine a situation in which it would be ethically unacceptable because what you are offering people, the chance to get penicillin to treat their child's pneumonia, which is**

otherwise fatal, is so desirous to them that they will agree.

But what you are asking them to do is so extremely risky in consequence, that it is not ethically acceptable. That really is the undue inducement. Whereas, if there is a closer proportionality between what you are offering them and the degree of risk they are taking then I think it is right to say that it is ethically acceptable. That is one issue.

The other issue is whether it is mostly hinged on the voluntariness, which is the conclusion on page 32, or whether it is an objective statement about that relationship.

In other words, the question is not that you are overriding the voluntariness, that it is wrong to put people in that, even if they would knowing what is at stake, voluntarily go forward. That is to say, it does not amount to a gun to their head but it is wrong for all the reasons of beneficence for a researcher to put a person in that situation.

I just ask that you consider adding some notion of proportionality there.

Finally --

DR. MIIKE: Alex, can I just comment on what

you just said?

PROF. CAPRON: Yes, please.

DR. MIIKE: I do not follow that argument because what is the case if you do not offer them the treatment -- the established effective treatment? You would be left with an unethical experiment where the risk is large already. So I do not see that proportionality argument about balancing the degree of risk.

PROF. CAPRON: Well, I mean, in the situation that you pose, I gather the argument would be that that research should not go forward because simply the risk is too great.

This statement focuses on the question of whether we should ever be concerned that the offer of good care will induce people to do something where it is wrong to have asked them to do it and it seems to me that the wrongness, or conversely the acceptability of that, is influenced by whether or not what you are asking them to do is in proportion to the good that you are offering them in the process.

I mean, the whole argument after all -- no one offers someone a $1,000 for a simple blood draw. They offer them $1,000 for going into a -- you know, one of those oxygen compression chambers or something

where there is some chance of actual injury, let us say, some brain injury or something.

And we say, "Well, if that is really very risky, at some point it seems wrong to offer them --" you know, "I will give you $10,000. I will give you $100,000. You know, go do this." Say, "Wait a second, that is not -- that is research which is too risky." The very offer that you are giving them is an indication that that is too risky.

Here we are dealing with something which on its face does not have that characteristic. It is established effective treatment that is being given to people in this country. Our concern is if nothing like that is available to the people in the other country where the research is going to be done, is it wrong to offer it? And on the face of it, we would say no.

But again I would say, "Well, but if you are putting them to some very large risk then I think it is wrong to offer it."

DR. MIIKE: But I am just -- I just cannot -- I cannot conceive of an experimental design where that would come up given the degree of risk that you are worried about.

DR. MACKLIN: I agree with what Larry is

saying entirely. Let me put it slightly differently.

Even before you get to this point, let's assume that the well-constituted research ethics committee, the IRB, has to look at the risk/benefit ratio. They justify the research on the grounds that the risks are reasonable in light of the benefits to the subjects or others. Even if the risk is high, they have got to determine that the risk is reasonable.

So it has already been established that the risk is not too great a risk to subject people, so the question is what then does providing the established effective treatment -- what more does it do to create a problem of inducement than the very fact that you have that risk? It has already been decided that the risk is not too great to carry out the trial and that was done precisely because whatever benefits were there justified the risk.

So again I cannot conceive -- I mean, I am right with Larry on this one. I cannot see what more you --

PROF. CAPRON: Okay. Let me -- on that one I will try to work out something for you because it is not -- and if, what I try to do does not work because the safeguard is already built in, then I will agree.

**The final question that came up from Dr. Pape's testimony this morning, the situation that he described where he was unable to participate in a research trial in Haiti on the effects of a drug that was being given for TB, which was not approved for use in the United States.**

**I just wonder as a factual matter and then,depending on what the answer is, as an issue for us to examine, is that generally true? That is to say that, if a U.S. researcher has set up a collaborative relationship with someone abroad and that researcher says, "I think we should study X, Y, Z," that the U.S. researcher cannot be involved in the research if it is a substance which is not approved in the U.S.? No?**

**DR. SHAPIRO: I think that was a case of the sponsor having the rule, right.**

**PROF. CHARO: He did not give us enough facts to be able to sort it out. There were questions. Was there an IND or not for that drug? What were the Cornell rules?**

**DR. NEIBERG: I am Phil Neiberg. I am currently a visiting scholar at the University of Virginia but actually am a CDC employee. My understanding of this issue is that an IND is required if an investigator will eventually wish to use the**

**data for marketing purposes in the United State but that there is no primary obligation to have an IND in place for an investigator to study a drug some place else.**

**PROF. CAPRON: So that whatever the problem he was describing, he misunderstood the objection of Cornell or Cornell raised an inappropriate --**

**DR. NEIBERG: There is a popular misconception about this. I think a lot of IRBs misunderstand the regulations. We have had to clarify it a number of times for international research about what -- for drugs -- for issues -- interventions where there was no intention to use it in the United States.**

**In talking with the FDA, their point is, if you do not want to use this intervention in the United States, if you do not plan to submit a proposal, then -- we are not interested in having an IND for it.**

**PROF. CAPRON: Well, given -- if part of what we always are looking at as our audience are IRBs and if, as you put it, this is a popular misconception or misunderstanding, then perhaps somewhere we should note it as a problem if other people -- in a circumstance --. I gather that he was pleased that eventually the research was done in another country**

and the result was to show that this was a drug you should not be using on AIDS patients because it had this or that incidence of this undesirable side effect. I assume that there is some other drug that could be used for TB that did not have that consequence.

DR. NEIBERG: Yes, there are alternative drugs. I agree this is something that would be useful for you to have a clarification from the FDA so it gets into the public record.

PROF. CAPRON: Okay. Thank you.

DR. SHAPIRO: Thank you.

Diane?

DR. SCOTT-JONES: I had a comment to Alex's first point and so I hope I can remember it from the notes that I took.

Alex was responding to the conclusion and recommendation on page 36 and he talked about what would deter a researcher from going to the very poorest country to conduct a study.

And I believe Ruth responded by saying that that issue did not really belong in this chapter and I wanted to suggest that the issue of the choice of country might fit very nicely on page 23 under the heading of the population.

As written, that really does not make any specific comments on doing research in an international context. It just talks about how you would choose participants for a study.

And I think Alex's point about --his more general point about how a researcher chooses a country, and thus a population for a study, really would fit very well here.

And I would also like to say that I like very much the language that is used here. The word "participants" is used instead of subjects. I think that is very much preferable throughout to use the word "participant" instead of subject.

But my bigger point was that I think what Alex talked about, about choosing a population or a country would fit very nicely there in that section.

DR. SHAPIRO: I think one of the issues you raised, Alex, was, I think, imagining a case where somebody went somewhere because it was the least expensive place to do it or some vocabulary to that -- and you wanted a deterrent against that.

I have been trying to work exactly that issue through my mind and I have not succeeded yet. But I started off with a bias only an economist would have, which would say, "Well, you know, what is wrong with

that?" I mean, you know, we make sneakers in Shanghai instead of Peoria or something.

PROF. CAPRON: But we do not want sweat shops.

DR. SHAPIRO: Yes, I understand. And so it cannot be simply that it is the least expensive. It has to be something else that is there. But I was not sure that I understood what you said.

PROF. CAPRON: But, you know, what I was trying to say was, -- suppose we were to be convinced by Steve that his basic version of the recommendation was the -- or conclusion was the right one, not the one that is here. Then I think we need to address the issue which would be now that we have removed any requirement, any obligation --

DR. SHAPIRO: I agree with that.

PROF. CAPRON: -- what is to keep people from doing that.

DR. SHAPIRO: That is right.

PROF. CAPRON: I think in chapter 4 we may talk about -- this issue of researchers -- if we create an obligation to provide after care -- say, well, if it goes to the country, I am going to pick the smallest country around because that will be the best way -- better -- you know, better Malawi than

**Zaire or some other large population.**

**DR. SHAPIRO: Okay.**

**PROF. CAPRON: So I mean these issues come in. I think we can live with that version but the notion that you would seek the country in which the -- now I am trying to avoid the word "standard of care" but the level of care there is the most basic and primitive so you can go in and say that is the placebo, now I am just doing it --**

**DR. SHAPIRO: I understand that.**

**PROF. CAPRON: Isn't that an argument? I mean, it is precisely because the economic incentive would be in that direction that the morals operate as a limit on --**

**DR. SHAPIRO: Right. So you have to specify whatever moral constraints you want.**

**PROF. CAPRON: Right.**

**DR. SHAPIRO: I agree with that.**

**PROF. CAPRON: And you do not do that simply on the basis of beneficence but keeping people from acting on their economic incentive.**

**DR. SHAPIRO: Solely on that.**

**PROF. CAPRON: Solely on that. Solely on that, yes.**

**DR. SHAPIRO: Okay. There are a number of**

people who want to speak now.

Rhetaugh, then Diane, then Steve.

DR. DUMAS: No, I do not have anything.

DR. SHAPIRO: I am sorry.

DR. DUMAS: I was just exercising my arms.

(Laughter.)

DR. SHAPIRO: Thank you.

Diane, then Steve.

DR. SCOTT-JONES: This is just a brief follow-up. I just want to try to say again that this is very much a design issue, how you choose the place you go to do the study. For some people it is because you met someone from that country or you have a former student who is in that country. But it really should be a design issue and there should be a strong rationale for choosing that particular country, and I think it should be addressed here.

DR. SHAPIRO: Okay.

Steve?

MR. HOLTZMAN: I agree there should be a discussion about -- just as we have talked in the past about not going IRB shopping, not going country shopping. However, just for what it is worth from a realistic point of view, Alex, if it cost me $10,000 per subject in a clinical trial, the test article, be

it the accepted candidate, is probably 10 bucks. That is not going to be the driver of choosing a country.

MR. CAPON: But in the kinds of cases that we are talking about, from what I have understood, that really is not the issue. I mean, if you could provide no care as the standard of care versus bringing in generators to run refrigerators, having a whole squadron of nurses, purifying water so that the formula can be given, get the women off breast feeding and into formula feeding, you are talking --

MR. HOLTZMAN: That is a different --

PROF. CAPRON: -- you are talking about a huge difference --

MR. HOLTZMAN: -- that is a difference. Okay.

PROF. CAPRON: -- in the cost of running a control group.

MR. HOLTZMAN: Okay. If you are putting in all that. I am just saying -- let's be clear on the cost of the actual test article and the drug itself. If you are the manufacturer, it is next to nothing compared to the cost of the trial.

DR. SHAPIRO: Eric?

DR. MESLIN: I just wanted to pick up on a conversation that Bernie Lo and I had at a break and

ask whether he is prepared to say a bit more about it for the commission's benefit. It relates to his concern about the relationship between ethics and science in choosing a research design.

It occurred to me that hearing Alex's comments about putting some of the ethics a little earlier, that somewhere around page 3 preceding the section that begins on line 12, research design methodology, might be the place, Bernie, a discussion about equipoise and some of the literature that comes from the philosophy of science, and elsewhere about the relationship between scientific validity and scientific value, might be helpful.

I do not know whether Alex and Bernie would agree to that but I thought your comments at the coffee table were very helpful and that might be a place to put that issue.

DR. LO: I think it would be good to move the ethics sort of higher up and give it more prominence because I think the audiences that are going to read this, a lot of them will -- I mean, very few people really understand the ethics. A lot of people think they do but that is what they need to learn.

I think a lot of the epidemiology depends on what background --

[Background noise.]

(Laughter.)

PROF. CAPRON: Turn your telephone back on. It is quieter.

(Laughter.)

DR. CASSELL: It was not a commentary under discussion, Alex.

(Laughter.)

DR. SHAPIRO: Okay. Bernie, I am sorry. I apologize.

DR. LO: There is a fairly thoughtful discussion actually mostly in the epidemiology about how you decide when something is proven effective. Actually, without necessarily using the ethical terminology, they really discuss where reasonable people might disagree. You know, Alvin Feinstein has very nice discussions over fastidious people who say, "The study has to be done in patients exactly like my patient," and others say, "Well, my patients are kind of different from the patients of that study but they are not so different that the conclusions do not apply."

There are cultural differences. The Americans tend to be much more rigid about how similar the study -- the population of study is to the

population you are going to extend it to. Whereas, the European say, "That is silly. Just include everybody in your study. Get 10,000 patients. Do the study real quick with simple endpoints and you know it generalizes to everybody."

Whereas, the Americans do it with such a selective group of people, they do not really know it applies to most people in a population.

You know, there are implicit ethical arguments there about how you value different types of information, -- how you weigh evidence and what degree of certainty you want. And it seems to me those all are sort of ethically, you know, very loaded and rich concepts.

DR. SHAPIRO: Thank you.

Eric, is there anything else?

DR. MESLIN: No.

DR. SHAPIRO: Any other comments this afternoon before we adjourn?

We reassemble tomorrow at 8:00 o'clock. We have a second day syndrome which seems to mean 8:00 o'clock means 8:30.

DR. MESLIN: This time we cannot do that because we have guests at 8:10.

DR. SHAPIRO: I was about to say. We have

**guests early so just in view of their accommodating our schedule, I would ask you to be here as soon as you can.**

**Thank you very much. We are adjourned for today.**

**(Whereupon, at 4:51 p.m., the proceedings were concluded.)**

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