34TH MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

September 16, 1999

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I N D E X

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P R O C E E D I N G S

OPENING REMARKS

DR. SHAPIRO: Let's call our meeting to order.

We are diminished in numbers but not enthusiasm today.

MR. CAPRON: I thought you would say talent.

DR. SHAPIRO: I do not know if I would go that far but I think we do have an important agenda.

As you know, most of our time today will be spent dealing with issues in the international research agenda. We have a number of guests and colleagues who have joined the Commission for today's discussion.

Dr. Killen is here and Ruth Macklin, whom you all know, Alice Page is next to her up here, and will be presenting to us this morning very shortly.

Just a number of very quick announcements. Unless the National Airport stays closed or something like that I need to fly out late today and so I will not be here tomorrow. I will ask Eric to take over the session because we have some important work tomorrow, too. I hope I will be able to be here for most of today's discussions.

Second, I am going to ask Eric to just

perhaps lead us in a few minutes discussion regarding our next stage priorities and how we might go about thinking about them. I do not think we are going to choose them today. I have just gotten that memo. I just want Eric to refer to it. There are not enough of us here today in any case to resolve that issue but I think we ought to get started on that and we will perhaps spend five or ten minutes on that before going on to a discussion of the draft outline with Ruth and her colleagues.

So, Eric?

EXECUTIVE DIRECTOR'S REPORT

DR. MESLIN: Right. First of all, for the folks who are here, as you know the Report on Human Biological Materials was sent into the President and it is up on our web site. It is being printed now and copies will be available in a short period of time as soon as our printer gives us the last deadline. I know everyone is anxious to get copies of that report but it is on the web and hard copy will be available shortly. Everyone knows that the Stem Cell Report was delivered to the President, a statement was released, a copy of which is on your table and is available to the public. The Executive Summary of that report is also on our web site and a manuscript prepublication

draft of the full report is available for any of the media who are here.

Please see Pat Norris to at least indicate your willingness to obtain one. And if there are any other public members here who wish to receive a copy of that manuscript version you will be able to do that.

And we hope to have that published and on our web site fairly soon. By "fairly soon," I mean within the next couple or three weeks. Again all of that depending on GPO publication.

Harold asked me just to briefly discuss a memo that I have handed out for you and obviously you have not had a chance to read regarding possibly priority setting. As you know, we are waiting to hear about the official extension of the Commission which we expect we will learn the fate of very shortly and all signs are that this is going to happen fairly soon. So rather than waiting for that news we have begun the process of establishing a proposal for setting priorities and that is on your table folder.

Largely what the memo says, and you can read it at your leisure and we can talk about it over e-mail as well, is that I am suggesting that the Commission take on a somewhat more systematic approach

to establishing their priority projects over the next two years knowing full well that it is possible that we could be asked for advice on particular topics. It is always a good idea to plan prospectively for how one wants to go about doing business.

So in addition to the International Project which you will hear about for the rest of the day and the proposal in your briefing books for producing an annual status report on human subjects protections the proposal for your consideration is that we contract out for a couple or three or four background papers that are systematic in their approach to a number of topics that have been on our agenda or have been mentioned by Commissioners or even by the public which is part of our executive order.

There are two background papers that are in process now. One being undertaken by Stu Kim, who I will ask to just indicate himself. Stu has joined our staff to help prepare a background paper on issues related to gene patenting and intellectual property matters. We will not talk about it at this meeting but just to let you know that that is under way. The gene patenting issue was contained within the executive order and I certainly felt it was appropriate that we give the Commission an opportunity

to decide whether they wish to write a report on this.

And rather than simply discussing it, the proposal is to give you at the December meeting, again assuming there is a December meeting, assuming there is an October meeting, this background paper and a number of others for you to carefully review, and then to make an informed choice about which next projects you wish to take on.

That is probably all I need to say at the moment if there are any questions or comments.

DR. SHAPIRO: I take it -- was this a memo handed out at the meeting here today?

DR. MESLIN: Yes.

DR. SHAPIRO: All right. Well, no one has had a chance to really think about this carefully but we might come back to it later in the day if there is time in and around lunch hour sometime. If you do get a chance to scan it this morning at least give Eric some initial feedback. As I said, we are not going to make any decisions today on this issue.

Larry?

DR. MIIKE: It is just that if we are going to go through this process we need to reach closure on it by the end of this year otherwise we will never get

it done.

DR. SHAPIRO: No. I think we need closure on it this fall, right?

DR. MIIKE: Yes.

DR. SHAPIRO: Absolutely.

DR. MESLIN: The proposal that I am suggesting is that you would have at your December meeting three or four of these background papers that you have had a chance to review and at that meeting we would decide which of the projects that would be put on the agenda knowing full well that the International Project is being worked on at this point so the decision would be made before the end of the calendar year.

DR. MIIKE: But we would be limited to those three areas. We would be limited to those 3 areas?

DR. MESLIN: No. I take your point. Certainly at the October meeting or even by e-mail if you think projects other than those that we flagged here would warrant a background paper, by all means. The only thing that would limit us is budget. We could have as many of those background papers as you would like to see. Right now there are four that are being proposed and there could be others.

DR. SHAPIRO: Any other questions or comments

with that?

MR. CAPRON: Well, the only thing missing from this document is anything about the current work on human subjects and I assume that is just an oversight. It is not a report which is finished but it is a report which has a series of probable manifestations.

DR. MESLIN: What I have said in the first paragraph is that this does not include the International Report or the Comprehensive Report, Annual Report on the State of Human Subjects Protections described in Tab 3. So my intention was to say knowing that we may be doing something on human subjects issues, which is already in the briefing book, here are other topics.

MR. CAPRON: It would just seem to me advisable that to the extent that there were two topics that really gave rise to the Commission, the human subjects growing out of the Radiation Panel and the gene patenting growing out of the senatorial interest, particularly Mark Hatfield's interest, the three areas that -- I mean, if other people outside the Commission looked at this, the three areas that have been identified come from requests from the White House, discussions among ourselves for the other two.

We ought to give some indication that we did not ignore the charter when we picked topics and the human subjects thing has proven to be a very large topic. It has branched in various ways and it is one where I think our existence can already be credited with some internal responses even though we have not reported about those in anything more than a cursory fashion.

DR. SHAPIRO: That is quite right.

Any other comments or questions?

Okay. Thank you.

So please review this and any further comments you have, and I think there will be quite a lot of discussion on it between us and in between meetings as we try to focus this down to fill out our agenda for the next two years.

As Eric indicated just a moment ago, our short-term agenda, that is the ones immediately ahead of us, of course are on aspects of human subjects and the international research. Those, I would agree, will be taking most of our attention in the next four or five months.

Okay. Thank you very much.

Let me welcome Dr. Burke. Thank you very

much for being with us today.

DR. BURKE: My pleasure.

DR. SHAPIRO: We have been look forwarding to hearing from you for a while.

Let me now turn the discussion over to Dr. Macklin, whom all of you know -- so I am not going to give you any long introduction, Ruth. You will excuse me for that because I think all of us know you so well. But let me say once again, however, how pleased we are with the help that you are giving us on this. And I think judging the draft outline, at least my own view of the draft outline, we are going to have a very exciting report when this project is done but, Ruth, let me turn it over to you.

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

DISCUSSION OF PROPOSED DRAFT OUTLINE

DR. MACKLIN: Thank you very much. I am pleased to be here and Alice Page and I will be together responding to your questions and comments in this first session.

We are going to give a very brief overview of the two documents that are relevant to our work today. These are the memos sent out to all the Commissioners at Tab 2A, a four-page memo, and Tab 2B is the 13-page draft outline.

Those of you who were at the July meeting in Cambridge saw a very different outline and in response to the Commissioners' suggestions and a subsequent meeting that the international consultants had, we radically altered the outline, added new material and responded to most, I believe, perhaps not all of the suggestions for changes, additions and so on.

You will see both in the memo, and my apologies to those of you around this table who had not received these materials before because we are not going to walk through the memo or the outline, assuming that you have had a chance to look at it if not certainly to memorize it but at least to look at it.

So let me say a few words about the draft outline and what lies behind it and a couple of words about the work plan and then turn to questions and comments and suggestions.

First a word about the order of chapters in the outline. The order of the chapters that we propose is not in the order of importance of the topics. Every topic is important. The reason that order was chosen was essentially for a logical flow of material so we can elucidate that or explain it a bit more later on. One of our international consultants

asked -- posed the question: "Why did you put informed consent first, is it because you believe that it is the most important topic?" And the answer is, "No, not because it is the most important topic but in a sense it introduces a lot of the items that will come later." It is almost a stand alone topic and as you will see when we move into the subsequent chapters there is kind of a logical flow so that is just to explain why we chose that order.

A second point is just a matter of a reminder and emphasis. When we met and had our brief discussion in Cambridge in July the question of global justice was raised and the question whether there should be a separate chapter in this report on global justice or whether the theme of global justice should be woven through the report throughout and there seemed to be a consensus.

There were not any votes taken but a consensus that since many of the items that arise in international collaborative research raise questions of justice, obligations, distributive justice, even compensatory justice for past wrongs that this report would emphasize at various points the themes of global justice.

Another point about the outline as it now

stands is you may -- some may find there to be an imbalance or over emphasis in the examples on HIV/AIDS. We hope to -- I will take the blame for that since it is one of the areas that I know the best and knew the best before I started working on this project and beginning to work on the draft outline. We certainly intend to correct what may be an imbalance although -- and the question arises at various times, the phrase, I believe, is "AIDS exceptionalism," whether or not things that come up in AIDS research should be unique or should be thought of as unique to HIV/AIDS research or whether the questions and criticisms and controversies should be seen as extending to all other forms of research.

We will correct the imbalance when we have more material and we will have some testimony from international researchers at subsequent meetings so if anyone is worried that the report seems too -- the draft outline seems too heavily weighted with examples or with a focus on HIV/AIDS we recognize that and we will try to correct -- as I say, correct the imbalance and welcome suggestions that anyone might have for other examples in other diseases or other forms of research.

A final point about the outline, at various

points the outline mentions other international documents and, in fact, quite a number of them are here in this -- I mean, I doubt if everyone got to read it thoroughly but one of the -- one of our plans in the work plan is to do a thorough going analysis and comparison of the international -- both the international guidelines comparing and analyzing them with the U.S. federal regulations and taking a look at some other countries' ethical guidelines or regulations to see -- essentially to have a thorough comparison and see where there may be gaps or holes in the U.S. federal regulations that are addressed by other countries or international documents. That is part of the work plan and will find its way into one of the chapters.

However, having said that, as I think probably most everyone knows, both the Declaration of Helsinki and the CIOMS document -- that is the red book, the ethical guidelines -- International Ethical Guidelines: Council for International Organizations of Medical Sciences. Both of those documents are currently undergoing revision.

We do not plan to enter the fray in a sense -- that is taking up the debates in the draft documents that have been produced both for -- well, for the

Declaration of Helsinki and the one that is in process for CIOMS. I mean, that should not be the work of this Commission.

On the other hand, we may be slightly hampered by the incomplete or ongoing process, that is if we refer to those documents in the report and this Commission's report will be complete, I have good reason to believe will be completed before the process of revising those international documents is completed, so we will have to, I think, be cautious in what we say since we do not want our report to be out of date in one year if Helsinki is radically changed.

On the other hand, we want to show some deference to those international documents because other countries pay more attention to the international documents than -- international guidelines than they do to the U.S. federal regulations. So that is a comment about those two.

So what we -- did I omit anything, Alice?

MS. PAGE: We were going to mention a couple of the other studies that we looked at, the TB and the breast cancer studies, and if anyone had any other ideas to please bring them to our attention.

DR. MACKLIN: Okay. This was back on the

other point.

MS. PAGE: Yes.

DR. MACKLIN: The imbalance so to speak.

The outline does mention a couple of other examples that are -- with articles in the published literature. They are referenced. That is one that is a -- was a TB study in which a medication -- let's find the outline and just point to where it is. Chapter 2. Right.

Some of the same questions or possibly criticisms that arose in the HIV placebo controlled maternal to child transmission studies, that is the criticism of withholding a proven medication or something that is available in the United States but not in the country where the studies are being conducted, those same questions could be raised and, indeed, have been raised in the placebo controlled trial of TB prevention among HIV positive individuals in Uganda. This is on page six in Chapter 3 of the outline.

So that is one example and there are -- there is an article in the literature and then there are letters to the editor so that is another example. Again even though the individuals are HIV positive the study was not an HIV study. It was a TB prophylaxis

study.

And one other example that we referenced was a breast cancer study. Now much of the criticism or comments and controversy that surrounded that were -- took place within a single IRB, not raised to the level of a national or international debate. The article that is relevant here is the one by Love and Fost in the reference list at the back.

It was a 1977 article that recounts a breast cancer trial that was being proposed in Vietnam and most of the questions that arose there were not in the trial design but rather in what could be disclosed to subjects and the researchers -- the researcher and others in the country where the trial was to be conducted wanted to withhold a lot of information that would normally be required to be disclosed to the subjects.

So those are just two other examples and we will look for many more.

Yes?

MS. KRAMER: Ruth, somewhere during the past few months there was a reference to -- there was some criticism leveled about a hepatitis study that was done in Senegal. It was a study done leading up to the development of the hepatitis vaccine.

DR. MACKLIN: I do not know that and I hope someone can speak to that.

DR. BURKE: I know a bit about it but I do not -- the specific question is?

MS. KRAMER: Questions were raised about the ethical standards under which those studies were done, too. I am sorry I do not remember any more about it. I just remember having read something about it.

DR. BURKE: It has been called into question before. Those were done about 15 or 20 years ago.

DR. KILLEN: Are you looking for controversy or are you looking for examples of problems?

DR. MACKLIN: Well, that is a good question. We are not looking for controversy per se but we are looking for -- and I think this fits in pretty much into the assessing risks and benefits. We are looking for examples that would fit a certain description, namely research that either could not be conducted or approved in the U.S. for whatever reason but where research -- for whatever reason, good or ill -- and where the research is being conducted or has been conducted, and I would like to say fairly recently rather than something much older because we can, of course, all point to all kinds of things that took place in this country years ago where what is required

is an assessment of why they could not be done here, why they are being done elsewhere, and could be doing else -- the conduct of the trials outside the U.S. be justified. I would say that is the kind of example.

DR. KILLEN: Yes. We certainly will be able to help a lot in that. We have -- the NIH has many, many studies that probably could be put under that rubric.

DR. MACKLIN: Okay. Good. Well, we will -- we are in the process, I think, of trying to gather that information.

Well, what we would like to turn to now in the discussion is a couple of very broad questions that we would like the Commissioners to respond to about the outline and for that matter the work plan, the way in which we hope to proceed.

And the questions are, first, what, if anything, is omitted from this outline? That is to say are there gaps? Are there holes? Are there things? Are there whole topics? I do not mean specific items but whole topics or areas of international collaborative research that is omitted?

Alternatively, what is in here that should not be in here? Namely one of the Commissioners

commented in response to the outline, "This is very ambitious." Well, if it is too ambitious, if it is not do-able perhaps there is something that should be or might be deleted or removed or at least set aside until we see how the work goes.

Another question is in the memo where we outlined the work plan we have listed individuals and groups that have been written to or will be written to in the course of the work of this project. For example, the deans of all the schools of public health. Also there is a contact that is being made with CEO's of some industry and others that you will see. Are there any groups or individuals or categories of groups or individuals that are not mentioned here that you think could be helpful to write to either to try to obtain some information from them or perhaps to testify at one of the meetings?

So with those questions -- yes?

DR. MIIKE: The deans that you wrote to, were those schools of public health? Why schools of public health if we are dealing with clinical -- basically clinical research? It seems to me those were the wrong deans to poll?

DR. MACKLIN: Well --

MR. CAPRON: It is not wrong, not

sufficiently broad.

DR. MIIKE: Yes.

MR. CAPRON: Yes.

DR. MIIKE: Because it seems to me that they would not know the kinds of projects and clinical studies that are being done overseas that -- that is just not that field.

DR. MACKLIN: I think some of them do actually get --

DR. BURKE: I happen to be on the faculty of a school of public health and I have done lots of trials internationally and I know Al Sommer has spent his entire career in the international health arena so it might not apply to some of the deans of schools of public health but at least others I know are very expert and are probably the best people to choose.

DR. MIIKE: Well, that may be true but I am just asking a basic question about why deans of public health or is there some other group?

DR. BURKE: I am sure there are other people who might be expert as well.

DR. MACKLIN: Probably not versus but I mean that is a suggestion that maybe we should think farther --

MR. CAPRON: Yes. I was going to come at

that from a slightly different point of view. There are some schools of which Yale is one which you went beyond the school of public health to the department head of epidemiology but besides having been on the faculty of Yale, I have been on the faculty of Penn and USC, neither of which has a school of public health but in each case has excellent people in preventive medicine and epidemiology. I mean, I think the people at USC are some of the strongest people in cancer epidemiology in the country and I do not know on the international side but I would agree with Larry that many medical schools will have faculty who have been involved in drug development trials.

You are also meeting, as I understand it, with the PhRMA people and I assume that that will link you into the studies that are sponsored by pharmaceutical companies perhaps without U.S. academic collaborators but directly with collaborations abroad.

And I think, as Larry's suggestion, we need to look at that development but I certainly thought that as -- maybe Dean Sommer's reply, which is the one that you highlighted, I do not know if you have heard from others, was unusual. But, I mean, Johns Hopkins has an age-old reputation for its excellence in

international health and the people there who have been involved with the international efforts to eradicate smallpox and so forth and so on.

So I saw no question that this was not a good list but an incomplete one.

DR. MACKLIN: Yes. Thank you for these suggestions. This is a question, not a comment. I am wondering whether writing to deans of medical schools will be a fruitful approach rather than trying to identify individuals who have --

MR. CAPRON: Yes.

DR. MACKLIN: -- that is the researchers themselves.

MR. CAPRON: But you could ask the deans or their -- if they have directors or vice-deans for research just to pass your letter along to those who have had projects that involve international collaboration, and I think it is possible -- I mean, it will go in the trash can at some point but in some places they would recognize the value of this particularly because it is an invitation to inform our process with experience that people have had not just with the controversies that have made it to the pages of the newspaper, and I think it is important.

The first chapter you have here talks about

or will talk about the value of -- for the world's health of this process of international collaboration and this would be an invitation to those who wish to participate with us by giving us examples.

DR. SHAPIRO: Dr. Killen?

DR. KILLEN: Just a thought. The -- a link to the academic world that is involved in this that is broader than just the schools of public health would be through the Fogarty Center at the NIH, which would have links more to people or might have categories of folks that have a lot of experience that goes beyond that realm. It would be a broader net of the academic world.

DR. SHAPIRO: Larry?

DR. MIIKE: I am beginning to feel sorry that I even mentioned it now because it seems to me that this might not be an area we want to put much more effort in it since you have got a huge plate to fill right now.

DR. MACKLIN: I think we would -- we should focus on what the goal is of contacting individuals. I mean, the first letter sent out to the deans was more information gathering. If we want to cast a much wider net and, of course, the industry is critically important -- if we want to cast a much wider net I

think we have to ask why.

I mean, sometimes one can look for too much information and then have it and then not know what to do with it so unless we think there are real gaps that will -- there will be gaps in the report if we do not cast the net more widely. We have to think what the goal is.

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

DR. LO: I wanted to shift the discussion a bit from the point Larry raised about who we are contacting to sort of the goals. As I read through that, and I certainly agree with Harold, it is very thoughtful and I think it is really going to be a very important and exciting report. There are two areas that I would like to see us really focus more attention on.

One is of how to resolve some of the conflicts that either are in the literature or are being identified by the empirical contractors who are working with us. I read their reports. Over and over again there were examples of problems with informed consent where people do not have a western concept of science and disease. You know, the issue cries out, well, how do you conduct a trial and get anything

resembling informed consent where there is such a basic discrepancy in sort of what causes disease and how you treat disease.

There seemed to be alluded to examples of how that apparently was done somewhat well by the investigators and I think for the sake of balance and also for the sake of being constructive it would be really helpful to try and highlight creative constructive solutions to these dilemmas because my sense is that some of them are philosophical conundrums and some of them get worked out by sort of finding a way to explain things that seem to make sense in the language and the culture.

So I think that in addition to the very dramatic front page stories it would be nice to get some sort of day-to-day success in the trenches so to the extent that we are looking for information I would like to see us collect more examples of sort of dilemmas that were well handled that sort of are no longer dilemmas because the investigators managed to figure a way to do this well.

My second area that I would like to see us put emphasis on are a different set of diseases than what is usually given attention. It seems to me a lot of the tensions in this area come from the fact that

there are studies -- there are conditions that are of great interest to the U.S. and other development countries where for all kinds of reasons it is considered desirable to do studies on those conditions in developing countries even though those may not be the most important or the most treatable or the highest impact conditions in those countries.

So I think, you know, a lot of the dilemmas with AIDS is from the fact that we are really testing things that are probably going to have more impact in the developing country -- developed world than the developing countries.

It seems to me that another dilemma is there are all kinds of diseases that are very prevalent which are sort of under researched for a whole host of reasons and it probably is unlikely that without significant input from developed countries' scientists that there will be a lot of dramatic progress made.

I think as we talk about justice -- I mean, I think just to focus on why -- what are we going to do for breast cancer and diseases like that in the developing countries, it is only part of the picture. What are we doing for things like malaria which are -- you know, do not really exist as public health problems here but are really terrible problems

elsewhere in terms of the amount of effort that we encourage in research and the types of collaborations.

Is there some way to kind of get more U.S. expertise to bear on problems that are primarily problems in developing countries and really have very little impact in this country and, therefore, do not have the kind of commercial drivers to carry out that kind of research?

So those are just some thoughts I would like to see us pay more attention to.

DR. SHAPIRO: If I could just ask a question, Bernie. I think the latter point that you made of the few points that you made, that is an issue really of the shape of the scientific agenda if you like is one way to describe it. And I understood your point to say that we might try to think or make recommendations or something regarding that, regarding just what it is we spend our time on, or did I misunderstand your --

DR. LO: Yes. I mean, I think that is certainly one question. The second thing is I think that the types of dilemmas, ethical dilemmas in the conduct of research that come up in trials where there is no concern about exploiting the Third World subjects and scientists because we are really gaining

information that is going to be most valuable to us do not necessarily apply but there may be other dilemmas that come up in that situation that we are just not as familiar with.

DR. SHAPIRO: Alex?

MR. CAPRON: I wanted to address the topic that Ruth had raised a moment ago about why we are engaging this. Unlike academic research it seems to me part of the reason that we would engage in a process of broader inquiry would be to put people in the relevant community on notice that this is a topic that over the next year we intend to put out a report about and obviously groups like the Fogarty Center that have all the international contacts, including the American collaborators, the pharmaceutical companies will learn fairly early on but it would seem to me advantageous that people in academic centers around the country who are doing biomedical research that takes them into collaborations abroad be aware of this.

Now most of them have busy lives and will not interact with others or whatever but as a public Commission it seems to me we have an obligation to make it known to people who do not necessarily follow what is going on here in Washington that this is

afoot. It may give -- yield the benefits that were inherent in the first of Bernie's comments that we would get examples that would be useful to understanding means of dealing with these dilemmas at something other than simply a philosophical level but it also serves the value that people will not be surprised by our report's existence. I mean, whether they agree with its conclusions or not.

I think that as a public Commission we have that obligation. It is unlikely it seems to me given my experience with this that we will be flooded with more materials than we can possibly deal with. If we get a lot more I think it is up to the executive staff to figure out what resources are available to encompass that. Obviously the two of you cannot alone handle a flood of responses but I think that is important.

I hope -- I want to end this comment and I hope we will have a further chance. Bernie was getting us into some further substance and I do not want to comment on that yet but I hope we will have a chance to get back to it.

DR. SHAPIRO: We will come back to that.

Trish?

PROF. BACKLAR: I was struck, Ruth, and I

thought that you had done a wonderful job. I want to say that publicly. I said it to you privately.

I was struck as I read through the material that you had prepared and that the researchers had brought of some similar kinds of problems that we have in this country that go on in the research in under developed countries and I am hoping that we will not let that slip by. You actually make some mention of it but I want to make certain that we do address it.

One of the things, of course, is the therapeutic misconception, which is a global misconception -- globally misunderstood aspect in people getting involved with research but the other was extremely important and that was that people -- the benefits of the research often do not reach the people who are the subjects.

And certainly when we were looking at issues in our capacity report, the people who were subjects of research for mental disorders, often they would be not -- the benefits of the research, the medication, would not follow them afterwards.

So that is two things that I think are important.

DR. MACKLIN: May I respond?

DR. SHAPIRO: Yes, please do.

DR. MACKLIN: I do not want to respond to everything.

DR. SHAPIRO: Yes, absolutely. No.

DR. MACKLIN: In fact, it is a very important point and we are going to have to struggle with just how to bring that into the report. That is the report could explode in size if for many of the topics raised we start exploring or giving examples of similar problems in this country especially since we have got the other agenda, that is the project that Jonathan Moreno is doing. That may be a good place to dovetail the two and to see from what we find in the international setting what some of those same problems and issues are in this country.

I mean this was noted a number of times by our international consultants, too, and we are going to have to struggle. We do not want to -- well, it may be a problem if we have to bring many of those examples in because then the report will lose focus but it is -- I take your point and we will have to find a judicious way to handle that issue.

PROF. BACKLAR: And one of the things that is so interesting in such a problem that remains in both places is where do you get the resources. I saw all the way through this gap between resource -- the need

for resources and the expectations of the populations who are being studied.

And I do not know a solution to that but I -- the issue of resources, Harold, is something that I am hoping that you will have some input on.

DR. SHAPIRO: Okay.

Larry, do you have a question and then I will go back to Alex.

DR. MIIKE: Yes. This perhaps can be answered better by Drs. Killen and Burke but I was thinking that getting back to your examples rather than picking on particular diseases that might raise issues, it seems to me an obvious area would be in multicountry international studies where you have the same -- basically same research going on where you are going to deal with all the different issues depending on the countries. And it seems to me that there would be an easier way of teasing out some ethical questions because you obviously are going to have no problem in this country but terrible problems in another country even with the same protocol.

DR. SHAPIRO: Alex, and then Eric?

MR. CAPRON: Well, I am not clear where we are in the discussion but it seems as though we are going into the substance of the discussion and I have

a point which is a direct follow-up on the point that Trish just raised.

DR. SHAPIRO: Okay. Let's focus on this question we started out with here and finish with that one.

MR. CAPRON: Okay.

DR. SHAPIRO: And then we will go on to some others but why don't you make your comment?

MR. CAPRON: Well, I am happy to wait if you would prefer -- well, let's resolve the other one here. I can wait.

DR. SHAPIRO: It seems to me on this issue of who to contact and so on that the point that Alex is made is quite right. There is -- beyond your needs as a researcher we have an obligation as a Commission to let people who might be interested in knowing what we are doing is let them know.

I think that, however, is a job, Eric, for you and the staff to figure out the best way to do that and not to burden you with that. That is a much larger group than you need to consult. So I think it would be helpful if we sort of split this into two where you can contact who you believe to be the most knowledgeable people to answer the kinds of questions you have specifically.

MR. CAPRON: But I thought that this list that we have here was a list of people that Eric had written the letters to; isn't that correct?

DR. MESLIN: The list of the people that are there are the first set of those who we have already written to and it is not an exhaustive list.

MR. CAPRON: No, but I mean that was -- that was not -- all of the burden was not on Ruth. It is just that the results may inform --

DR. SHAPIRO: No, I understand that.

MR. CAPRON: Yes.

DR. SHAPIRO: And so I think that is an issue that, Eric, you in consultation with Ruth, you can just think about who it is --

MR. CAPRON: Right.

DR. SHAPIRO: -- that might have some interest and might want to know, as Alex said before, so we do not surprise relevant people or at least it will be their fault if we surprise them. We will surprise them no matter what but I mean people get too much mail but at least we have to make an effort to do that.

And then we have the more focused effort that you have. Let me focus on that question, that is who to contact that might have knowledge who can

contribute to this. Schools of public health, obviously deans of medical schools or other people at medical schools and elsewhere would be useful.

I have a question which came up in another connection, namely do we have any reason to believe that there are nonprofit organizations outside of universities that are sponsoring and/or conducting research of the kind that you are interested in and whether that is a trivial number, which is not worth our attention, or whether that is a significant number, that is, for example, a foundation just to take an example?

I do not know. Perhaps colleagues here do know.

MR. CAPRON: Rockefeller.

DR. SHAPIRO: And then the question is whether those might be sources of interests because as I looked over the material in our briefing book which lays out what NIH is spending, of course it raises the obvious question what are the private companies spending, and that is something we will try to get a hold of. But then there is this other set of agencies and I have no idea myself what the volume of that is, whether it is large and interesting or small and uninteresting. I just do not know but it just may be

a source that you want to look at.

Yes?

MS. PAGE: In response to your question I know that the -- several of the consultants are putting together lists for their projects and one of the lists they are putting together is a list of applicable foundations and not-for-profits so we are hoping to draw from their list.

MR. CAPRON: Jack, is the Gorgus (?) Center still in business?

(Simultaneous discussion.)

DR. KILLEN: The Gorgus Center per se is not but there are research outposts, if you will, supported all over the world.

MR. CAPRON: I mean that was a federally associated center.

DR. KILLEN: But that is again by the Fogarty. The Fogarty link here is really critical.

MR. CAPRON: Yes.

DR. KILLEN: And asking them for help figuring out who to contact.

DR. MACKLIN: We are in constant and ongoing touch with them and I see Rob Eiss (?) sitting back there so we will -- they have been very helpful to us and we, in turn, are hoping to be helpful to them and

work together because they are exploring a lot of the same issues.

DR. SHAPIRO: Eric?

DR. MESLIN: Just a quick suggestion to try and answer the who should we call, it really came up from, I think, Larry's very good question of why public health. You may find it easier to answer that question if you give us some feedback as to whether the type of studies that you think this report should focus on -- Larry mentioned clinical trials as opposed to preventive medicine studies would be an appropriate focus of the report.

You have not read fully, I appreciate, the priority setting suggestions memo that I sent around but one of the suggestions is that there may be so much international research that this report might best focus on clinical trials that are conducted or sponsored in other countries and leaving aside the "public health research" projects for another study. There may be so much overlap that it is indistinguishable.

Rather than simply asking should we write to deans of medicine or public health or nursing or pharmacy or health administration, which we can write to all of them for all of the reasons that you have

suggested as we have written to heads of national bioethics advisory Commissions in other countries or international bodies. So there may be either from our speakers today or from Commissioners a sense that the type of study or the areas of investigation can help focus the report more than simply to whom should we write letters.

DR. SHAPIRO: Ruth, what is your view of that?

DR. MACKLIN: This particular point?

DR. SHAPIRO: Yes.

DR. MACKLIN: I guess my view is we want to take all suggestions and I mean I do not have a priority here but whatever might yield the most fruitful information for us and I think here we are relying both on the consultants and on Donald and Jack who know a lot of this area is probably the best way to --

DR. SHAPIRO: Perhaps we can discuss not only that specific point but two of the other issues you raised that have to do with the ambition of the report and what is omitted, both of which focus on the agenda, the report itself, and perhaps we can now focus on those issues.

I think, Alex, you had -- did you have some

comments you wanted to make?

MR. CAPRON: I had comments on what is a central issue that is raised here that ties in with the global justice question.

DR. SHAPIRO: Yes.

MR. CAPRON: Is this the appropriate time?

DR. SHAPIRO: Absolutely.

MR. CAPRON: On page 3 of the outline you -- the first paragraph begins with a discussion of what you call four over arching ethical requirements. Three of them are the substantive requirements and the fourth is the requirement for independent ethical review and actually I would say that all four are aligned in the Belmont Report, which talks about IRB's as well in passing, but it is really on the third one that I wanted to address your attention.

You go on in the bottom of the page and over to the next page to draw out four questions which then become the focus of the subsequent chapters. One from each of these three -- the three central ethical principles or requirements that underlie research. And it seemed to me that the first two statements of the requirements and, therefore, the questions that grow out of them were pretty straight forward.

The third one you describe as the requirement

of distributive justice. I do not think that is what the federal regulations require but maybe they ought to. They require the equitable selection of subjects and unlike if one consent and an appropriate ratio of benefits of risk, which as I say I think are well reflected here, transmogrifying equitable selection of subjects into a fair distribution of benefits and burdens of research is a big step.

Now it is -- I am not raising this as something we ought not to do. I am raising it as something which connects us back to what Eric and Harold mentioned before, which is our comprehensive report and our re-examination of the basic tenets of the Common Rule because when equitable selection of subjects was written I think what was in people's minds was closer to one of the points that Hans Jonas made in his famous 1967, '69, published finally in '69, Daedalus article where he talked about the -- sort of the idealized hierarchy of subjects would be starting with the researchers who are the best informed about research and then people who are in a position not only to know a lot but to make -- have a lot of free choice working one's way down to those people who are, in fact, or at the time were disproportionately represented among the people who

were, in fact, research subjects, that is to say people going to public hospitals or to public clinics, people dependent upon their physician or the health system for their care and with very little choice and often very little understanding that they were entering into a situation in which they were research and teaching material as people then said.

And saying that that was not going to pass muster and that there was a notion of being fair in the selection of subjects was the focus. That is a good focus. It is one we probably have not fully achieved. Saying that if you have been in research you are now owed some obligation by those who conducted the research for your future care is a different concern.

Now obviously if you select people, all of whom, have free access to the health care system and can afford anything you come up with, it is not an issue, so if you were using Jonas' ranking you would not have a problem but you see my point.

And it is to the extent that this is, as it were, misstated that it ties it more directly into the global justice issue and I have, therefore, a suggestion about this. Either that right at this point -- at the top of the page you correctly state

what the thing is and then when it comes to the question perhaps we say this question, you know, sort of -- you know, this requirement hints at or could provoke this broader question of being fair but in a way this report offers the opportunity by raising questions of what would be -- what is equitable in the bigger sense into this and it is the same way that Bernie separated his points.

If you do studies abroad that you could just as well do here, if you study contraception in Puerto Rican women and develop the pill in Puerto Rico and then bring it back to Scarsdale, you have a question about the equitable selection of subjects in part simply because the population is going -- is less able to make choices for all those reasons and, in part, maybe because maybe they will not be able to get access to it and likewise with AIDS vaccines or whatever you are doing.

But if you say that raises this question of the long-term relationship between the process of discovery and then the fair access to the drugs afterwards you are raising a question which is provoked by that but it is different and which then does move it seemed into the question that Bernie is raising which is where do you choose to spend your

money, how do you select the topics in the first place.

I, for one, do not think that our report probably should get into other than noticing that in the world at large our efforts at achieving this kind of microjustice as to any particular project may seem odd if the Health Minister of Mali is saying, "My real problem is malaria or river blindness or some other – cysticercosis/cystinosis -- I mean some other much bigger killers than what you are here to study." And, you know, this seems like dancing on the head of a pin, some of the refinements you care about when you are not making money available for research on what to me are the world's big killers.

I mean that would be a question that we could raise. I do not think we can address in this report on the actual process of carrying out these studies on the larger question. We can raise it as a connected question and as a question that puts these issues into perspective.

I do not think we can say this is how the research agenda of United States companies or the Fogarty Center or NIH should be set but, I mean, I am trying to raise two or three points here both about greater candor about where we are starting from and

then maybe being willing not in some unnoticed fashion but very obviously to take the leap and say maybe point three, the equitable selection of subjects, needs to be changed even in the U.S. to ask these broader questions.

DR. SHAPIRO: Yes, Ruth?

DR. MACKLIN: Yes. I have actually -- it is a -- I do not disagree at all with your analysis when you say the U.S. federal regulations do not deal with this requirement of distributive justice and this is not to defend what is here but to explain.

The Belmont Report includes this concept. It does talk about the beneficiaries of research, not just the equitable selection of subjects but that the people who are selected as subjects should also be beneficiaries. So that goes beyond the selection of the subjects in the trial.

This -- the question as posed here and as restated at the top of namely --

MR. CAPRON: Page 4?

DR. MACKLIN: Yes, the top of page 4. Where is page 4? Right. What is owed to research subjects during a trial and after the completion of research is not quite rightly in our federal regulations. It is, however, something that is elucidated and elaborated

in the CIOMS document and in something called -- you will have to help me here -- the interim guidelines from the MRC that is a more recent document than the guidelines by which the MRC that governed our research -- they have kind of inserted something as interim meaning probably they are going to revise the whole thing. They also address the question is what is owed to research subjects.

MR. CAPRON: Right.

DR. MACKLIN: So that question here is not meant to flow from our federal regulations.

MR. CAPRON: I know. I see -- I did not state what my starting premise was, which I thought reflected the Commission's discussion before you joined the project about a year-and-a-half ago or something when we were going through this. Maybe the last time Jack was here.

We had to ask ourselves are we writing a CIOMS document? Are we writing -- what are we doing? Why are we doing this topic? And I thought that we said, "Look. Both the FDA and the department and everybody else who is concerned with the Common Rule start off with a set of regulations. American researchers have to comply with those regulations. Are there problems in those regulations which make

compliance difficult? Are there gaps in those regulations which allow research to go forward with a blind eye towards important considerations?"

In other words, taking our regulations as the starting point we are supposed to be under our charter addressing issues that have a direct federal impact and here was what I thought was a direct federal impact.

And so I agree with you. The topic here and the way of looking at it is not new either to our federal government or to these international documents but to the extent to which the Common Rule departs from those documents.

I think we need to be more explicit in showing what the starting point in the Common Rule is and where further thought has led us because one of the recommendations that we may be coming up with is the need for the change. It is not just general guidelines. I mean, the CIOMS document, and as one of the people who were involved with writing it and so forth for CIOMS, it is a document that I think is valuable but it is not a binding document on anybody. It is used very widely now because many countries were looking around for a document to guide this international collaboration and so forth but the

federal regulations are binding documents on people who receive federal funds.

Do we think that this broader view of justice needs to be more explicitly incorporated? That is I guess where I would stand. I do not -- what I am saying is I do not think we can do that just sliding along into it. I think we have to confront the fact that the Common Rule takes this fairly narrow view of what justice is, which is the equitable selection of subjects.

DR. SHAPIRO: Let me make a comment on this that also relates to the question of the ambition of this report. While I think the point that Alex makes that we ought to be explicit about where we are dealing with something that is not yet incorporated in the Common Rule and may never be and so on is a very useful one and I think would help ground the discussion, however I really cannot see how we could have this report without in some way -- and I do not know -- raising these broader issues they are really so critically important.

MR. CAPRON: Well, I agree.

DR. SHAPIRO: They are very much related in my own mind to informed consent because what you owe someone -- I mean, that is a premise. It is not a

fact. You may not owe them anything depending on the situation that has developed and what the informed consent was and maybe they are paid or unpaid and there are all kinds of issues. I am a little bit worried about going too far because it is a huge subject. Distributional justice is extremely important but very difficult and so that in terms of just the ambition, not -- we should find some way to put a bound on it in this area because that can lead us anywhere.

The issue that Bernie raised, which is also related, that is what does the scientific agenda look like, and where are we spending our resources, is also related to this issue. Also a very, very difficult issue. We cannot -- I mean, not that we cannot.

It would be very difficult for any group like this to take the whole scientific agenda and say we do not think it is properly allocated and it ought to be allocated in this way. That is a tough, tough issue. We can raise it. We can discuss it. We can highlight the issues that it raises but in terms of just the ambition that we have, I am referring to that part of your question, we should be somewhat modest as to where we can come out there. That is all at least in my judgment.

Bernie?

DR. LO: To follow up on what I think is a very useful discussion that Alex started, I think the main point should be that we should be very clear both in our own minds and in the report to separate out what is part of the regulations and what is part of sort of the international bioethics consensus that is emerging.

And it seems to me that if we look sort of to the end product, the types of recommendations that we are going to come out with, I think there are some recommendations which have to do with given that these are the current recommendations, current regulations, there are some problems with how they are implemented in practice and some solutions to how -- some recommendations to how to better resolve those issues and that is why I raised the first point about trying to get some more practical, you know, on the field -- in the field on the ground guidance.

I think there are other issues where we want to signal we are not happy from an ethical perspective with the way these current regulations are and we want to raise the questions as has been raised in the Belmont Report and now increasingly being raised by these other national/international Commissions that we

need a broader conception of justice and I think, you know, we may want to recommend -- well, it seems to me one of the recommendations can be that somehow we need to broaden our view of justice from that which Alex described as being part of the current regulations, this broader view.

And then there are other issues I think we just want to signal we are concerned. We are disturbed. There are huge issues, I think, of the larger issue of distributive justice in the scientific agenda. We may just say someone else ought to study it and the NIH ought to look at it or the other Commission or something. But I think if we sort of try and clarify for ourselves the types of recommendations, I mean, which we have done in our other reports, some things we have said this ought to be changed in the regulations, others have said given the way the regulations are they ought to be interpreted this way or they ought to be this way, and these are other issues that someone else ought to take care of and we are just saying for the record other groups ought to take care of them.

But I think the grounding -- the sine qua non is that we are very clear as to what is a regulation and what we would like to see in sort of an ideal set

of regulations that we could rewrite but all throughout our existence we have recognized we cannot, unfortunately, go back to a clean slate. We sort of have to start with what is there.

DR. SHAPIRO: Could I -- let me make a comment, Ruth, and then ask a question in a somewhat different area, really just a question of fact.

One is going back to the ambition. I mean, one of the things that worried me about the first draft, which is not in the second draft and, therefore, I thank you for it, has to do with some of the historical cultural evaluation of these societies, which seemed way beyond what we could accomplish. Very important but way beyond what we could do so I am really very appreciative of the work you have already done to make this something we could really manage in the time we have.

With respect to -- I do not know whether to call it omissions or not -- there is a reference, I think it is on page 2, you referred to an article, I think, in the New England Journal or somewhere, which is a comment that the rate of increase of work in this area by the for-profit organizations is increasing rapidly. Something like that.

And you gave a reference -- the reference at

least when I looked it up did not have any facts behind it. It was an insertion.

MR. CAPRON: Right.

DR. SHAPIRO: And the question I have is how important is it for us to really try to get at least the best estimate we can of what is actually happening. I do not whether the parameter we are looking for is dollars or whether it is number of human subjects or number of projects or other ways you might -- other metrics you might use.

MR. CAPRON: We got that information already.

DR. SHAPIRO: On NIH.

MR. CAPRON: No, on government versus private and I thought --

DR. MESLIN: We had some of it in Elisa's work.

MR. CAPRON: Yes, didn't we get some of it from Elisa? I am sorry.

But I agree with you, Harold. Troy Brennan's article is just a bald assertion with no substantiation.

DR. MACKLIN: Well, we are -- just to -- I mean, he is one of the individuals whom we are going to invite to provide some testimony.

DR. SHAPIRO: Yes.

DR. MACKLIN: So if he has something behind his bald assertion then he should tell us.

DR. SHAPIRO: All right. And if he does not I think we need to get that together to the best -- to the extent that we can. I mean, I know this -- we are not quite sure just how the data is kept. I am sure that the NIH has its data and so on, I am not worried about that but whether these firms -- private firms do, whether nonprofit or other nonprofit organizations that are not government sponsored, whether they have information, I just do not know but it seems to me that we need to at least get our hands on what is available.

DR. MACKLIN: What would be the best source of that? I mean, Elisa Eiseman's project is going to give us a fair amount of hard data. Can we ask her to say a word about that now?

DR. SHAPIRO: Elisa, you can say what you are going to put together.

DR. MACKLIN: Do you have a microphone?

DR. EISEMAN: Well, I was hoping to present some more of this afternoon so I will try to be brief this morning but the tables that are laid out kind of show you what I am trying to do. Most of the information that we have so far deals with federal

funding of research abroad and that is because that is the easier numbers to get my hands on right now but we do plan on getting information from the pharmaceutical industry as well as private foundations and to try to get a more global view of what the United States is funding in these areas but not just looking at funding but trying to also get more information than just numbers.

So questions like Alex was talking about, what types of research are we funding, is it all AIDS research, is it malaria research, and that is the type of information that I am going to present more this afternoon.

DR. SHAPIRO: Great. Okay.

Okay, Alex?

MR. CAPRON: Ruth, I had a question if this is the appropriate time to raise it. On page 6 at the top a sentence appears and then you come back to this with the same sort of brush of the hand, back of the hand later, you say, "Care and treatment normally available to the majority of the population in a country has been termed 'the standard of care,' a phrase adapted from an entirely different context with a different meaning all together. This report questions the use of that phrase as it is

systematically ambiguous and misleading in an ethical analysis of international research."

Can you elaborate a little bit on what that means?

DR. MACKLIN: Yes. Well, here again I have to take the blame because this is one of my pet peeves and I let my voice speak here in this and others have heard this before about I am happy to say that our colleague, Alice Page, when she and discussed this and her background is in law and public health, agreed with the -- I guess the transporting of this term from the other context.

Now what is the other context? The other context or the context -- and you can correct me if this is mistaken but it is clearly somebody, whom we all know, George Annas (?) has written about this, and I know from the other context. The context is malpractice and the showing that has to be made in order to convict a physician or to claim or to show and demonstrate that a physician has been guilty of malpractice by pointing to the "standard of care." Did the physician in his behavior that harmed the patient depart from or fall below the standard of care? So that is the original context.

I do not know when or by whom or how this

term has now crept into the international research conversation but I can tell you the first time I heard it. This is just an autobiographical remark. It was about four or five years ago, four years ago roughly when a research from the CDC who was designing and beginning to conduct the placebo controlled AZT trials came with the problem or the dilemma that he saw, namely we are withholding from people or giving them a placebo, "is this wrong because we know this stuff works in some other way and we believe that the short-course works. I mean, that is what he said.

MR. CAPRON: Right.

DR. MACKLIN: This was an informal conversation.

And he said, "One thing that could justify doing it is what is the standard of care in the country and if we are not going to fall below the standard of care..." which in this case is no care basically for pregnant women, this was in Thailand, "...then..." he said, "...maybe we can provide an ethical justification."

Now as I say that was the first time that I heard it. Since then it is in all of the arguments and the literature. The question here -- I mean there are two questions. One is one cannot -- can one

simply take a term that has meaning and application in an entirely different context, namely malpractice, and use it as a justification in another context without further analysis or further elucidation?

There has been no analysis and there has been no -- essentially no justification for why a term like "standard of care," which has to be demonstrated in some way in the courtroom in the malpractice situation is now being used to describe essentially no treatment, no care, no access to care in a lot of developing countries. So that would be the way it would be elucidated and questioned and there are other -- there might be other ways of describing what is relevant here in asking the question of -- and that is the question, what is owed to people, to research subjects in a trial.

MR. CAPRON: Yes, and I would prefer to see us ask the latter question because I am not as convinced as you are that the term is being misused here. I mean if you put it in the following way: If a Thai researcher were practicing medicine -- if a Thai researcher or a person who did, indeed, practice medicine and did not deliver the same care that a person would get at Montefiore or Mt. Sinai in New York, would that person be departing from the standard

of care? The answer, I think, would be no, not in Thailand.

Now if that person is now engaging people in research, why isn't it relevant to ask the same question? And if it is relevant it is not because the term "standard of care" is being misused or is being used out of the right context, it is because there is another question which says basically if I am coming in to develop something for my people, if I am the NIH or for my profit if I am a pharmaceutical company, do I have some greater obligation towards the people who are aiding me in this process than a local physician would have if he or she were simply taking care of the person according to the standard.

I mean, the big movement in the United States and the reason "standard of care" actually was an important concept was that for a long time we had a locality rule, which exactly recognized that the care you got in Woburn, Mass. may not be the care you got in Boston, or maybe Woburn is not far enough out but somewhere further to the west, and precisely because people in that community did not have access to the same resources and so forth. And if you wanted that other care you would have to go to the medical school in Boston to get it or, you know, come out of your

locality.

And then in time people say, "No, all doctors in the United States are really practicing according to the same standard and get educated at national medical schools, have access to the same literature." It is still true that if the hospital does not have a particular piece of equipment and it is not wrong to perform care without that equipment, you cannot say the absence of the equipment was wrong but, you know, the basic standard of care is going to be a national one but it is not an international one.

We have to recognize that and the question is, is the research context enough to provoke us to say that is unjust but I do not think we are going to get to that result by saying, well, it is somehow a misapplication of the phrase "standard of care." That does not seem to me -- I mean --

DR. MACKLIN: I guess one other --

MR. CAPRON: -- it strikes me as a quibble on the side that does not get to the heart of the issue.

DR. MACKLIN: Yes. Well, maybe it is a quibble. I mean, I do not like verbal quibbles but I think terminology is important. I think there is an inherent ambiguity in the word "standard" and again this will sound to some like a quibble. A standard

can mean what is standard or what is normally done, you know. In other words, that is standard of care. Or a standard can mean we do not -- it can mean what is the -- what standards do we hold people to? That is as a bench mark. Now those are two very different notions for asking what is normally done.

MR. CAPRON: But we derive the one from the other is the point. Including in the malpractice context that is all it was, all you had -- it was not as scientific a process as you have described. You simply needed a credible expert.

DR. MACKLIN: Expert.

MR. CAPRON: On each side saying the standard of care is X. Well, what is your source for that? Well, this is what we in the community do. You know, maybe -- have you read Cecil's book. You know, open to page -- what does it say to do there? I mean, these are the kinds of things that establish the so-called standard of care.

And it -- you know, it was not as though someone came in being able to recite anything that had much of any empirical basis. I mean, it is only now with the development of practice guidelines that we, in fact, have much of any empirical support for anything that is done in medicine. You know, 90 some

percent of common medical practices have never been validated in terms of any controlled study or anything.

So I think you are over stating what the origin of it was. The standard of care really was standard care. What is standardly done? That is where we got the so-called standard to which people would be held and I think it is no different here. So I really would like to see us address the ethical issue and not have that quibble over whether the term is slightly different in this context or not.

DR. SHAPIRO: Trish?

DR. BACKLAR: But it seems to me, Alex, as though Ruth is really wanting to say that there is no standard of care in certain places and wants to make it very clear that when you use the words "standard of care" it does not mean that there is something there.

Am I wrong?

DR. MACKLIN: I think that is right. The question is can one refer to -- I mean, without playing verbal tricks -- the absence of care as the standard of care.

MR. CAPRON: No, the absence of particular modalities, Ruth. I mean, certainly if you were to

say that a person with HIV in a country that does not have access to antiretrovirals goes to the door of a hospital and they just say, "You do not have a disease, go away, you are not relevant to the health care system," as I gather things are done at the level of care taking but they do not involve the antiretrovirals because they are not available in that country.

Now what -- that is separate. That is an empirical statement, the standard of care there. As I understood it, the real origin of this was that the declaration of Helsinki talks about something that is much more exalted. It talks about -- what is the phrase? "The best --"

DR. MACKLIN: "The best proven diagnostic --"

MR. CAPRON: -- proven diagnostic and therapeutic methods." And there was the hang up because that certainly had a reference. It sounded like there was a global looking out for the best practice. And if I came from the United States to do research and the best therapeutic modality was this set of antiretrovirals, how could I turn a blind eye and say, well, they just do not happen to be available here. Well, bring them with you, Mr. Researcher.

And that it seemed to me is where that

tension comes up but again it is not helped by -- I mean, there is a standard of care. You could go -- I mean, as I say, take -- put a Thai doctor on trial for not giving the antiretrovirals and the Thai doctors would come into trial and say the standard of care in our community does not include those antiretrovirals. They are not standard of care here. You are not falling below good medical practice in this country when you fail to do that. Acquitted. No malpractice. And it seems to me that is the same common reference point.

DR. MIIKE: I think we know what the issue is so why don't we just stop quibbling about it?

DR. SHAPIRO: Bette?

MS. KRAMER: You know, maybe all we need -- maybe all we can do really is to provide a discussion of the issue. I just -- what I focused on as I read through this material and granted I do not have the background that Alex has but -- and I read it quickly but it is a sentence beginning in number 6 where it says, "Arguments invoking the standard of care have been used to justify providing no treatment to subjects." And that was -- that is where I -- that was where -- what I focused on as possibly the misuse of the term, that it was an effort to absolve the

researchers from doing anything.

DR. SHAPIRO: Well, I think there are two issues here and we will have -- we should get on to another subject here. One is whether there is benefit if one thinks about it carefully to replacing the term "standard of care." I guess we will have to think that through. Maybe there is. I do not know what the answer is.

Then there is the issue, I think, we all agree on, namely that what is owed to the human subjects is a critical issue and I think we all agree on that, and let's just see what happens as you think this through a little more.

Let me ask another rather simple question, a fact. You referred before to the current revisions underway of CIOMS and Helsinki. And I have heard very -- maybe -- I have heard some various estimates of when that process will continue.

So Bob Levine in a meeting we had at the University of Virginia gladly said, "Oh, five, eight years," referring to Helsinki. And so that seemed so far away that one did not have to worry about the issue you raised.

But do you have a better since of that? He was not, I do not think, making a serious remark. He

may have just been exasperated or something at that point.

DR. MACKLIN: I think the -- from what I understand, the time table is constantly under revision.

DR. SHAPIRO: I see.

DR. MACKLIN: Bob Levine was, indeed, exasperated since he is working on both -- the drafter of both documents and has met with some opposition at various meetings. The -- let me say something about CIOMS because I have the most recent information about that.

There is a draft of a revised CIOMS. There was originally to be a meeting in December. That was -- has now been postponed to March, mid-March of the year 2000. And the process that is now underway is Commissioning background papers that will then be available at that March meeting which will include a much larger group than a group that was convened by CIOMS as the steering committee that was looking at the original draft.

This is now going to be a much larger open conference and background papers are being Commissioned so at that meeting, which is now going to take place in the middle of next year, that seems like

the beginning of a process since it relies on Commissioning papers, having a large meeting, getting some comments and feedback and then taking the next step after that. So the endpoint is not in sight but given the nature of the process I think it is fair to predict that that will go on.

Helsinki, the drafts of Helsinki that had been prepared by Bob Levine and discussed at numerous meetings of the Ethics Committee of the World Medical Association, those talks stalled or those meetings stalled on the distinction between therapeutic and nontherapeutic context, not on the issue that is of so much concern: global justice and what is owed to research subjects, and what is owed to them afterwards, but on the best proven diagnostic and therapeutic method and some other revisions that are troubling to very many people.

But on this distinction, which may look like it is not a very important distinction to some people and I think Bob Levine has argued fairly persuasively that it is time to abandon that distinction and there are some inherent contradictions.

But if the individuals who have the authority within the World Medical Association to say -- have the authority to say, "I am sorry, we are not going to

accept this. We want to retain the distinction." They are stalled on that issue.

The most recent development that I have heard about from several individuals, although there is not an official report, was a meeting co-convened in London on September 3rd and 4th by the British Medical Journal, and the Ethics Working Group of the Royal Society. There were several coordinating European groups. Groups from the U.K. and from Europe. And the discussion -- I mean, that was a discussion that was essentially focused on the proposed revisions, on the draft revisions of the Declaration of Helsinki.

At that meeting, among other comments, was an urging on the part of some people that the World Medical Association, which is a consortium of national medical associations, no longer owns the Declaration of Helsinki and that the process -- this was several people that have said this -- the process of its revision or its -- well, I guess revision -- should go beyond not only a small group of individuals but should actually go beyond the organization that has been the primary or sole organization.

Now that would, if adopted, take this even farther since it would not be under the purview of the World Medical Association, which might be able to

convene its ethics committee and then have votes at its national assembly but then would require an entirely new step. Who then owns it if not the World Medical Association any longer?

So perhaps Bob Levine's exasperated comment of five to eight years might actually have some validity given what has transpired really quite recently as a matter of only two weeks ago.

DR. SHAPIRO: Larry?

DR. MIIKE: You made a comment earlier and you said that depending on when these things come out our report might be obsolete in a year. I do not understand those kinds of comments at all because these are not one trumping the other. These are parallel voices and they all stand alone. If your earlier comment holds true then our report on stem cells is useless because the AAAS came out before we did and the NIH came out before we did. So I think that as long as we put out a decent report that it will stand alone regardless of what these other groups do.

DR. MACKLIN: Yes, I agree. I perhaps did not specify what I meant. That is, I only meant if we are going to reference what is stated in other -- as a mere reference, not necessarily to agree or disagree

or adjudicate but if we are to say, “by way of comparison here are the various international documents, other national guidelines and so on, and here is what they say” we will just be wrong about what they say if it changes drastically. So it was really a point of reference of citing a document that is current that could at some point change.

MR. CAPRON: Another way of looking at that, Larry, is on page 9. The paragraph begins, "The NBAC report will have to say here at some point whether it recommends adding some such statements to the U.S. regulations or whether it is acceptable simply to continue to omit them." And then you go on and say you would have to give a justification for the omission because the international guidelines cover a certain point.

But certainly one response, not one I am necessarily recommending, but one response would be to say some of these international concerns will have a -- will not actually be implementable domestically. That is to say, if we came up with some sense that the world-at-large thought that when developed countries went to under developed countries then there was some obligation for those who sponsor the research to have some ongoing role in the provision of the research

product to the country or something. You might say, well, that is internationally.

But when Merck develops a drug in the United States for Americans it does not then become obligated to make sure every American has free access to the drug and so we will leave that out of the U.S. regulations and we will have a provision, however, in the U.S. regulations that researchers doing research internationally are expected to comply with applicable international guidelines.

Now doing that would say, well, when they get out there they will face whatever those guidelines are and so if they change out of an international consensus that some requirement is important, so be it. And we do not have to incorporate that in the U.S. guidelines. So that would be one way in which we take account of it. We recognize that the standards are themselves going through a change internationally but we do not have to know exactly the point that they are added when we finish our report.

And it may be that is a way of dealing with perhaps the most difficult issue, which is this expansion beyond equitable selection to the whole question of what does justice mean to the population that has been studied.

DR. SHAPIRO: You have a comment in the outline, I do not remember exactly where it is, related to this issue of justice. It was -- I could not make up my mind whether this was just an after thought or you really had something in mind which I could not quite grasp and that is compensatory justice. You said that that might be something like -- you made a comment it might be applicable or it might be interesting, and so on. And I just want to know whether you would like to say a word or two more about that. I mean, it is a very tough issue like all these issues, but I could not get a sense of what you really had in mind here.

DR. MACKLIN: Perceptively you could not get a sense becasue I am ambivalent. I discussed this --

DR. SHAPIRO: I am quite satisfied with that actually.

DR. MACKLIN: On the one hand -- I mean, compensatory justice would work something like this: There have been past wrongs of various sorts, past omissions, indeed exploitation of perhaps more years ago than recently, and the question whether some compensation is owed to countries or developing countries, however we put it, for past wrongs is a question at least to raise.

Now taking it further than raising the question puts us into a very difficult and different debate. I mean, it really in a way revisits an affirmative action type of analysis. So I did not want to omit mention of it but I have no firm view about whether it is well beyond what we could reasonably include in this report or whether it -- at least the report requires some mention of this because it is another and a different notion of justice, one that is applied in other contexts in other connections.

Possibly the best single example in the research context is the payment to the survivor or few survivors or families of the survivors of the Tuskegee. I mean that was a move of compensatory justice in a very direct way and it was money. It is also a question that the Radiation Committee faced and addressed and could not agree on. I mean, there were some on the committee who thought there ought to be some form of compensation that went well beyond an apology to people who had been wronged or even if not harmed by the radiation experiment.

So it was against that context of other -- in other research areas that I raise the question but perceptively, Harold, you did detect a little

ambivalence on my part.

DR. SHAPIRO: Thank you.

Okay, Alex?

MR. CAPRON: I am sorry to have so many questions but it does seem to me that -- I -- one of the most interesting issues here is the whole risk/benefit calculus and I wanted you to respond to a hypothetical that I think is relevant to your chapter 3.

Suppose that a researcher in a poor country were to want to do research, perhaps even research of the type that Troy Brennan highlights in his critical thing about the Helsinki Declaration, which is in the materials here, his New England Journal piece, and that was not being presented to the Harvard School of Public Health to its IRB but simply to the X, Y, Z country local medical school IRB where the absence of care was something -- whether it is a standard -- I do not want to get into that standard argument -- the absence of care in the sense of a medical pharmaceutical intervention was, indeed, the standard at the time or was what was happening at the time.

Is that different than the same research being proposed by Dr. B instead who comes from the Harvard School of Public Health and wants to come in

and do the research?

Is the risk/benefit ratio affected, in other words, by who is doing the study or only where it is done, do you think?

DR. MACKLIN: Well, certainly I would not argue -- I do not know if someone might -- but I would not argue that it is who is doing the research because it is a separate and separable question.

MR. CAPRON: With what sponsorship I mean as well. In other words, not just was he hired -- were they both to be hired by the same company to do --

DR. MACKLIN: You mean the local -- the host country researcher is doing things --

MR. CAPRON: It is not a host country anymore. He is simply a researcher.

DR. MACKLIN: Yes, right. Within the country.

MR. CAPRON: Within the country.

DR. MACKLIN: Yes.

MR. CAPRON: Versus becoming part of an international collaborative trial.

DR. MACKLIN: Well, I think we probably need to be clearer and it will become clearer especially when we have our -- the meeting here that will draw on the experts in the risk/benefit. What we intended in

talking about risk/benefit was essentially the research design and the anticipated or predicted harms that might befall the subjects and the benefits including benefits to -- in the way it is usually understood not only as to the subjects, the participants in the trial, but also others after the trial, including whether those benefits would be made available in the host country.

So it is a risk/benefit analysis that looks at the research design and the consequences of completing the research. I think your question asks about -- or brings in other factors extraneous to the design but possibly relevant in asking questions about what may be done within a country that might not be done --

MR. CAPRON: I did not mean them to be extraneous to the design. What I meant was if you have one of these trials which proposes to study, in effect, the natural course of the illness with no intervention versus some intervention and the no intervention becomes the placebo as it were because -- I mean, you might give literally the sugar pill but you are not intervening therapeutically as far as you know with this. And you say, well, clearly in the developed country because there are therapies your new

therapy cannot be compared to nothing. This is too dire a disease just to watch it go on.

But in the under developed country that is what happens to people and the objection that Troy and others had (and the whole attack on the AZT -- the maternal transmission study) was that it was wrong for people from the developed world to be going in and pretending as though there was no treatment when they had a treatment which they could have brought with them.

And I am asking whether, in terms of risk/benefit, whether it is different if the study were done domestically and where the -- it is not just the design of the study in a narrow sense but, you know, let's say the Health Ministry was involved and said, "For our country we are not even going to be studying that fancy regime that is available in the United States because we know our health budget could never afford that regime so we are willing to take greater risks in terms of the type of treatment that will even test out than you would be willing to do in the United States because we would get more benefit even from that maybe not as fully successful but much cheaper treatment."

Is it a different issue than if there is an

international -- what I am asking is, does the international collaboration color what is ethical within that country? Because I recall -- is it the fellow who was at the AIDS meeting in Washington, the Health Minister from -- is it St. Kitts and so forth or Barbados?

DR. MACKLIN: Trinidad and Tobago.

MR. CAPRON: Trinidad and Tobago.

DR. MACKLIN: He is not the health minister. He is a researcher there.

MR. CAPRON: A researcher there.

DR. MACKLIN: Yes.

MR. CAPRON: All right. Sorry.

But he was very firm on a view of do not impose your standards as to what is appropriate care and he had carried over into the population's behavior and whether they would comply with a more complicated regime. A lot of questions.

But I do not think -- I do not want to begin by assuming that I can dismiss those as just self-interested -- a view from someone who wants to carry on research in that country. I have to say, well, there is a different risk/benefit ratio in a country that is very poor in terms of the risks they are willing to take to get a benefit that would not be

seen as that beneficial in our country.

DR. MACKLIN: Well, but in the -- whether or not it is -- I mean, it is a hard question to answer becasue there are many points to address. I do not see that on an analysis of the risks and benefits that it makes a difference who is conducting it or authorizing it. There is a different question raised by the comparison of these two and that is whether or not there are different obligations in an international trial where people can afford to provide something in the trial versus what the obligations are as decided by a Ministry of Health.

I mean this becomes a question of what outside agencies, organizations or individuals can impose on decision making within a country. I mean that is a critical question. Surely if the research is being done by the Ministry of Health with its own resources there is no international body or group or guideline that could affect that but the risk/benefit ratio of the study design would be the same regardless of who it is that is sponsoring it or has the economic means. The difference is the economic means.

MR. CAPRON: You do not think it is risk/benefit then?

DR. MACKLIN: I do not think so.

MR. CAPRON: Okay.

DR. SHAPIRO: Bernie, and then I have a comment.

DR. LO: It is always hard to keep from jumping into substantive issue when what I think we are really supposed to be doing is talking about the -- sort of the outline and the structure and the plan.

I think that one of the problems with these debates is depending on how you frame the issue you come out with a different answer and, you know, there has not been a lot of attention given to the pertinence of the research question or I could also frame an analysis that research is unethical unless it poses a question that is of pressing importance and is going to have significance and affect the health of people in decisions about medical care.

If you are asking a question, which is irrelevant to what is going to happen to health care in the country in which the subjects reside, you could argue that there are ethical concerns about doing a study that will have no pertinence to future health care.

So I think just to focus -- the problem with all this is you have to look at lots of different

issues and if we are only focused on justice or only focused on risk/benefit it looks different than if you look at other things and it is going to be hard, it seems to me, as we do our analysis to sort of present the coherent picture of the whole study as opposed to just different sort of takes on it.

DR. MACKLIN: A very quick point about that. I just want to call your attention to this and then maybe at some other point you can comment that some of the same -- in the outline some of the same -- I do not know whether to call them issues but the same themes or topics are addressed in chapter 3 on risk/benefit and in chapter 4 on what is owed to subjects. This follows directly from Bernie's -- from your observation.

And in chapter 3 they are raised with a focus of risk/benefit analysis. In chapter 4 some of the same items are raised by focusing on justice. I mean, I am just -- it was just an observation that if you can enlighten us on how best to do it, that is we are not talking about the whole trial but that is why chapter -- we have chapter 3 flowing into chapter 4 that is revisiting the risk/benefit questions where the aim in chapter 3 is to focus on how to make that analysis and what is the appropriate way to make the

risk/benefit analysis whereas chapter 4 takes some of those same questions and frames them in terms of justice so any guidance you can give us on how to do that.

DR. LO: Again, sort of trying to think in terms of outlines that in a sense are preconceptions that we assume hold for a trial before we begin the analysis of respect for persons and beneficence and justice and they are traditionally stated as the scientific merit and validity of the study and we often view that, as you know, qualifications of investigators and rigor of the design.

Part of that is that the research question is ripe for that kind of study. It is a meaningful question. It is a significant question. We are not wasting, you know, people's time in a trivial study that has no impact and it seems to me it is the level of the posing of the research question that a lot of these issues can also be examined where I do not think they have really necessarily been examined up to now.

DR. SHAPIRO: You know, one of the -- we are going to have to break now in a few seconds because I do not want to keep our guests waiting longer than scheduled but an issue just as I review this outline and I look at the literature that surrounds this whole

topic, the issue -- addressing the risk/benefit issue now.

A lot would be clarified in my own mind if it was always clear when someone was raising risk/benefit whether they are raising that as if they were considering the people involved in the trial and asking what the risk/benefit ratio is for them vis-a-vis asking what the risk/benefit ratio is for some larger group of concern, the country, the world, somebody else.

And it is my observation that it is often extremely unclear as I read various articles. I am just never sure which risk/benefit ratio they are talking about and -- not always, I am often not sure and that makes a very big difference to, for example, asking -- answering the question that was just raised by Alex and Bernie and others.

So I hope as we get through this that we try to bring as much clarity to our own analysis. We cannot change other people's analysis on that issue.

Well, let me suggest --

MR. CAPRON: Could I ask --

DR. SHAPIRO: Yes.

MR. CAPRON: -- one more thing. It is a procedural point. You describe your plan with the

order of the chapters that will be addressed at the next meetings, chapter 3, 4, 2, 5, 6. I want to suggest to you that our experience with prior reports indicates that it would be a major impediment to having this report done when you predict if we only get to chapter 6 on recommendations at the end of four prior meetings which have looked substantively. Neither we nor you are tabula rasa on this. Clearly you have already indicated some conclusions you have, a few of which I hope you will modify or just --

(Laughter.)

DR. MACKLIN: Do you want to know what those are?

MR. CAPRON: Hit the delete button on standard of care. But anyway --

(Laughter.)

MR. CAPRON: -- but it would be helpful, I think, for us to begin well before that fifth meeting on this topic to see where the recommendations might be headed, topics, you know, get some guidance for us early on and then begin to give us some language because we need time to chew it through and obviously we will continue to rework those and it is not as though the things -- the sessions on the other topics that come after we see a recommendation are proforma.

We may, you know, throw out what we thought was a recommendation as we are better informed on something but we will not get to the end if we wait and have a session on recommendations at the end it seems to me.

DR. SHAPIRO: I very much agree with that. I was going to make a similar comment. So I -- well, if we have a not quite fully informed recommendation it will become fully informed as we go along so to the extent that that is possible that really is very helpful for us given the process we use.

Larry?

DR. MIIKE: Yes. I would go even so far as to say that for the next meeting you let us know what areas you want us -- you think we should make decisions on and we will see where we stand.

DR. SHAPIRO: As soon as we can get to some of those the better, I agree.

Okay. Let's take a break now and break for 15 minutes and then we are going to hear from Drs. Burke and Killen.

Thank you.

(Whereupon, a break was taken from 10:15 a.m. until 10:35 a.m.)

DR. SHAPIRO: Well, colleagues, if we could assemble. I would like to get the meeting underway.

Ready, Trish?

We are very fortunate this morning to have two people to address us who have long and extremely distinguished histories in this area and that is Dr. Burke and Dr. Killen have both been here this morning listening to our discussion and as Dr. Burke said just a moment ago to me he was just bursting to get into this discussion and restrained himself most of the morning.

(Laughter.)

DR. SHAPIRO: So now is his chance.

I really welcome you here and thank you very much for taking the time to be with us today.

Dr. Burke, you have got about a half an hour and also for Dr. Killen about a similar amount.

I understand you are both going to be using either slides or overheads.

DR. BURKE: That is correct.

DR. SHAPIRO: Okay.

So those of us sitting at this end either can -- depending on how you feel you can either turn around or sit elsewhere. I am going to sit at the other end.

Thank you very much and welcome.

DONALD S. BURKE, M.D., JOHNS HOPKINS SCHOOL OF HYGIENE AND PUBLIC HEALTH

"EXPLICIT RISK-SHARING" AS A FRAMEWORK FOR ANALYSIS OF INTERNATIONAL HEALTH RESEARCH ETHICS

DR. BURKE: Thank you very much.

(Slide.)

I do not pretend to be an expert in bioethics. I am an infectious disease physician and have worked in international health for my entire career, most of which has been involved in vaccine development in the international arena. I spent 23 years in the U.S. Army working for the Army Medical Research and Development --

(Fire alarm test.)

DR. BURKE: I have spent the last two years at Johns Hopkins University.

MR. CAPRON: Say the magic word.

DR. BURKE: "Bioethics."

(Laughter.)

DR. BURKE: I lived for six years in Thailand. I know Thailand quite well. It is sort of a second home to me. Two years ago during the controversy about the AZT in Thailand my daughter was doing her master's degrees in Cheng Mai and so I had

firsthand opportunity to discuss the problem with her because she knew many of the participants in those trials.

I am going today to speak about explicit risk-sharing as a framework for analysis of international health research ethics. I wear two hats here.

One in my position from Johns Hopkins where I have been involved in some teaching and Ruth and I had an opportunity this summer to co-teach in a course on research ethics that Nancy Kass was running and so we had a chance to talk about these issues and it was a wonderful opportunity for me.

I also work for the International AIDS Vaccine Initiative, a group that has tried to promote international AIDS research on vaccines, as a senior science advisor and I have been with that organization since its founding a couple of years ago.

(Slide.)

What I am going to do today is try to present to you some -- what I think are some relatively simple models for looking at north-south interactions in international health research. I will present six models of the way I think that people have looked at this kind of research and I will call them, as shown

there, the south only problem, the south passive, the south exploited, the south piracy, the north-south limited partnership and the north-south full partnership.

I will point out to you that not only are there risks that are taken by the individual participants in the trial but there are risks taken by everybody who participates in such a trial and that there are benefits that accrue. As Dr. Shapiro pointed out I think we need to be clear exactly about what risks and what benefits we are talking about if we are going to make sense out of distributive justice and any risk/benefit ratios.

And that I think that this body rather than saying that these are too difficult to deal with really should embrace this area and say that there are ethical issues in all of these interactions that need specific attention and specific guidelines. I would find them helpful.

(Slide.)

The first model is the -- what I call the "south only" problem and I have chosen, as Dr. Lo pointed out, malaria as an example. Now malaria is not a serious problem in the United States at all and although there is basic research that is done, largely

supported by the National Institutes of Health and some to the Department of Defense, the U.S. industry is simply not involved in malaria.

There is no intention to make products on the part of U.S. industry. There is no investment in malarial drugs and no investment in malaria vaccines. So what happens is although basic research occurs, very little movement has occurred in this field. You can argue about whose responsibility it is to set the scientific agenda that includes malaria but these are the facts.

(Fire alarm test.)

DR. BURKE: Apparently the magic word is "facts" and I will avoid it in the future.

(Laughter.)

(Slide.)

The second model is the "south passive" model and, in fact, I think this is the most -- one of the most common, that is that there is a health problem that is common to both the north and the south and examples would be hemophilus influenza, pneumococcus, rhode (?) virus, a lot of things that vaccines have been developed for.

(Fire alarm test.)

DR. BURKE: And basic research has been done.

Human trials, for the most part, done in the north. The technology has been produced, in this case vaccines against these diseases. The technology has been deployed in the north with good effect essentially eliminating some of these diseases but there is an additional 10 to 15 to 20 year time period before there is a trickle down and the technology is deployed in the south.

(Slide.)

The third model is what I will refer to as the "south exploited" model and in this case although the health problem is common to north and south and basic research is invested in the north, human trials, because they are simpler, are done in the south and the benefits of that go to technology production and technology deployment in the north and then again we still have a 15 to 20. In this case an example would be the hepatitis B trials where they were done where there was not an immediate benefit. There was subsequently a benefit in that hepatitis B has been deployed in many countries in the developing world but it has taken that 10 or 15 years for that to occur.

(Slide.)

The fourth model is the one where the south now -- the countries -- developing countries are

trying to find ways to solve the problems for themselves if there is not particular interest in producing the technology for the developing countries. Some of the developing countries, India, China and others are in the health arena beginning to -- depending on your point of view -- pirate the technology.

The southern countries, of course, feel quite legitimately that with the WHO regulations that this is a compulsory licensing that they can invoke in their own countries like on the AZT in South Africa but depending on your point of view, if you are the United States Department of Commerce, you feel otherwise. In the vaccine arena I do not know any good examples of this but the AZT production in South Africa is probably the simplest example that most people are familiar with.

(Slide.)

None of those are very good examples of the way things should be. All of those are examples of the way things should not be. So what we have been struggling with is how can we set up interactions so that we have partnerships between the north and the south where we solve our common problems. I speak here from the point of view of the International AIDS

Vaccine Initiative.

We have consciously thought about this, about how can we solve a problem where AIDS is a serious problem, both in the United States and the developing countries, and we have consciously set about to develop partnerships between the north and the south. The question is, what can each party bring to the solution of the problems? So what we have agreed is that we have tried to develop vaccines that are tailored to the countries in the south.

For instance, a C-clade HIV vaccine because that is the virus type that is prevalent in South Africa. We are investing to make a vaccine that is most closely structured so that it can work in South Africa and we expect the South Africans, in return, to participate in this in the human trials. The deal is that if we do have a technology that is produced, that we will get it deployed in the south as quickly as we can, and we have promised to our South African colleagues that we will do that.

Maybe a better example would be the case of the Vax-Gen trial in Thailand of a gp120 AIDS vaccine where the basic research was done. There are now ongoing Phase III trials of that in Thailand and there is literally a written agreement between the company

and the Ministry of Health in Thailand that there will be every effort made to produce the vaccine so that it can be deployed in Thailand.

This is -- you might argue that this looks an awful lot like the exploited model and, in fact, one of the Thai investigators at the meeting in Geneva was asked whether or not he -- whether or not he felt Thailand was being exploited by Vax-Gen in this process and his answer was that no, in fact, he thought that Vax-Gen was being exploited by Thailand. The reason was it was a high risk venture for the company and for them to go into the trial there was much at stake as well with a low probability of success.

(Slide.)

The last model now is what I will refer to as the "north-south full partnership" and here it is do the basic research, do trials both in the north and south, wherever the disease is most prevalent and the answers can be obtained the fastest, and then to produce the technology not only in the north but in the south. There are several discussions with India about the possibility if any vaccines are effective, whether or not they can be produced off shore at cheaper cost. And then the idea would be that these

technologies could be deployed north or south.

So there are, I think, six models here. What I am trying to impress on you is that for most of the diseases that are common in the developing countries if they are common to both north and south there is a 10 to 20 year time frame before they get deployed to the south and if they are not present in the north then they do not get -- then it does not happen at all. So, the notion that there is exploitation of people on these diseases is, I think, a bit misguided.

(Slide.)

So how do we get to foster these international health research and development partnerships? I think that our common goal is that we want the technologies to be deployed in the south and the problem we face with this is how do we construct these product development teams, these partnerships that are going to promote the technologies?

Well, we have found it useful to try to identify the risks for all of the parties that we want to bring to the table and then to have them all negotiate the benefits as they seem them for themselves and for the others and you would be surprised how infrequently this happens where there is an understanding of all the parties to the agreement

about what are the perceived risks and benefits to the other parties to the agreement.

(Slide.)

So who are these parties that when you put together a research consortia in developing countries? I have been engaged in this -- in several of these for vaccines. We did this for Japanese encephalitis. My colleagues did this for hepatitis A for trials in Thailand and we have been doing it for AIDS vaccines now and we run into the same general sets of perceptions of risks.

The research partners in the north, particularly industry partners, are obviously concerned about financial losses and liability. For many of these diseases, tuberculosis, malaria, HIV, they are not guaranteed money makers at all. In fact, there is a high probability there will be a loss for many of the diseases.

There is some concern about liability. Industry also has opportunity costs, meaning that things that are in the pipeline might get backed up because of the production of the lower priority products. And there is concern by industry that there will be political pressure for them to make these available freely in the future because of the

perceived need and the perception of justice.

The scientists in both the north and the south put their professional prestige on the line. Nobody wants to back a loser. Don Francis is a scientist who has committed to making a company, Vax-Gen, to test the concept and most people think he is foolish. I happen to disagree. I think that this -- I think he is courageous on this issue because he is testing a concept but he has put his professional prestige on the line and no one else would do it. So there is a risk there.

There are also the politicians that are involved in the developing countries. Invariably the political opposition accuses the persons who agree to participate in studies with lackey-ism. I have seen it in virtually every country so far as it quickly becomes a political issue. The politicians have to risk their future loss of trust in case things go wrong. It is not a simple matter for politicians to agree to do trials in their country.

And then lastly we will get to the individual research subjects who do have their personal health and potentially their social involvements at risk as well.

But the point here is that when we talk about

the risk/benefits there are many parties to these that need to be put together and from the point of view of someone who has tried very hard to put together research consortia, to ignore the risks that are taken by these parties and to ignore the risk/benefit ratio that all of these have to face I think is focusing on only one very narrow part of the overall equation.

(Slide.)

To highlight some of the risks that are involved -- this is the cartoon that appeared in one of the Thai-English dailies the very day after I had my very first discussions on the possibility of AIDS vaccines with the Thai Ministry of Health. It is in 1991. This was well before any trials actually occurred and I was as discrete as I could possibly be. I did not talk to anybody other than the Ministry officials and I am sure that this was motivated by the political opposition.

(Slide.)

In the same newspaper about three years later there was another cartoon. This time showing the AIDS having knocked out mankind with the medical researcher there counting out the years, 1980, '81, et cetera, '93, '94, implying that medical research was indifferent to the needs of Thailand and that they

were not taking action. So over the course of a three-year time span -- and I think this reflected the national opinions as well -- first the worries about exploitation, and then the worries that there was not sufficient action, and finally the accusations of indifference.

(Slide.)

So I apologize for this being a fairly simplistic and quick overview but I thought it would be useful to put it in what I thought were fairly stark terms for the committee. So the summary here is that all the partners have to take risks. They are not trivial risks for any of the parties, not only the participants, the medical participants, but you would be surprised how much courage it takes on the part of all of these parties, not only the scientists but also the companies, the politicians as well as the participants in the trial. And I find it very helpful if all of the parties who are trying to work together towards a common objective understand the risks taken by others.

(Slide.)

So I will summarize here that this explicit risk-sharing approach as a framework for analysis has some conclusions that the old "south exploited" model

I think is outmoded frankly when you have these pressing health concerns like HIV or malaria or TB in the developing country. We have people in those countries asking us, they want us to participate with them, and we want to be able to do something about it. The notion that this is exploitative is, I find, a little difficult and I think that perhaps we need to broaden the definition of what is the role for ethicists in looking at some of these problems.

I think we need to foster these north-south partnerships as a means to solving international health problems. The notion that the only way at times that we can justify international research are when we cannot do it at home I do not think is a good model. I think that we should be -- that this is a positive thing, that when we do reach out to cooperative international health research, as long as it is understood that the benefits need to accrue to all parties that are involved but to start with the premise that it is somehow tainted if it is -- if it could be done at home rather than done abroad I think is probably just starting at the wrong place and you may want to relook at that as your framework.

The third item there, the risks taken by the partners in international health, they should be

explicitly defined. I find, as Dr. Shapiro pointed out, I find that in many of the arguments that this is not very well done and I think that we could sharpen our conclusions if we sharpened our definitions.

And then lastly that the -- I ask you, and forgive me if I am a bit presumptuous here but I wrestle with this on a daily level -- that I would ask you to help me do this and the way to help me do this is to say, can we devise guidelines that are not strictly focused on the medical participants themselves but guidelines that are a little broader, that do encompass all of these parties because these are difficult issues and I would ask you not to, as was suggested, limited your scope but I think that in the -- that you can do considerably greater good if you help us follow some guidelines because, frankly, we do not have them now and we need them.

(Slide.)

I have got some simple reading materials here. The Economist had a wonderful issue just a couple of weeks ago that had several articles on this. There was a nice article in the British Medical Journal that came out after I had prepared these slides on north-south research partnerships. And I recommend a book on the whole politics of the politics

of International Health: The Children's Vaccine Development. And then the organization that I work with, the International AIDS Vaccine Initiative, our web site is shown there and I recommend it to you because there are a number of good links there as well.

Thank you very much for your attention.

DR. SHAPIRO: Thank you very much. That is very helpful. We have a few minutes for any comments and/or questions.

Let me just ask one or two myself. First of all, I mean it is appropriate to point out that there are risks taken by lots of people but somehow I feel -- my reaction to that was that industry sort of knows all about this. That is what they do every day. They do not need our help in thinking about their risks. And pretty much the same thing is true of scientists, they know what risks they take. And probably true of politicians, although I am less able to say in that area.

But that leaves research subjects and it seems to me that there is some asymmetry here. These are not all of the same standing or all of the same nature.

DR. BURKE: True.

DR. SHAPIRO: Could you say something about that or how you think about that?

DR. BURKE: Yes. I think that definitely is true, that there still is in terms of power relationships an understanding that certainly the participants in the trial are at a disadvantage and they do need to have some greater assurances and greater protections but I do not think that needs to be exclusive and my point here is just to point out that many people assume that the companies are out there waiting to do the trials in the developing countries. In fact, they are not because in their own risk/benefit analysis they are not interested.

So our job is to help change their own risk-benefit equations and that I have been surprised regularly when I have conversations with people who are generally fairly knowledgeable who assume that there are companies out there who want to make AIDS vaccines and are going to exploit the countries in the process of making those AIDS vaccines. Nothing could be further than the truth. They are not particularly interested and they are not about to exploit and we need to engage them simply because their own risk/benefit equations are different so we need to recognize that. I want explicit recognition not on

our part and not on the part of the companies.

DR. SHAPIRO: The partnerships you have talked about all have the kind of health problems shared. It is sort of that first square, it is right on the line there, meaning that a problem both exists in the north and the south. But it may be quite rare when -- even though the problem exists both in north and south. Its order of magnitude of its important is the same.

How do you think about these partnerships when the order of magnitude of a problem, although shared, is just very, very different in the south and the north?

DR. BURKE: I may -- I will have to think about that but my initial reaction is that that does not change my opinion very much. My opinion would be that if the problem can -- if it is a serious health problem anywhere that just because it is international should not present an obstacle to getting the problem solved. I do not see that as an inherent barrier.

I do not see that, you know, my living in Washington and working in Nebraska is any different than living in Washington and working in Thailand. That if we have the same problems present in both places and if they are done in an ethical way then I

want to get the problem solved by the means that I can do that and make sure the benefits are available to both parties.

DR. SHAPIRO: If you just take one of your categories, let's say politician risk, this surely must be impacted by the nature -- the size of the problem they are trying to help deal with. The problem in Nebraska is very small and very large in New York. The risk of the problem is entirely different.

DR. BURKE: Yes. It certainly would factor into the risk/benefit equation for all parties that are involved is if -- even the individual participant if it is a greater risk in their community is much more likely to become engaged in it.

But from my point of view should I think about this in a different way just because it is international? I do not think that that really is the issue.

DR. SHAPIRO: Alex?

MR. CAPRON: I want to thank Dr. Burke very much.

It seemed to me that with the kinds of tweaking that you were just doing, Harold, about where on that dotted line the problem falls that the basic

setting out of these six models you have I think really does help thinking and I have no idea whether you have published this elsewhere or whether that article -- I mean, the other people that you --

DR. BURKE: No.

MR. CAPRON: -- but I hope that with your permission to the extent that Ruth finds it helpful in the process, I really think it -- something like this makes it accessible to people. The model, the "south exploited," which is sort of what -- the purpose of these other five is to show in relation to that stereotype.

The other comment is to follow on this question of the risk/benefit ratio because I think I agree with our chairman that it is, of course, relevant for many of the considerations as to whether or not the research will go ahead where different people see the risks and benefits. But within the context of human subjects research the risk/benefit ratio that we are most concerned about is as it relates to the research subject and the issue it seems to me is in the United States a decision was made that informed consent is not the only criterion for acceptable research, that we, in effect, paternalistically impose upon the research process a

requirement of IRB review that looks at the acceptability of a project as to whether a group of well informed outsiders of mixed competency, some scientists, some nonscientists, et cetera, view the risk/benefit ratio as falling within an acceptable range and when it does not supposedly the research is not going to go forward even if there would be people lining up who say, sure, do it on me.

And it seems to me that one of the questions that arises in the international context is to what extent do other parties besides just a traditional IRB play a role in that assessment and what range of benefits are counted as well as the risks to the subjects because as I understand the interpretation, sort of the standard interpretation, I stand to be corrected on this, of the requirement of a favorable risk/benefit ratio, the view has long been that you can include benefits to the larger population and to science.

In other words, it does not have to be the research subject who stands to benefit more from participating than the risks. That person might agree to accept risks that are greater than the benefits than he or she will derive, but only when people judging it say, yes, this is research that has some

probability of producing good broader benefits.

And what about the Health Ministry saying, "We have a say in making that judgment before you come in and do research here in our country," et cetera, et cetera. So, I mean, there are other participants that make it more complicated in the international settings.

But the question that Harold, it seems to me, is raising was, well, how might one legitimately categorize the range of benefits that would be counted there and in a way the global justice issue comes in here if the country does not have a real prospect of being able in the near term to bring in the product that has been developed.

Doesn't that count in whether or not it seems legitimate for them to be saying do the research here? To what extent do benefits to their infrastructure, better trained scientists, equipment left behind and so forth count on the benefit side but it is not the same kind of benefit. It is benefit to other parts of the system that do not help the sick people at all, these sick people, et cetera, et cetera.

And these are some of the complexities that I think we are going to have to get into but I would not include whether or not the politician or the

researcher feels there is a risk to his or her career. I mean that -- we can note that that goes into the decision whether or not the research will ever get done.

DR. BURKE: The reason for having the risk based analysis, that is -- what got me into this in the first place was the question of distributive justice and the claims that if a treatment or a vaccine were studied in a country then it should be made available to everybody in that country, and that always troubled me.

I did not quite understand what the principle of that was and then the more I thought about it, who actually is taking a risk such that there is a benefit that comes from that, and trial participants are not really taking a risk for the rest of the country. Some of them do not have any particular interest in another tribal group on the other side of the country.

It is really the politicians who are taking the risk and so should we be thinking of this in terms of rewarding the politicians because there will be a benefit to the society for the risks that they have taken as the representatives of those people or that kind of approach where there is a -- being explicit

about who is taking the risks and who is getting the benefits.

And I have not worked it all the way through but that is at least one way of getting at some of these problems rather than to make these sort of the hand waving notions that there is an obligation and whether or not it is a historical obligation or some sort of distribution of the wealth obligation but another way of looking at it is who is taking risks and who is getting benefits. It is just -- and I am not sure it is any better but it helped me anyway to come to terms with why we were willing to do this kind of thing.

DR. SHAPIRO: Well, thank you very much.

There are a lot of hands.

Diane and then we will go to Bernie.

DR. SCOTT-JONES: I have a question about how one would make the decision to do the research in another country. So could you sort of give us your thinking as a scientist how you would decide to do the research outside the United States and then perhaps how you would imagine a private company deciding that they would support research done in another country? What would be the criteria and the lines of reasoning?

DR. BURKE: Rather than to deal with that in

general I will deal with it relatively specifically in the case of AIDS vaccine trials. We decided that we would work with South Africa, this International AIDS Vaccine Initiative, that we would work there, and the major criteria were that they had such a severe epidemic that we could get answers faster that would be of benefit to them, that there was political will on the part of the people in the country, that there was a sufficient infrastructure that would allow us to do the research, that there were technically competent persons who could participate and to make sure that it works.

All of these things would be factors that were positive factors. It would make us less likely to want to do these trials up front in Malawi or Angola or other places where a lot of these things just simply are not true right now. But the idea is to try to forge partnerships to take a group where they believe it is their problem and we believe it is our problem and to try to solve this as fast as we can.

If we could do it in the United States in Baltimore we would do it in the United States in Baltimore but if we can get it done faster through international cooperations to both of our benefit then

that is what we should do and the notion that it is -- that it could be done in Baltimore is not as strong as compelling as can we get it done as fast as we can for the greatest benefit for both parties.

DR. SCOTT-JONES: Okay. So could I just follow up and make sure I have heard you. First it is the needs of the people so you identify that the needs of the people in that country were somehow greater than in other places and then the infrastructure that would allow you to do that. Those would be the two questions.

DR. BURKE: I was speaking from the point of view of a nonprofit. I was not speaking necessarily from the point of view of a company. A company might not use the same criteria. They may not use the criteria of the needs of the people. They might use the criteria of which is the most expeditious way of solving a problem, of doing the smallest trial with the least amount of cost because if the incidence is high then you do not need to do a 10,000 person trial, you can do a 1,000 person trial.

I think those are perfectly legitimate decisions on the part of a company as long as the provisions are there so that there are -- the benefits accrue in proportion to the risks that are taken.

DR. SHAPIRO: Bernie?

And then -- let me just -- what I hope we can do, I think, Bernie, after your question and the discussion, we will turn to Dr. Killen and then we will have time for questions for both Dr. Killen and Dr. Burke but I want to make sure we give Dr. Killen a chance to make his presentation also.

DR. LO: I also want to thank you for coming and making a presentation. I think it is very helpful to sort of try and develop a model for thinking about risks and benefits and it does clarify things. Like any interesting model it raises a lot of questions. I wanted to raise a question and ask you to sort of think through the issue.

This falls really on what Alex and Harold were asking about. What are the different kinds of risks and benefits? It seems to me when you -- you very nicely laid out the different actors or players here. They are facing different risks and they get different benefits.

Traditionally in ethics -- in research we have thought about different kinds of benefits and there are sort of benefits that are sort of personal and self-centered benefits, whether it is the politicians or the scientists, or maybe even the

subjects, and try and distinguish those between benefits that really are sort of patient centered or health centered.

So, for example, even as a scientist, certainly part of my decision to enter into a clinical study, clinical trial, are these very pragmatic factors about what is it going to do to my reputation, my career, and whether I am going to get funded and stuff. But in the sort of ethical analysis we like to do we like to also say, well, are there other reasons that sort of are more centered not on me as a scientist but on the population with the disease. Similarly I think with the politicians.

So I guess I want to ask you have you sort of thought through how one distinguishes reasons which we all operate on because we are selfish people but somehow in research we want to have sort of the altruistic patient centered reasons also be given more weight. How one sort of takes into account the different kinds of benefits that different actors might gain from participating in a study.

DR. BURKE: I do not have a good answer for that. That one is harder than the other kind of more easily to define risks and benefits on the individual level. You could -- I am sure there is a sense of

altruism that permeates through all of the players here and that there is also the successful completion of a trial for an AIDS vaccine and the benefits would extend well beyond the individuals that were participants in this particular single partnership and everybody is aware of that.

But how you factor that into this kind of risk based analysis I myself am uncomfortable with right now. I do not have a good answer to that one. I know it is there and I know it is across, and I know it smears across all the participants but exactly how that weighs in and how it should weigh in on an ethical framework I do not know the answer.

I have a feeling it should. That is what motivates me. I think that I probably do care about my personal scientific career and things like that but I do feel a strong sense of motivation from this altruistic feeling that I am trying to do something that matters to a lot of people but how do I calculate that. I am not sure.

DR. SHAPIRO: Okay. I am sure we will have more questions but I really do want to turn to Dr. Killen for his presentation.

We are starting a little late but you are welcome to the full half hour. The person who is

assigned for public comments will not be able to be here today so we have that extra time to spend on our discussion.

JACK KILLEN, M.D., NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, ETHICAL ISSUES ON INTERNATIONAL RESEARCH FROM AN NIH PERSPECTIVE

(Slide.)

DR. KILLEN: I want to thank you all for the opportunity to be here this morning. It has been really enlightening and interesting to listen to the discussion and a lot of what I wanted to talk about has already been talked about so I will try to go fast over some of the stuff.

I am sort of coming to you from a perspective of the NIH, which you can sort of think of as a hybrid of a sponsor and the public sector. I think that the reason I say that will become evident in a couple of minutes. The thrust of my presentation is going to come out of AIDS and AIDS research because that is what I do but in having spent a lot of time thinking about these issues about international research I do not believe that anything that I say here or talk about this morning is specific to AIDS and that the points and principles are fairly generalizable.

I want to just talk quickly about three

things. One is sort of objectives and goals of international research. I want to talk about this issue of benefit being multidimensional and finally and most importantly I think what I want to get into is to talk about dilemmas because that is what we are dealing with here.

Dilemmas that are complex and inevitable in the context of perhaps unequal distribution of research and health care resources in the world and that the resolution of those dilemmas requires an understanding of the local context in which research takes place and the involvement of many stakeholders. So those are the points I want to make, I hope, in the next couple of minutes.

(Slide.)

This may be another way of looking at what Don just put up. There is a whole lot of different reasons for doing research in developing countries ranging -- maybe this could be more appropriately called a spectrum ranging on the one hand from an interest in addressing a major health problem in the developing country as the reason for doing the research on the one hand to on the other hand taking advantage of some very practical opportunity that presents itself and there is a spectrum that maybe it

goes beyond this but this is a spectrum of motivations for doing international research that perhaps one might worry a little more about exploitation at the bottom than at the top but I find this is a very useful way of thinking about doing research in developing countries.

(Slide.)

The next slide sort of gets more into where I think we at the NIH are coming from. We believe that our research is more focused on the top end of that spectrum rather than the bottom, not to say that one is better or worse than the other. They are both good but when thinking about public health oriented research we kind of believe that the agenda around ethics and assessing ethics of clinical research needs to take account of this category of research very carefully.

This is simply a list of some examples of research to which NIH has contributed in various ways and in various degrees, some a lot, some a little. We could get you a lot more detail if you are interested in this but there have been many studies carried out in developing countries where the goal has been very explicitly to address a health problem in the developing world that has very little relevance to the

United States. We could get a lot more information and a lot more examples that I think are very useful in elucidating. I will not go into any more detail about these. Just to mention it and keep this kind of thing in mind.

(Slide.)

Now I want to use for the next couple of minutes the mother-to-infant transmission studies as a case study. I hesitate to do this. My interest here is not to be defensive. My interest is simply to uncover complexities of the dilemmas and so I hope that what I say is taken in that spirit because that is how we are looking at it. There are dilemmas here and we do not feel like we have a good framework for thinking through the ethics involved.

(Slide.)

The situation you all know very well. In the United States the epidemic of perinatally acquired HIV is -- has taken a dramatic down turn and, in fact, more recent figures show that the down turn continues even further. This is a direct result of intervention in the treatment of pregnant mothers or using antiretroviral therapy to treat pregnant women to prevent the infant.

(Slide.)

However, in most of the world the epidemic is exploding in cases completely uncontrolled and the reason for that is very simply that the interventions that are available in the U.S. and other western countries are simply not accessible in the rest of the world.

(Slide.)

What has happened here, and this gets a little bit to I think what I heard Bernie talking about a little while ago, is that there are two totally divergent research agendas. In the north, if you will, if I can use those abbreviations, the goal is to find more active and better regimens to eke out more incremental progress. In the south the research agenda since the O76 clinical trial results have been very simply to find something that could be put into place and they are completely divergent research agendas.

(Slide.)

This has resulted in a series of studies. I will not go through the details of this. The O76 trial was the original one in the U.S. The Thai study followed on to that. A Petra study. All of these were studies progressively aimed at finding interventions that could be used that were much

simpler, cheaper, practical, feasible. They showed results but to date essentially what we have seen is that even though cheaper, more practical interventions have been proven in research they have not been put into place.

(Slide.)

The most recent development in this has been a study that was carried out in Uganda in 645 HIV infected pregnant women that were randomized in a study that was designed at the time that the controversy around the perinatal transmission studies was erupting. This was originally intended to be a three arm trial that would include a placebo. The placebo arm was dropped at the time that the Thai results were made public and turned into a simple phase -- originally intended to be a Phase II study to find a regimen that might be put up against the simpler Petra regimen to see in a subsequent trial what was best. This was HIVNET-012.

(Slide.)

Just a couple of weeks ago these data were published and a couple of months ago they were made public. There was actually again an astonishing degree of effect of the simple nevirapine arm which was highlighted on the earlier slide, the details of

which were highlighted on the earlier slide, that resulted in about a 45 or so percent reduction in the likelihood of transmission from mother-to-infant with a regimen of nevirapine which is given -- a single dose to the mother orally at the onset of labor and one dose to the baby after birth.

(Slide.)

The important point here is that this series of studies has generated an intervention that can reduce by approximately half the transmission from mother-to-child and reduce the cost from approximately $800 per case to approximately $4 per case. Now we have yet to see whether this intervention will actually be put into place around the world but I think it is illustrative of a line of research which needed to take place which was not generally in the interests of the U.S. even though the implications may have some bearing on what happens in the U.S. There is an entirely different research agenda going on here compared to there.

(Slide.)

I want to just talk for a minute about benefit and maybe we can come back to this in the questions at the end. We think of benefit as multidimensional. I have made direct and indirect --

those two categories which are enumerated a little more on the next transparency. The direct is sort of what we have all been thinking about and talking about. That is benefit to the study participants. Improving health in some way as a result of the research.

There are in -- particularly in the case of research in developing countries a number of areas of more indirect benefit which are extraordinarily important if one takes a long view about doing clinical research. One of them is to build research capacity and that includes the people and the places where the research is done. There are parallel improvements in health care that result -- that spill out of research that are not directly a result of the research. The development of independent review capacity for both science and ethics.

And finally what Don was talking about before, the business of long-term relationships and trust that get established as a result of research are extremely important.

I say this all because on the next slide --

(Slide.)

-- behind the success of HIVNET-012 and all the other perinatal studies is essentially that, those

other benefits of research that lay -- that set the stage for happening. Behind that success was not -- was strong political support but also a history of at least 15 years of intense collaborations in a broad area of research in Uganda that had resulted in the development of extensive research capacity in-country and strong local ethical review that permitted HIVNET-012 to take place. HIVNET-012 could never have taken place without the benefits that had accrued to research before.

Now I do not mean to argue that those should justify things being done that are wrong by any stretch of the imagination but I do think it is a dimension of benefit that is perhaps more important in thinking about research in developing countries than here.

Finally, ,let me just try to shed a little bit of light on the next -- the last point which is this business of dilemmas. I think the point that they are complex and inevitable is, I hope, obvious.

On the next two slides, which I think -- skip the next one and go to the one that talks --

(Slide.)

Well, there was before this one a series of criticisms of the mother-to-infant transmission

studies. The justifications that have been given for them are highlighted here on this slide. I think the one that has not -- has been given short shrift to me really gets to the kernel of it all, is that the studies were designed specifically to answer the public health issue of relevance in developing countries.

All this other stuff about, you know, the local standard of care is being provided or is not being deprived and all that are justifications but I do not think they get to the real nub of the point and that is that the point of the study is to answer the question of relevance.

(Slide.)

When you start to probe into the dilemma of these studies and ask what is the point of the study. Exactly what question must be answered is the design appropriate, what is best proven diagnostic and therapeutic method in this context. I think you begin to shed light on the complexity of the dilemmas and the complexity of the answers.

(Slide.)

Just to take the case of the mother-to-infant transmission studies -- the relevant public health or resource allocation question, if you are the Minister

of Health in a developing country, is whether or not the new intervention is better than the care which is currently available in your country.

So talking about no care versus care in the context of the perinatal transmission debate is wrong because the studies were not that. They were something quite different. The appropriate study design was, we think, to answer that question. The care which is currently available plus the new intervention or placebo. That was the design of the study. Women and their infants did get care. The question was the intervention.

And then that begs the question of are there alternative study designs. There are alternative study designs but they do not answer the question of relevance if you are trying to make a decision about how to allocate health resources when those are extremely limited. If you are the Minister of Health trying to decide whether or not to provide clean water or treat -- prevent HIV and you have got to make that kind of a choice, what you want to know is how a new intervention compares to what is being done now.

(Slide.)

The other point is another set of questions that probe into the dilemmas. I will not go into this

in any detail either. Sustainability of the tested intervention after the study is completed is a big point that gets made but the fact of the matter is that there are a whole lot of individuals -- of entities who have responsibility for making sure that that happens.

Responsibility -- the ability to do it and the authority to do it. So far this has been cast in terms of sponsor, but governments and funders have key roles in this. Also sponsors cannot make something available in the absence of a lot of participation of others, particularly in developing countries. Furthermore, the fact of the matter is that availability and sustainability cannot be guaranteed up front. You cannot get anybody to agree that that will happen.

An example here comes from another realm. I will not talk about the specifics of it but in a different realm of research a vaccine study in another African country, not an AIDS vaccine study, where the Health Ministry resented the requirement that some commitment be made up front feeling that that was a patronizing requirement and that they would be able to make a commitment when they saw the results of the study and could do an appropriate analysis of cost and

benefit. And that gets to some of the perceived paternalism and rigidity of the current guidelines.

So I will stop basically with the next slide which is a set of thoughts about ethical review that are pretty much regurgitations of what I have already said or what has been said by others this morning.

(Slide.)

I also believe that considerations of justice here need a lot more development than they have been given so far because they become a lot more important in weighing overall risk and benefit, particularly if one thinks about benefit in a bigger context and over the long term.

The resolution of these dilemmas is very complicated. It requires a lot of stakeholders of the nature that Don was talking about in terms of partnerships.

Thanks very much.

DR. SHAPIRO: Thank you very much.

Ruth, and then Bernie?

DR. MACKLIN: Thank you for enlightening us.

Jack, I want to know how much some of the considerations that you raise could justify studies that -- for which there would be good scientific evidence that they are distinctly inferior to other

possibilities? I am going to be more specific in a moment. And I say this against the backdrop of debates that have taken place on the ethical review committee of UNAIDS where people have expressed different views, so I mean there is nothing behind this but the notion that there are reasonable people that are disagreeing and there are two examples here.

One is studies of vitamin administration and vaginal washings as an attempt to decrease maternal-to-child transmission given everything else that we know and the belief that they would be distinctly inferior. So one of your principles or one of your views -- one of the things you said is would it be better than the alternative which is no treatment at all. I mean that was one of your -- the justifications that you had and that could justify what some would argue is a distinctly inferior regimen. That is, is the new intervention better than the care which is currently available and that was your point here.

DR. KILLEN: That is the way I put it, yes.

DR. MACKLIN: Yes. But I mean that is the -- that notion, that idea could be used to defend what some have said are distinctly inferior or known to be inferior and to do research on them is unethical.

That is the first one.

DR. KILLEN: Yes.

DR. MACKLIN: And the second also in the dilemma is what might be a contribution to knowledge but at the same time is argued to be unacceptable again given what we know about maternal -- to what is effective in maternal-to-child transmission and that is natural history studies. There are some who are arguing that it is ethically acceptable to do natural history studies in precisely those areas where there is no intervention and people do not get the care and it is not available, et cetera, since you are not making them worse off. I mean that is the argument so could you address both of those?

DR. KILLEN: The first is a little easier to address. I think the answer to it changes over time, of course, as new things become available as the possibility -- I think the way --

DR. MACKLIN: Given the nevirapine, for example. Given the results for nevirapine.

DR. KILLEN: I guess, you know, what you have to -- what you have to ask is whether or not the -- whether or not what you study will provide useful information at the end of the trial, number one. And, number two, whether or not what you study can be put

into place at the end of the trial.

I think -- I do not think that there is a right or a wrong answer completely here. It would clearly be wrong to study something that cost $4 or, you know -- that cost the same as nevirapine if you did not think that -- I am sorry. It would be wrong to study something that costs the same as the nevirapine regimen if you did not believe that it was equally effective. That would be wrong.

On the other hand, I think if -- you have got to -- well, not on the other hand. You have also got to factor in what can be put into place, what is the -- what is the nature of the question being asked, I think, or where is the question coming from. If the question is coming from a public health standpoint of helping to inform the distribution of resources you have got to take into account what is practical and feasible in the context of where the study is being done. I do not know if that sheds light on it or not but that is --

DR. MACKLIN: What about the natural history studies?

DR. KILLEN: Again I think you have got to -- you have --

DR. MACKLIN: I mean, there is nothing to

implement at the end. That is not -- that -- so the other --

DR. KILLEN: Yes.

DR. MACKLIN: -- justification does not even apply.

DR. KILLEN: Again I think you have got to know what the -- what is the purpose of the study. If the purpose of the study is to inform health or health policy in the context in which the study is being done there is more justification for doing it than if the purpose is to go in and do natural history to exploit it for the purpose of bringing it home and using it for other purposes than the health of the setting where the study is being done.

DR. SHAPIRO: Bernie?

DR. LO: Jack, I want to thank you for your presentation and in the tradition of Commissioners here who only get one question I will ask you a double barreled question as Don answered two to maximize my efforts here.

DR. SHAPIRO: Maybe you could assign one of your questions to one of the other Commissioners?

DR. LO: That would work too if I could delegate it.

One, in your presentation you made a bit

point in the HIVNET-012 study that the infrastructure that had been built up in Uganda, both the scientific infrastructure and the kind of ability to do independent ethical review were crucial in your view to the success of the study. I take it that that -- the existence of that infrastructure in the developing country is not universal.

DR. KILLEN: Correct.

DR. LO: Would that -- what are the implications for doing studies in countries where neither the scientific nor the ethical infrastructure exists? Does that mean it is unethical to do those studies until we wait to develop that infrastructure somehow through the training programs? That is one question.

The second question goes back to your point about sustainability and the difficulty of reaching up front agreements. Again this is one of the areas where I have seen a lot talked about in very general terms but I would be interested in going to the next level. What in your view -- and, Don, I guess I would ask you the same question -- what would be a reasonable agreement between all those parties up front, not knowing the results yet, as to what commitment they are willing to make?

What would you think would be a satisfactory solution that is both practical and could be ethically defended in terms of if the results -- I mean, I always ask my students if the results come out as you hope and you have a clinically and statistically favorable result for one arm, what commitment would be reasonable to expect the different parties to make in advance?

DR. KILLEN: The latter -- on the latter, again I think it is very circumstance dependent and it could range from a commitment by a Minister of Health to marshall the resources to put it into place to a commitment that the WHO and the World Bank will -- you know, the Minister of Health will go to the World Bank and seek a loan, which might be the best that they can do to put in place the health care infrastructure and the company might give somewhat of a cost break to -- you know, some kind of an agreement or an understanding up front that does not say, yes, we will make it available because that simply is impossible to do several years in advance I think.

DR. LO: Don, do you have any thoughts on that?

DR. BURKE: Yes. We wrestled with this quite concretely on the International AIDS Vaccine

Initiative when we were trying to build these international partnerships to say we are going to develop vaccines to test in your country and one of the ways we did this was to -- in the -- when we funded companies to prepare vaccines for South Africa we built into their contract that they agreed to make vaccine available at no more than 10 percent above cost to that country, that they could sell it for whatever they wanted to in the United States and Europe but for the developing countries, as defined by the World Bank the poorest countries, that they had to agree that they -- so we would give -- we built in a tiered pricing system into the agreement. And I am not aware of anybody else that has done this so far but at least we are struggling with this idea of building into the contractual agreements the obligation of access downstream and whether or not it will work I do not know but it was at least a running attempt at it. So I think it is do-able.

DR. LO: If I could just say I think it will be very helpful to us as a Commission if you could give us specific examples of the kind you mentioned to sort of -- so we could help develop a standard of what it would actually mean to have a meaningful and realistic prior commitment because I think in the

absence of some examples that clearly are context specific that at least would give others some starting off points for discussion.

DR. KILLEN: Yes, that certainly could be done.

DR. SHAPIRO: It strikes me, Bernie, on this issue if one is talking about obligations to those who participate in the trials, that is the subjects themselves, that is one way of doing it.

DR. LO: That is a separate. Yes, I think it is a separate.

DR. SHAPIRO: That is a smaller problem but it is an important problem. Then there is a much more complex problem of does this involve some obligation to the country or whatever larger group it would be, which is the --

DR. LO: Right.

DR. SHAPIRO: -- on the former problem is now probably not that different. In this country and other countries it is a common ethical issue concern no matter where you do your trials.

The second one, the larger one, differs a lot by country or it might differ. I have not thought it through myself.

DR. KILLEN: I am aware of the discussions

about another bacterial disease vaccine, without revealing any of the confidentialities, where the company said quite simply, "We cannot make a country specific agreement for a study that is being done in a small country because we are also doing another study in a much larger country where we could not possibly commit the resources and we cannot be in the position of saying -- giving special treatment to one country compared to another."

DR. SHAPIRO: Let me take just a brief pause in our discussion. Those people -- as I mentioned before, those who have signed up for public comment were unable to make it here today but just in case there is someone in the audience who would like to address the Commission for no more than five minutes let me just ask the question and then we can continue our discussion.

Yes, please? Just tell us who you are and so on. Anywhere that is comfortable for you will be fine. The table would be fine. Sit down.

PUBLIC COMMENT

DR. LURIE: Thank you. Good morning.

My name is Peter Lurie. I am with Public Citizens Health Research Group in Washington, D.C.

I did not come with prepared remarks since I

-- there -- the sequence I suppose is the sequence in which they came up and which I wrote them down so I just want to share my thoughts on a variety of -- not necessarily completely related issues.

The first question that I heard come up this morning was what the Commission ought to do in terms of contacting other people and who to write to and so forth. I heard a discussion that was about the importance of speaking to deans of public health and whether or not we should speak to deans of medical schools. That is really not the issue at all. The issue is not whether or not the research industry will be adequately heard at this table. It will be.

The issue is whether the voices of people in developing countries will be heard and, therefore, I think one needs to go much beyond that kind of group and I am willing to do what I can to help provide such people. It is not easy because those people are under a lot of pressure and find it difficult to come forward and oppose not only people in this country but even the research leaders in their own countries but really that is where the work needs to be done. Not in helping deans of public health to make their points clearly because they will, including this afternoon.

The second issue is distributive justice and

I heard at least some notions that -- whether or not this should be in the report and to what extent it ought to be and so forth. I cannot strongly enough emphasize how important it should be. I would suggest, in fact, that the survey that is being done of the national principal investigators should include specific questions on this.

The suggestion has been put forth by ourselves but especially by George Ennis and Leonard Glass that we need to have agreements up front. Nobody says it is easy. Jack has pointed to some difficulties that exist in writing agreements up front. But the fact that there are difficulties is not an excuse to have no agreement at all. It is an excuse to work harder at finding an appropriate one.

I think that the survey that is being done by the Commission on behalf of the Commission should ask the questions of did people, in fact, conclude the kinds of agreements that Glass and Ennis have acquired. And then if they actually concluded them, which they may very well not have, I suspect in very few cases will they have, and I think by the way that what Aobi (?) has done is an example of what can be done rather than pointing to problems, it is a finding of some kind of a solution.

The second part should be if they actually went so far as to conclude such a thing did they actually implement it so it would be a second part of that and I would like to see that as part of the survey.

The third point is there was discussion of whether or not it is appropriate for your committee report to address the totality of the international research agenda and whether or not things are focusing on questions that are too small as opposed to the larger ones and certainly I do not think that one can go on a research project by research project basis and say, well, this is unjustified because it is on a disease of rare prevalence. If one were to take that as the principle then everybody would be doing only research on the most prevalent disease so clearly that is not the way to go.

But I do think that for institutions like the NIH or the CDC who have large research portfolios your Commission could recommend an annual review in which they are forced to go back and look at the totality of what they are doing and say in totality how does this meet or not meet with the totality of requirements from the developing world or for the particular countries in which we are looking. I do not think you

can do it again study by study. I do not think that makes very much sense but I think that is in a way -- in many ways the most important question and I think for your committee to sort of shuck that aside would be a mistake.

Ruth made some interesting points on standard of care and I tend to side with her on this. I think that the term "standard of care" has been used in an extremely sloppy fashion. There is -- people just use it in a way that is not thoughtful. I think the distinction between the two standards as Ruth described them is a very useful one and it is interesting that the standard of care is applied in a quite inconsistent fashion.

For example, if it is standard of care to reuse syringes in a particular country would an NIH funded research project go in and reuse syringes? I do not think so. If -- would an NIH funded research grant go in and not use the very best laboratory counters, laboratory -- you know, like CD4 cell counters for example? Of course, they would not. They would bring in the very best.

So unfortunately the term "standard of care" is not applied to those elements of research. It is instead applied to those research -- those areas of

research which involve the actual provision of care to patients. And that I think highlights the very conflict of interest that is operating here.

No, we do not -- we will raise the standard of what we provide in the research setting but if it involves decreasing the incidence of the endpoint that we are interested in then suddenly the sloppy word, "standard of care," raises its ugly head.

Standard of care has a meaning. It has a medical meaning. It has a scientific meaning and it is based on the best available knowledge of what we think actually works in a particular setting. Now agreeably sometimes there will be honest disagreements between scientists about whether something works or whether it does not and that is fine. That is acceptable.

But the term "standard of care" as applied to what is provided in a country is not very helpful at all. If you go to South Africa, for example, you have no difficulty finding -- well, if you could find HIV positive White pregnant women you would have no difficulty finding people getting triple drug therapy I am quite sure. On the other hand if you go into the townships most of those women are getting absolutely nothing.

So standard of care is not between countries only. It is also within countries. And if we were to take that kind of notion and apply it to the developing world and say you are a poor Black woman in South Africa, you get nothing, and were you to be a White HIV positive pregnant woman you would get it. Well, what if we applied that same kind of standard to this country? What if we were to say the standard -- well, yes, we are providing, you know, poor care to you, for argument sake, person of color, injection drug user in the intercity, but that is because you are poor in effect. I mean that is really what the standard of care means. This is what you are getting precisely because you are poor.

What can be more objectively evaluated is the scientific data and that is a meaning of standard of care that actually has some scientific credibility and the one that we should be adhering to. So standard of care as used in this unfortunate illusion is not as -- and Ruth points us out quite correctly -- it is not standard of care. It is substandard care. And most of the times or many times, excuse me, it is no care at all. And to dignify it with these terms sloppily used I think is extremely dangerous and not what -- the kind of thing that this Commission should be

endorsing.

I would not have talked about the vertical transmission studies but Jack sort of invited it particularly when you offered the defenses of the studies but not the criticisms.

The question there is not whether or not the sequence of studies found something useful in the form of nevirapine because it did. The question is whether there was another way to have done it and the question is did anybody expect a sequence of events much different, setting aside nevirapine itself where I think people were honestly surprised, much different than what happened.

Ruth tells us that the CDC investigator in Thailand said that they thought that short-term AZT would work. In fact, I am not surprised to hear her say that because the CDC's protocol for that study says that they thought that short course of AZT would work. In fact, they thought short course might be about as good as the long course. So the investigator from South Africa, James McIntyre, wrote in a published article prior to the Thai study, "We believe the short course will work."

So in all of this the notion of equipoise is critical and we have not heard that discussed.

Somehow in all of this we seem to be hearing equipoise is somehow for us but we can go overseas and throw away these notions of equipoise and do studies to which we actually think we know the answers when we go in. That, I think, is a very dangerous precedent to set.

So the question then is was there another way and we believe that there was. We do not think, especially since most people seem to think they knew what the answers were going in, we do think there was another way that would have protected subjects better and, indeed, the study results show that.

We now have four, I believe it is, placebo control trials from Africa on the vertical transmission and lo and behold they are all positive and they are not even close to being negative with one exception of the intrapartum (sic) only in the Petra trial. They are very, very positive. In fact, they are so positive that everybody would have known that they were positive had there not even been a control group, let alone a positive control of placebo group. The reduction was so substantial that as it happens in retrospect no control would even -- would have been sufficed to even realize that these things worked.

And 012 is put forward as if this is some

great accomplishment and in a certain way it is but itself is -- 012 is itself unethical. Let us remember that 012 provided no prenatal AZT to anybody in either arm of the study.

Whereas, in fact, they -- whereas, they continued to recruit people into that study for 14 months after the Thai regimen had proved that antepartum AZT was an important part of the regimen. So it was antepartum and intrapartum worked in Thailand and for 14 months they continued to recruit people without providing an antepartum AZT and they went on to do it for five months after the WHO had recommended the Thai regimen for places that had an adequate infrastructure. So even that was -- was itself not an ethical study.

DR. SHAPIRO: Excuse me. Are you bout to finish your remarks?

DR. LURIE: Yes. I am on my very last point.

DR. SHAPIRO: Thank you.

DR. LURIE: The final point is on observational studies. There was a question about this. And, you know, I guess -- you know, Jack's response to this is, well, as long as we are trying to do good for people it is okay.

DR. KILLEN: No.

DR. LURIE: Well, that may be --

DR. KILLEN: That was not my response. I am sorry.

DR. SHAPIRO: Let's not do this.

DR. LURIE: Okay. Let me --

DR. SHAPIRO: It is not a personal issue at stake here.

DR. LURIE: Okay. Let me --

DR. KILLEN: That is a misrepresentation of my response.

DR. LURIE: Let me rephrase. Let me rephrase. Okay. Fair enough.

What I understood Jack to say was that an important way for deciding between an unethical or not unethical observational study was what the intent of the researcher was, that if the intent was to improve for health or health policy purposes, that if it had a legitimate purpose of that kind that you can say it would be ethical but that would weigh in the favor of being ethical -- in favor of it being ethical.

I suggest that divining the intent of the researcher is difficult. I think people are trying to help but I do not think that -- I do not think that that in the end is the way that one should distinguish between these things.

If you are in -- and my final -- very final point is the observational study -- Ruth's question is excellent because if you are in the placebo group of a randomized control trial either before or after the Thailand study it still feels like you are in an observational -- it still feels like you are getting a placebo. I mean, it feels -- you know, you are still getting nothing. You know, you might as well be in an observational study when you are in -- from your own personal point of view.

That is it.

DR. SHAPIRO: Thank you for your very helpful remarks. Thank you.

Are there any questions regarding these particular remarks?

All right. Well, let's return now to see what questions we have for Dr. Killen and Dr. Burke or other issues that surround what we have been discussing the last hour or so.

Diane?

DR. SCOTT-JONES: I have a couple of questions for Dr. Killen.

First I would like to know what proportion of your research portfolio, the research you oversee, is conducted in developing countries?

And then the second one, I noted that when you listed the points that you thought were in favor of the studies of the perinatal transmission of HIV you said that the most important one was that the studies were designed to answer the public health questions of developing countries and I would like you to say a little bit more about that because I was wondering if the research is motivated mainly to answer questions of other countries why should NIH -- why should a U.S. federal agency invest so much in it given the needs of our own citizens for inexpensive health care?

I know you noted that the perinatal transmission has declined in the U.S. and it has gone up in other countries but there are still great needs here especially in particular segments of the U.S. population so I was hoping you could say a little bit more about that justification, the needs of other countries.

DR. KILLEN: Sure. I do not have the percent figures available. I could get that for you and provide it after the fact if you would like. I am sorry I do not have it. It is a relatively small percent.

DR. SCOTT-JONES: Okay.

DR. KILLEN: A very small percent I would say but I do not know what that would be.

DR. BURKE: I would say a very small percent.

DR. SCOTT-JONES: Okay.

DR. KILLEN: And then the second point, I think, is one of -- it gets back to the question of what are the global -- what is the global research agenda and what are the global priorities. I do not know. I think as the head of the Division of AIDS Research I could not conscionably stand back and say we have got it conquered or nearly conquered in this country so I do not care about the set of the world. It is just not -- you know, it does not work.

The epidemic -- approximately -- you know, in this country -- what is the number, Don? Less than a percent I think of the HIV cases are --

DR. BURKE: Worldwide?

DR. KILLEN: No. In the U.S. Less than one percent of -- or approximately one percent of the cases of AIDS/HIV are in children. On a global scale it is now approaching about ten percent because of the disparity of men and women. And that is a huge number. It is a huge burden and you saw the graph of it exploding through the roof with nothing being done and there is obviously the potential to cure so all of

that taken into consideration we feel like we have got a large obligation to do a lot.

Technically speaking, you know, the agenda of the NIH or the budget of the NIH is largely oriented towards the needs of the U.S. and that is kind of how the appropriation is delivered to us but we go well beyond that for a lot of obvious reasons.

DR. SHAPIRO: Thank you.

Any other questions?

DR. MIIKE: Just one.

DR. SHAPIRO: Larry?

DR. MIIKE: Listening to the discussion it strikes me as very -- if you substitute developing country with minority health problems in this country and the agenda setting by NIH and the criticism to come up, it sounds almost parallel. It is just an observation that I make. That is because there is an issue about which diseases to study, how much money to put in, what you count as good research, participation, all of those things seems to be exactly the same.

DR. KILLEN: Yes. There was an Institute of Medicine --

DR. MIIKE: I was on it.

DR. KILLEN: Yes, you were a part of that.

Some of the work that you were talking about, about what is the big agenda, has already been done by another Commission. Yes, there are many similarities for sure.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I have a question for Dr. Burke because we like very much to get the facts. Is it the case that the studies that you referred to in South Africa are -- the participants would be predominantly people of color and not White South Africans?

DR. BURKE: Yes. That has not -- we do not have volunteers yet. We are still in the product development phase and our approach is to make these -- part of what we refer to as product -- vaccine development partnerships up front. We do not have a specific population defined who will be the persons who will be in the trials. Our expectation is it will be essentially 100 percent Black South Africans.

DR. SHAPIRO: Any other questions?

Well, let me thank you both very much. We very much appreciated your participation this morning both before and now and we look forward to continuing conversations with you as this study continues to develop.

We will now take -- Eric, what is our agenda in the -- excuse me.

Trish?

DR. BACKLAR: I just would like to say that in response to the person who came -- am I allowed to say one thing, yes?

DR. SHAPIRO: Sure.

DR. BACKLAR: Okay. In response to the person who just spoke to us, your name was Mr. Lurie. I think that you made a very important suggestion and I hope that we consider it seriously and that is that we invite people from developing countries to come to speak to us and I, too, like Larry, was struck with the similarity of our looking at vulnerable populations in this country and the same characteristics attain for people in developing countries.

DR. SHAPIRO: Okay. Thank you.

We will reconvene here in one hour.

Thank you.

(Whereupon, a luncheon recess was taken from 12:00 p.m. until 1:17 p.m.)

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

DR. SHAPIRO: This afternoon we will be continuing our discussion of ethical issues in international research.

And I want to apologize both to the members of the public who are here and to our guest, Dr. Sommer, for getting started a little late.

We never seem to be able to keep our lunch hour down to an hour for one reason or another so I appreciate your patience in waiting.

First, I am going to make an announcement in a moment but I just wanted to apologize to Dr. Sommer for keeping him waiting. He was here on time. We were not.

I do want to announce to the Commission that -- for those of you that do not already know -- that the Executive Order extending the Commission has been signed and so we will proceed with somewhat more confidence in our plans for the future. It extends to October 3, 2001, if my arithmetic is right. So you will hear more about that as time goes on.

But Dr. Sommer, Dean, Johns Hopkins School of Hygiene and Public Health, of course has been working in areas of direct interest to us for a very long time. So we very much appreciate you being here and

we look forward to your remarks, Dr. Sommer.

ALFRED SOMMER, M.D., M.H.S., JOHNS HOPKINS SCHOOL OF HYGIENE AND PUBLIC HEALTH

"THE ETHICS OF HUMAN RESEARCH IN DEVELOPING COUNTRIES: BALANCING THE IDEAL, THE PRACTICAL AND THE NECESSARY"

DR. SOMMER: Thank you.

By way of clarification if I am not addressing the issues you really wanted me to address it is Ruth Macklin's fault.

(Laughter.)

She gave me a one-half hour preparatory about which things I had written in my letter that she felt were important and which things were not.

So let me begin by saying that my own perspective and career has been very much as a pragmatist, someone who is devoted to finding practical solutions to problems that impair health and survival often in poor countries so you know the background and the focus of my work has to do with that so, therefore, it leaves out a lot of other things that might otherwise be on your agenda.

I think it is important to recognize that human research in developing countries differs from that in the U.S. and other market economies in many ways.

Let me suggest one other thing. I have not been at your proceedings. I do not know quite how they function but I gather that most people around the table do not actually do research and certainly not research in Third World countries so if I have missed a boat or you are not quite certain what in the world it is that I am referring to I would feel comfortable if you wanted to stop and ask a question but it is up to the chair.

DR. SHAPIRO: The more accurate way to describe that is most people around the table have not done research in this particular area. You are quite right about that. And we will feel free to interrupt as --

DR. SOMMER: That was the point. Feel free to interrupt me.

So I think that to set the stage I think that doing human research in developing countries differs from that in the U.S. and other market economies in a number of ways.

First we are often dealing with diseases and conditions that have long disappeared from the U.S. and other market economies and sometimes what we need to know is why have they disappeared from our societies when they have not disappeared from others.

My approach on those issues has always been is there some simple potentially inexpensive but critical change that was responsible that one can tease out from what otherwise is the broad base of socioeconomic development that has gone along at the same time as these diseases have disappeared?

And one example I will give you is trachoma. Trachoma is caused by recurrent infection of the eye by an organism called chlamydia. There are many trachoma controlled programs in the past set up around the world and there is very little evidence that any of the former programs ever accomplished anything.

On the other hand, I have lived and worked in places like Haiti and Indonesia where trachoma disappeared spontaneously and it disappeared when there was even just a modicum of socioeconomic development so one begins to ask the question what is it that happened early on and so you do what we do what we call case controlled studies.

You go into communities in countries where trachoma is still a problem and you say why does this village or this group of children -- what is different about them, the ones that have trachoma from the children who do not, and what you might discover as we did, no great surprise, that one group washes their

face. Even if they only wash their face once a day and do not use soap, that washing their face once a day somehow clears up the discharge around the eyes and reduces the transmission of the agent from child to child. That is just an observational study.

But you cannot prove that, in fact, once a day face washing will, indeed, make a difference and before you launch that on the world even though you are not going to hurt anybody by telling them to do it -- in fact, most people who live in trachomatous areas spend a lot of time and energy getting water. If you go down to the Chiapas area of Mexico women are walking 5,000 feet down a mountain and then 20 miles to get a cistern full of water and then putting it on their back and walking it back up so you do not recommend things like casual face washing to somebody who has to lug water that far unless you can show it makes a difference.

And so we set up trials in a number of countries, Mexico, Tanzania, what have you, in which we did one thing. We had some villages wash their face and we did not do anything to the other villages and, indeed, it made a huge difference.

So now there is the global trachoma eradication initiative that is based on five

strategies. One of which -- it is called the SAFE Strategy. Each one of those stands for another intervention and the "F" stands for "face washing." So, you know, that is the way research goes forward and these are the kinds of things we think about.

So what it means basically because we are dealing with conditions that have often disappeared spontaneously from our own cultures is that we have to observe what is different between cases and controls within an environment in which these diseases still occur and then we often have to attempt clinical trials to demonstrate that what looks like makes a difference is really responsible for the difference and is not just something that is going along with other things that you have not recognized.

Another example, of course, which is even closer to my work, although I did work on the trachoma, is the vitamin A and child survival story, which I think I brought today handouts that describe that relatively succinctly. You can use that for bedtime reading or whatever. We observed quite accidently when we were doing something else a difference in the mortality rate of young children that was associated with their vitamin A status. This was not something we had expected to find.

We were doing this observational study for entirely different purposes but we found that children who had poor vitamin A status died at a higher rate than did children who had a better vitamin A status. The trouble is that children who have poor vitamin A status are different in many other ways as well. Some of them we measured their protein energy malnutrition, their risk of respiratory disease and diarrhea, and what have you, but the nature of all observational research is you never measure everything, and it is impossible in an observational study to say with any degree of certainty that a single factor, indeed, was responsible for this important outcome.

So we did set up a randomized trial in which some children were given vitamin A and some children were not even though we knew that giving all the children vitamin A was certainly not going to hurt them. On the other hand if we could demonstrate that it really made a profound difference this would be very important.

So the fact is it is not a problem in our culture. It was at one time. Up until the 1930's vitamin A deficiency was important in the United States. It was important in Great Britain. It is no longer.

The second thing -- the second parameter, I think, which differentiates research in the two areas is that the burden of proof that something is important and useful has to be greater in poorer countries than in wealthier countries. Now that may seem counter-intuitive at first and let me go through the reasonings for you.

In the U.S., more or less, and these are sort of formed thrusts if you will, in the U.S. all we need to do to launch a new intervention if it is a pharmaceutical -- if it is surgical we do not have to do anything. The surgeons, we can do anything damn thing we want to do and there is no FDA for surgical interventions. That may scare you and it should scare you but it is the truth.

But let's assume it is a device or a pharmaceutical. All we have to do is satisfy the FDA's requirement that this new pharmaceutical is safe and effective. That is the only thing we need demonstrate.

Then it is up to doctors and their patients to decide whether or not they are going to use this device and sometimes patients know more about it than their doctors do and sometimes it is the reverse and sometimes it gets used and sometimes it does not get

used. There is a lot of variation in what we do. But the only official position we take is we have to prove it is safe and effective and then it is up to everybody else as to whether or not they incorporate that into practice.

Poor countries operate totally differently. Poor countries have very limited health resources, and I will give you an example. When I first got involved with vitamin A deficiency, the reason I did, I did as an ophthalmologist. We did know that vitamin A deficiency was an important cause of childhood blindness in the developing world.

And after we demonstrated and documented just how large it was, the largest cause, I would go around and meet with Ministers of Health and say, "You have to do something about this problem because there are children going blind unnecessarily and it is a very inexpensive intervention."

The Ministers of Health invariably would say to me, "We feel terrible about the fact that a large number of children cannot see at night, a significant number of children are going blind but, you know, one-third of our children die before the age of five. We only have one or two dollars per capita to spend on health care. How can I divert that one or two dollars

from trying to prevent a third of the children from dying to something like preventing night blindness or blindness?" And that is a real issue for them.

Fortunately as it turned out or unfortunately, depending upon how you look at it, the vitamin A also had something to do with child mortality and then we were able to wrap the whole program and justify it on mortality and then they were very interested in doing it and by the way we prevent blindness at the same time.

So an intervention in a Third World country must not only seem to work and be effective and be safe, it must be almost guaranteed to work and to work in large segments of society. In addition, it has to be cheap and it has to be highly cost-effective.

So unlike the U.S. where the FDA approval provides a license for laissez faire adoption by changing patient and physician perceptions, poor people do not receive new interventions in that manner.

In developing countries there are very few doctors and poor patients rarely have access to those few doctors. So in poor countries you have to convince the government that it is worth their while to shift their limited resources to this particular

intervention because it invariably means shifting it out of some other part of the health sector so it is -- it becomes a societal issue, you know, if you will a public health issue, rather than a simple patient-physician issue as it is here.

Hence the results of trials in Third World countries almost always have to be unequivocal from the point of impact, from the point of relevance, and from the point of cost-effectiveness. And within that country's unique milieu of available infrastructure, available health resources and, of course, all those competing demands -- I mean, are they dealing with malaria as a horrendous problem and that is sapping all their resources or are they dealing with drug resistant tuberculosis or HIV or what have you?

I mean, they have major health issues we do not even begin to think about here and they have far less resources to deal with them. The government makes the decision about how those resources are going to be spent and so you have to have a compelling case for them moving resources to the particular issue you are involved with.

So one must not only convince yourself it works. I could be convinced that something works but, of course, I have to convince other scientists that it

works and I do not only have to convince other scientist locally, I have to also convince them globally because very few local scientists in developing countries feel sufficiently secure in their standing to make a decision and advise a government in contrast to "the great scientific community out there in the wealthier world." So it really means bringing a lot of people along.

I will tell you early on after we did the first control trial a well-respected -- and we found -- this first control trial where half the kids got vitamin A and half the kids did not get vitamin A, there was a 35 percent reduction in the mortality rate amongst the children who were to get vitamin A.

And they quoted a relatively well-known U.S. scientist in print in the scientific literature saying, "We would believe Sommer if only he claimed a more modest reduction, say on the order of 10 percent." What am I supposed to do? Throw away the real data and come up with data that would justify in this person's mind what the real results should be? I mean, this is real life. You are dealing with real people.

Scientists, as some of you read the recent article in the Times, got it right, I mean scientists

do not work together as a great collegial enterprise all the time. There is a lot of personalities that get in the way.

Once we have convinced the scientists, of course, we have to convince the policy makers of the relevance of the work as well. Now let me give you an example. For ethical reasons, that is because Indonesia decided that they were going to do a vitamin A program to prevent blindness -- it was the only country. They were going to do a nationwide vitamin A program to prevent blindness.

When we stumbled upon this mortality issue and wanted to do a randomized trial they, first of all, said, "Well, how can we do that becasue we are committed to giving everybody vitamin A?" Well, we were able to work out a scenario.

They knew they could not give it to everybody starting the same day. It was going to take them five years to cover one particular province where the disease was most severe so what we worked out was they allowed us working with our Indonesian counterparts to randomize the order in which villages were entered into the program. So we did not slow down the progress of the program but we were able to carry out a randomized trial simply by taking advantage of what

they were going to do anyway.

However, because they were committed, even though they could not get to this village for five years, they did not want to use a placebo so it was a trial. I had a no problem with that since usually the major problem with placebos is the placebo effect "I feel better when I otherwise would not because I think I got something."

But the endpoint of the study was death and it is very rarely that placebo effect makes a real big difference on death. It is a kind of hard endpoint if you will. So I had no great concerns with the validity of a study in which we were counting deaths and did not use a placebo as long as we randomized villages appropriately and, of course, did not lie about the results.

Well, it turned out most scientists around the world totally disregarded the first observational study which appeared as the lead article in the Lancet with a supportive editorial. It did not elicit a single letter to the editor. I mean here was a potential intervention that reduced childhood mortality by a third and there was not one letter to the editor. That meant there was nobody prepared to actually follow-up and do anything about it so then we

planned this first randomized trial which did not have a placebo. We published that. Also a lead in the Lancet. Also with a supportive letter. And then all the letters came but they were all negative and the biggest negative issue was we did not use a placebo.

So we were following what Indonesia thought was an ethical approach. "You do not need to use a placebo. It is rational not to do it. We feel more comfortable if you will not." I said, "Okay. I understand that. We can do this."

But it required then two more placebo controlled trials even though I am now convinced. Two more placebo controlled trials to convince the Indonesian government now who did not believe it because it did not have a placebo that this, in fact, was something they ought to act upon and it took five or six more trials to convince the rest of the world. So trying to go by one group's feeling of ethics in fact slowed down the whole process considerably.

The third way, of course, which is very difficult to deal with and probably the thing that is going to be most difficult for you is that populations in Third World countries are often illiterate, particularly where you do these studies because most of these diseases are most common out in the rural

poor areas.

Many people are illiterate and do not have the vaguest of any experience with the understanding of even routine medical practice, let alone with the scientific method. It is often even culturally inappropriate for people to make individual decisions independent of that of the rest of the community.

So traditional and exhaustive lists of potential side effects and complications -- if any of you came to me for cataract surgery and you actually read the list of potential side effects you would never have cataract surgery done because it includes loss of the eye, overwhelming infection, bleeding to death. It is hard to bleed to death from a small incision in the eye but it is potentially possible. So you put that in there and to a relatively unsophisticated and illiterate population it gets very difficult, indeed.

And the people who it will scare off the most are the 20 percent of the people who need the intervention the most and this is a general rule of thumb that most people even in medicine do not recognize. Any time you launch a public health initiative, even an entirely proven initiative or a medical initiative, about 15 to 20 percent of the

population will not comply and invariably they are at higher risk to begin with.

It is something about them that is poor health seeking behavior and it goes -- it includes noncompliance, unwillingness to participate. It is a very interesting phenomenon and if we have time and you are interested I could show you there is good empirical data to show that this group of people in any country -- I can name ten countries where you can make exactly the same observation, always end up doing worse off than the placebo recipients who were willing to take placebos. In theory, they should be exactly the same with the same endpoint. Placebo recipients get nothing. They get a placebo. But the people who are enrolled to either get a placebo or an active agent and do not comply always do worse off than those who are placebo recipients who do comply. It is a different group of people.

So what we do is we work intensively with traditional community leaders. We educate them about the issues. We answers questions usually in a very open and formal discussion that may stretch for days and multiple sessions. We try to obtain their approval. If we cannot we do not even start. And we only consider leadership approval valid if they truly

represent the community and they are not somebody who has been forced upon the community.

They then take on the responsibility of explaining it to the community in the presence of our own local field workers and colleagues. Even with "community acceptance" every individual participant, of course, has the right of refusal regardless of the leader's position and people often exercise that right. Almost invariably again these tend to be the most traditional and conservative families within the community and again they tend to be that group of people who have the worst health indices to begin with and who probably would have benefitted the most.

And even after you have done all that, things can be still be stopped. We had a very large trial that was about to get underway in the Philippines in Albay Province. Since my name is Al everyone jokingly called it "Al's bay." But, in fact, it is Albay Province.

And we had spent literally a year-and-a-half and probably $3 million preparing this, had all the leadership's approval, essentially all participants' approval, and again in a rigorous and compulsive way we were doing one more run through to be sure everything was working right, and then -- and there

was actually a guerilla insurgency in the area, and we were well respected.

People knew we were trying to help the people so both -- when the army came and wanted our maps because we have to map the villages we are working in so we know where the children live, we would not give the army our maps and we got the head of the army to approve that because then the guerrillas, of course, would have been after our field workers. The guerrillas wanted us to do something. We said, "We cannot do that."

One person, who was a physician, had come down from the mountains and got on the radio and essentially announced on the radio because you can buy radio time in the Philippines and said that we are, you know, American imperialism and were there to test high dose vitamin A capsules on Filipino children because we do not want to test them on American children, forget that American children do not need high dose vitamin A capsules, and that stopped the study like that.

There was no way we could overcome that. I flew there four times. I brought colleagues from India, from Indonesia, from Bangladesh, who had worked on similar studies. They knew what the reasons for

going forward with this were. The Ministry of Health -- the Ministry of Health, of course, was in a battle with the guerrillas. They said, "We are going forward with this study over your dead body." I said, "Not over my field workers' dead bodies you are not going ahead with the study." And we just pulled out and moved on and did the study in Nepal.

So it can be stopped very easily if there is local opposition.

And then, of course, you always have to be sure is the intervention safe. What do I use in a very pragmatic sense when I am trying to think about in my own mind outside of an IRB before I get to an IRB, is this something I am willing to undertake, is this something I feel comfortable doing.

Well, the first thing, which almost does not even go into the equation because it is the first thing, is this a safe thing to do? Am I putting anybody at risk by giving them vitamin A or asking them to wash their face and teaching them to do that? So that is sort of the first criteria almost without saying it.

The next and very important criterion to me because again I am interested in getting programs going that are effective in areas that have very

little health infrastructure and no programs. And so I ask myself am I depriving anyone of a potentially useful intervention that they might otherwise receive if I were not carrying out this study? In other words, I would be very uncomfortable going into -- I would not do it, in fact -- going into an area where there is an effective vitamin A distribution program and saying, "I want to see if vitamin A really works. Let's stop the program." I could not do that.

Now I have to tell you that there are ways to get around that and people have done that and done that effectively. Earlier in my life I worked at the Cholera Research Laboratory, which was then in East Pakistan and now in Bangladesh, and now has the unpronounceable name of ISDDRB but it will ever remain in my brain as the Cholera Research Laboratory. And the philosophy there was can we make an effective cholera vaccine?

We knew that the existing cholera vaccine was absolutely useless but the government had an official policy of vaccinating everybody with cholera vaccine and so while I was not involved in setting this up, I was sort of the young kid on the block and just walked into it, what they had done is set up an extensive and elaborate system of local people who went around

basically and saw everybody every day and if anybody had diarrhea a speed boat showed up within an hour and took that person to a specially built hospital to treat them for diarrhea. And if they had cholera, cholera. Those people never got cholera vaccine and that was a site in which we studied the epidemiology of how did it transmit it itself and also the site at which we tested alternative candidates for cholera vaccine.

Now you could say, "But you deprived people of a cholera vaccine." That is true. On the other hand, as it turned out the cholera vaccine was, indeed, useless and nobody died of cholera in this area because the health infrastructure that was put in place was so much better than anything that otherwise exists. And, of course, that has never been replicated anywhere outside that study area. It would be far too expensive for the country to do that. So we still keep seeking an effective cholera vaccine since that is the only thing that is really going to help the population at large.

I will tell you in the U.S. we have very similar problems. Perhaps some of you have read the paper about the continuing controversy over the number of caesarean sections done in the United States. In

1970 five percent, one in 20 of all deliveries in the United States were by caesarean section. Fifteen years later by 1985, one in four, 25 percent. We had a quintupling of the number of caesarean sections.

Now if any of you think that the physiognomy of women changed dramatically in 15 years I would argue with you about that. What changed -- one of the major things of change was the introduction of an unproven technology, fetal monitoring. You cannot have a baby delivered in this country now without fetal monitoring.

Now it turns out that some very smart and diligent people have actually carried out now subsequent to its introduction and dissemination throughout our health infrastructure randomized trials on the value of fetal monitoring. There have been 11 randomized trials. Not one of them has demonstrated any benefit from fetal monitoring and we cannot turn the machine off. It is too much a part of our culture right now.

So we have the same sort of problems here. So that is my first real pass. I am not hurting anybody. I am not taking anything away that is useful from anybody. So I am at least neutral to what the situation was before I got there.

The next question I ask myself, which is sort of icing on the cake in a way, will I help anybody. I mean, if I am not going to hurt anybody, will I at least be helping someone.

Well, as it turns out, of course, if I am right in my assessment I will immediately help that half of the children who are going to be the vitamin A recipient arm of the trial. If it turns out that I am right and it proves effective I am going to help the other half of the trial because those children are now for ethical reasons going to receive the same intervention that the control children did. So that is my next test.

My last test, which is the super icing on the cake but it almost is -- I do not do it unless this is reasonable and likely -- is if this trial turns out positive, is there a reasonable likelihood that this will change government policy because if there is that is the only real reason for doing the trial. If there is then all the children in Indonesia or the Philippines or Nepal are going to get vitamin A. So I have gone into a situation where nobody gets anything and hopefully leave the situation now with all children or as many children as the government can afford to reach, reaching everybody.

I can tell you an interesting reverse example where people, I think, got unnecessarily hung up on ethical considerations as they understood them. There was a major U.S. university that decided they wanted to get into this vitamin A clinical trials business, as it turned out, in Bangladesh, but they were so contorted about their concerns.

One group would get vitamin A that might be effective and the other group would get a placebo, that they wanted to give the placebo recipients the equivalent of what benefits might accrue from vitamin A if vitamin A worked so they were going to give the placebo recipients vaccines, clean water, ORS, you know, pediatric follow-up examinations, what have you.

Even the Bengalis realized that is absurd because any time you do a trial the first ethical requirement is that it is going to work. If -- at least the study design is appropriate. If you are already giving the control arm so much that you know this no longer represents the status quo, how will you ever prove that, in fact, vitamin A did, indeed, work and the Bengalis refused to go along with that study design and that study was never done.

So then the icing on the cake and the whole thing is will I affect the larger population? Now

that does raise another issue and one that I face repeatedly and certainly within the vitamin A world, and that is we have no formal stopping rules or in the jargon that I made up in the letter that I sent you is when is enough, enough. I mean, how many clinical trials do you have to do before you are starting to feel really uncomfortable doing any more even if the whole world has not started to buy the story?

In Indonesia it took two or three clinical trials of different design and nature for them to decide that this is real and we are going to do it. For the rest of the world, as I say, it took six clinical trials to get going. I have already told you the original observational study was ignored. The first interventional study people objected to and that becomes a real problem.

It also involves real believes, sometimes valid, involving racial differences, although I am convinced that most of these are often more racist than they are racial. India will not accept a study that was done in Indonesia. I will tell you that right now. It does not matter how it was designed, how eloquently it is conducted. They will not accept a study that was done in Indonesia and they certainly will not accept one done in Bangladesh and Nepal

because they consider themselves culturally superior and if it has not been done in India then it has not been done.

Africa will not accept the results from Asia and, indeed, for a while Kenya was refusing to accept the results from Ghana. That is when I called it quits. I said, "I am sorry. You know, we have done six in Asia. We have done one in Africa. I am not doing any more of these trials. You guys are going to have to work out whether or not you think it is relevant and applicable to your population."

And then there are always personalities and do not underestimate the role of personalities. There is an individual, a very, very senior, no longer scientist but one time scientist in India, who has had a vendetta against the use of vitamin A from the first observational study. I cannot tell you why since he was, if you will, the father of the original vitamin A work in India but he has enormous influence over Indian scientists and policy makers.

And while India does have a vitamin A distribution program, they try to keep it as quietly as possible and they will not talk about it at major meetings because they do not want this person to know that they really do believe it works and they are

really trying to do something but the roof may fall in on them if it should ever get out.

These things are real. I remember when I worked at the Cholera Lab I was not involved with this particular activity but that is where the use of oral rehydration solution in order to combat high mortality from diarrhea, particularly in children, was proven for the first time and our guru and godfather was a wonderful epidemiologist, a legend in his own time, not only in his own mind, Alex Langmere.

And Alex chaired the advisory committee and every time he came out, we said, "Gosh, isn't this exciting? We just did this trial in this children and we have just published this study in the Lancet that oral rehydration therapy reduces diarrhea mortality rates in children." He said, "Well, that is okay. Six months from now I want to see one on oral rehydration therapy reduces mortality in Nepalese children and then six months later I want to see one on oral rehydration therapy reduces mortality in Indian adults."

And he was right. You know, the basic philosophy he had was one study does not change policy, at least rarely changes policy. You have got to do it over and over and over again to convince

people and that, of course, raises ethical concerns about if you think it works, how do you go off and do these other things over again.

Acceptance by the wider community is, indeed, a fickle thing. And their levels of data and convincing that they need varies all the time. So I have communicated it took six randomized trials and the first observational study to convince people that giving vitamin A to young children would significantly reduce their mortality.

We did one trial, a very small hospital-based study at a mission hospital in Tanzania because we thought maybe if we looked at the very high measles related deaths in Africa, and measles was a real major problem in Africa with very high mortality rates, 12, 15, 20 percent, and so we said, "Gee, this looks a lot like vitamin A deficiency. We will give half the kids vitamin A and we will not give half the kids vitamin A and we will see what happens." And we reduced measles mortality by 50 percent. That was one small study. It had 100 children in each arm.

Before I could even turn around that had become an official WHO UNICEF recommendation that every child with measles get two large doses of vitamin A. Nobody asked me. If they had asked me I

would have said, "I did this study. I think that study was right but I would sure -- you know, but it could be due to chance. I would sure like to repeat that at least one more time in a different setting in a difficult culture."

I talked about again six studies to convince people that giving vitamin A to children really made a difference. A year ago we finished a study in Nepal in which we gave smaller doses on a weekly basis to women of childbearing age. The maternal mortality rate or the mortality rate amongst women related to pregnancy and delivery declined 50 percent. It is only one study.

It immediately went around the world and countries started planning programs and I am the one who is saying, "Wait a minute, team. I mean, I am really excited about this. I think Nepal needs to have a program. There is no question given their nutritional status, given their density of population, given the infectious diseases, given their iron status and anemia and what have you, it works there. But I do not know that this is going to work in Africa or even another Asian country. Don't you think we ought to repeat this once?"

Well, everyone agreed. "Yes, I guess if you

want to bother to do it and can find the money to do it. We are going out and doing programs."

I only point that out because they are wrong and I am right but trying to keep some form of consistent standard is not the way decisions are made. Decisions are actually made by emotions, personality, how people are feeling. Now in truth the maternal mortality and the measles mortality was preconditioned by now having shown a lot of people are giving vitamin A to kids would stop mortality over the next six months. So people were preconditioned to accept something they would not have accepted earlier but was it an adequate level of evidence?

To my way of thinking it was not adequate to make global policy on it because remember global policy of this nature is not recommending that your doctor advise you to stop smoking. Global policy here is telling poor countries to take limited resources and invest them here as opposed to investing them there.

So what would I suggest in some generic sense for establishing stopping rules? I do not think it is easy but one might consider some sort of international body, not WHO or at least not WHO alone, some international body combined with academic

representation that might periodically review all the available evidence that relate to a specific issue and then offer their "expert opinions" and function very much like we have consensus panels. Now does it work? Doesn't it work?

We did this in a very informal way. In 1992 I was convinced we had all the data we needed and I was tired of doing these particular trials and embarrassed to be doing any more. I was not going to do any more. And so I convened a group of people who had done trials, had not done trials, policy makers, scientists at the Rockefeller Study Center in Pelagio (?) and we took a whole week and we went through all the data and people expressed their opinions and then we came up with a consensus and we wrote it up and then we all went out and wrote it up for our favorite journals and it appeared in five or six journals, and we created the policy. That stopped the debate.

Now that is not an infallible process and I will not take the time and go into the various issues but I will give you one example. One of the things that helped is we had an outside person absolutely unrelated to any of this work and very highly respected, George Beaton of Canada, to go ahead and do a meta-analysis of all the trials that have been done.

Now the problems with meta-analysis -- meta-analysis is where you take every study and lump them all together and you say, "Well, all right. If we look at all the available evidence where does it come out?"

There is a problem here. The problem is some studies are well done and some studies are poorly done and you almost cannot tell the difference by reading the article because by the time the author is done writing it up and the editors are done cleaning it up every study sounds like it was done in the highest standards.

We knew two of the studies were absolutely horrendously done because we were out there trying to advise them and saw what was going on in the field but this was an independent exercise. We did not get involved in it. He included that.

All the studies but these two found interventions that reduced mortality between roughly 35 and 50 percent. These two had no reductions in mortality which was not surprising since they kept on confusing which kids got placebos and which got vitamin A so on average everybody got a little of everything and we predicted there would be no

difference.

George Beaton having published that now says, "If I had only known I would not have included those two studies." But it is too late. It is out the door. We did not want to influence it. We wanted it to be absolutely clean. And so now everybody repeats as a mantra that if you do a vitamin A intervention trial you can expect a 20 percent reduction. Well, it is a 20 percent reduction only because there were two crummy studies that did not have any impact for obvious reasons.

Ultimately one is balancing the potential value of the outcomes to the local populous and all those things that go around the costs and so forth in having to come up with what is an ethically acceptable design.

Let me finish by putting down, as Ruth suggested I do, some criteria that I would suggest are immutable. It does not matter where you are, where you are doing the study. These are immutable in my humble opinions. No one is ever forced to participate against their will. I mean, we do not have to go back further than Nuremburg to know that.

An original observational study and then in this first clinical trial we did whole villages,

usually the most conservative and the most politicized, and unfortunately those with the worst health indices had the highest rates of refusal at the individual level. Well, that was their right and they refused and they did not participate. So that is number one. Nobody is ever forced to participate.

The second one I think that is important is that subjects should never be deprived of an intervention that is already available just to study whether or not it is effective unless you have really good evidence that it may be harmful or its ineffective but basically if you have what you believe is an effective intervention you cannot stop it to see if taking it away makes matters worse. That I would consider a problem.

A trial should not be undertaken, at least I would not undertake one, if the results, if positive, would not be a viable candidate for intervention in that society. So if what you are studying is too expensive to be done there, if it is culturally inappropriate or for any reason if it cannot inform and does not have a reasonable chance of altering the health policy of that country it is probably inappropriate to do that there.

Now you cannot get guarantees ahead of time

that they will implement it because again, you know, public health, public policy, it comes from the body politic, lots of things are made -- decisions are made in the political arena but nonetheless it should be something that is a viable candidate within that particular culture. And, of course, unless subjects truly provide truly informed consent the intervention must have a very high likelihood of at least being safe.

Now I have my small short list of mutable issues. Mutable issues would include degree and level of individual informed consent. Often potential participants are unaccustomed and culturally disinclined to make individual decisions at least in the way that we usually consider it, let alone sign their name to something, which is often left to communal leadership.

It does not in my experience stop individuals from saying I am not doing this even though we all agreed I would do it, I have changed my mind, that is fair enough. But to expect the same level of individual informed consent in my experience is really unrealistic in most Third World settings.

In most instances it is as unethical to provide controls with the best known interventions as

it is to provide the treatment arm with the best known interventions for the same reason. That is if it cannot be there after you are gone you have set up a very unhappy situation. These are not viable, sustainable options in this environment than a transient introduction and their inevitable withdraw causes not only ethical concerns but it causes huge political and economic concerns.

And then Ruth also asked whether I had any feelings about ethical obligations of sponsors. Should they be ethically responsible for paying for solutions if it proves to be effective? That is a very difficult again sort of balancing act I think that one has to think out in each situation.

If I had to encapsulate it I would do it as this: It depends upon who the sponsor is and why they are sponsoring the study. If the sponsor is a not-for-profit organization, whether it is USAID or the Ford Foundation or the Rockefeller Foundation, and if the purpose is to find or demonstrate a cost effective intervention to meet a pressing local health need in that country then the answer is no, you cannot expect them to then sponsor and pay for the intervention after it has been proven. They cannot afford it.

The fact that they paid to conduct the study

on behalf of the local population is their contribution. Besides, sustainable programs always require government commitment, government resources, and at least local resources and local ownership.

Even in the private sector institutions we have seen examples where people have accepted responsibility for this when they have not had to. Of course, the classic example is Merck's provision of irermectin for anyone whoever needs it for as long as hey need it to fight river blindness. This is a major commitment.

Now to be very honest with you, they did not make that commitment under any ethical reasons. They made that commitment because one of their scientists, an old friend of mine who has now passed away, Mohammed Asis, had the bright idea that this drug, which was available for the agricultural industry, might, in fact, prove effective and the magic bullet for river blindness.

To their credit Merck allowed him to go ahead and set up some trials which we participated in. We carried out the earliest trials. And then when it became apparent and they got all these headlines all around the world that they had this drug that could prevent this absolutely horrible scourge amongst

people who could not afford to buy anything they were left in a pretty ticklish situation but what actually -- at least according to Roy Vagellos (?), who is a friend and was then the CEO and chair of Merck, for him the decision rested on the fact that the ethics of the country (sic) are that anything produced by Merck Labs that will help humanity will get to humanity. And the idea that they would not make it available would be so de-stabilizing to the culture of Merck Labs that he felt he had no choice.

I thought he had no choice because everybody knew they had this drug and that they were going to be morally bound but that -- and the good business sense was not it.

I am watching another country -- another company which I am trying to help through the process -- address that now quite tentatively and that is Pfizer.

Pfizer makes a drug called zithromycin or zithromax as its name in the drug stores. This is a phenomenally effective antibiotic. It is a phenomenally expensive antibiotic and they make a lot of money on this antibiotic because it is the primary drug of choice for the treatment of sexually transmitted diseases and upper respiratory infections.

It also turns out that maybe one of the secrets to that SAFE five part strategy is through the elimination of trachoma but nobody in the trachomatous area could ever afford to buy zithromax, when it is one pill they only have to take once or twice a year. And so they have with a lot of concern and a lot of safeguards because they are worried about slippage into their profit making market agreed to make the drug available in five countries and see how it goes as it were. And if they can do that without losing market from the areas where they do make a profit from it then they will continue the program.

The study is still on behalf of local people. One would hope that as these companies have done other companies -- as some others have done -- will make effective drugs available at an affordable price but it cannot be a requirement since they are not doing it there on behalf of wealthy countries.

In contrast, and I know this is another thing you will be struggling with -- I do not struggle with it because I do not do this. In contrast, if a trial is being carried out in a poor country to prove something that is someone is going to make a lot of money on in a wealthy country but they are doing it in

a poor country because it is easier and cheaper to do there then I think that has -- raises very, very serious ethical concerns.

The last point, and that deals with who do you talk to, what do you do for IRB's locally. I have been in this business a long time so there are a lot of countries where I have worked and set up studies that have never had an IRB before we got there. We take it as an ethical responsibility to work with them in developing an IRB so we have started national IRB's, sometimes located in joint ministries, sometimes -- well, they are almost always located in joint ministries but then with academic representation totally local.

We try to bring in people totally unrelated to our study who are involved in the IRB process to advise them and help these things get going and many of our studies -- perhaps the most important thing they have done in the end is not left them with a new health intervention but left them with a functioning IRB process which they understand and they can use in the future.

I am sorry I went over my time.

DR. SHAPIRO: Thank you very much. It has been very interesting. I am sure there will be other

questions too but I have a particular question.

The examples you used seemed to be cases where at least you felt there was very little, if any, risk to the participants. Is that a fair characterization?

DR. SOMMER: Yes, that is a fair statement.

DR. SHAPIRO: And you -- that is something, which if I understood what you said, that you insist on for the trials that you are involved in.

DR. SOMMER: Those are -- as it turns out, those are the only times that I have been involved in them but there are certainly other circumstances where other people do other such trials and I am sure there are valid reasons for doing them but that is why I started by saying that to give you the fact that the answers I am giving you are predicated only on the areas where I have had experience and my experience have been in those things where I have felt completely safe.

You are saying have I purposefully avoided things that --

DR. SHAPIRO: I am not saying. I am asking.

DR. SOMMER: It is a good question. I mean, I must say I have never thought about it before. I guess maybe I have.

DR. SHAPIRO: Okay. Other questions?

Alex and then Diane.

MR. CAPRON: A couple of questions to you. I like to think of the kinds of things you said, which are very helpful and the illustrations will be very useful to us, as though you were writing our recommendations. In other words, I would like to know which of Dean Sommer's recommendations could just be turned into NBAC ones.

And one of the things that you said is do not remove anything that works. I was trying to put that in the context of -- that you were speaking from where health ministries find themselves hard pressed to pay for any number of things, even something that you come in saying will work.

And I wonder how you think you would describe the process of reaching a trade off. Suppose there is something which may work but maybe not as well as the new thing that you are thinking about but is -- is really quite expensive. And the ministry would be happy not to be doing it if the work that you had done say in another country, and you are trying to satisfy the sense that you were describing of Nepal does not want to go on Indonesian data, Kenya does not want to go on maybe even Ghanian data or whatever, is there

any way of deciding the trade off between something that works and something that works sufficiently well for the price that you are paying?

There is a difference there.

DR. SOMMER: No, that is a very good -- that is an excellent and a difficult issue. What would make it easy -- I will tell you how I would work it out, you know, sort of in a simplistic manner. Usually if something is already being done then the government or the society has made a decision they can afford it. I have never been in a position where they have said -- have I? Maybe I have. I have to think about it.

A position where they have said, "We are doing this. We know this is terrific but, boy, it really is costly. We would like to know whether this new thing would be almost as good and so what we are willing to do is stop doing what we are doing that we know is very good and see whether we can do half as well but at one-tenth the price."

Those situations may come up. I suspect they do not come up too often. I suspect what really -- the way it usually happens is, gee, we would like to do what really is the best for our people but we know we cannot afford to do that.

MR. CAPRON: I understand that.

DR. SOMMER: So what can we do for less money?

MR. CAPRON: I understand but that is, in effect, the easier case. The reason I ask is at the very beginning of this process we had what I thought was a fascinating presentation by a fellow from the FDA about controlled trials.

DR. LO: Bob Temple.

MR. CAPRON: Yes. Bob Temple. Yes.

And I came away with the sense that the argument in favor of placebo trials is very strong but it has to be understood that what is really at issue is cost versus ethics. That is to say if you had an intervention of the type that I am thinking of that is very expensive, the country has strained its resources, does provide it, and you come in and say, well, I have another thing which I believe will work as well. It might not work quite as well but it costs a hundredth what you spend. It is a simple vitamin instead of something that requires medical care.

The tradeoff would be doing an active control versus a placebo control and you would -- and from what I got from that you just need a much bigger N. In other words, the study would cost a lot more, take

more time, because the complications that the active control adds in terms of the science of controlled trials.

Now maybe I -- that is the message I came away with and that seems to me a dollar versus --

DR. SOMMER: I do not see it that way.

MR. CAPRON: You do not see it that way.

DR. SOMMER: I know that. I have seen that argument but that is not from -- let's forget the question of cost for a minute and talk just about -- because that -- I mean you are using that as a way to think about this but let's talk about the issues of placebo versus nonplacebo trials.

I described to you an example where there was nothing being done and we did not use a placebo, which should in theory have been equivalent to nothing being done and we gave the other group therapy. So there is the clearest, you know, there is no problem of difference in -- it was not believed. It was not believed because, you know, well, maybe the people who are going around in the field noticed that there were fewer deaths in this group and they can guess, you know, they are not getting anything and they are not reporting the data exactly the way -- you know, sort of human emotions is coming in.

To me -- while I have heard the argument and I am sure there is some validity to the business of cost and there certainly is a validity to the issue of sample size when you are looking to reduce something that has already reduced an event by 50 percent and you want to reduce another 50 percent, you need huge sample sizes to do that because now you are looking for a 25 percent effect. That is not to me the major issue. To me the major issue is what do you compare it with.

Let's say for argument's sake we are giving everybody -- everybody gets prenatal care. There is an obstetrician in every village. And the maternal mortality rate is ten. Let's say ten. And I say, you know, you really cannot afford an obstetrician. I mean, they come to me and they say we cannot afford an obstetrician in every village. We saw this vitamin A thing in Nepal. Gee, if it could reduce maternal mortality to only 20 we would accept 20 because there is no way we can do this 10 thing.

The problem is -- so you say, all right, we are going to do it. We are going to do it -- run the -- half the village is going to have an obstetrician and half the village is just going to get vitamin A. Well, let's say the vitamin A comes in at 23. Do I

know that is better than nothing? I do not know what nothing is anymore. Everything else has changed in the interim unless they just started the obstetricians yesterday. So many other parameters change.

The reason for the placebo or the reason for the control in the first place is to change one parameter. That is why our observational study as strong as it was, the kids and it was actually a nice dose response effect, the more vitamin A deficient you were the higher your mortality was, is not sufficient to say if I give vitamin A I am going to reduce mortality because maybe those kids have something else that the same reason they are vitamin A deficient, they also have these other things. Well, we do not because -- so you have to change one parameter. That is why you do a clinical trial. If you do not have a placebo to compare with that you do not know whether you have changed it better than baseline.

Now there are certainly situations -- you know, that -- so you have set it up exactly -- the situation where you would want to test it. You could be in a position where you say we know this is very effective but we think this cheaper thing is equally effective.

Well, one could under certain safeguards and

rules come up with a scenario in which that would be an appropriate way to do it but when you have something that has been going on for a while and you know is super effective you really do not know any longer what noneffect really means. So that vitamin A intervention could be reducing mortality by more than 50 percent but I will not know that because I do not know what the baseline maternal mortality is any longer.

MR. CAPRON: And you cannot test it. I mean, it would be unethical at that point to remove the obstetrician.

DR. SOMMER: Well, unless --

MR. CAPRON: If you are on placebo where you are comparing --

DR. SOMMER: -- the government says -- unless the government says we are out of here. You know, we will give you one chance but we are out of here, we cannot afford to do this. We have got to do something about AIDS or we have got to do something about drug resistant TB or we have got to put in a safe water supply. We are out of here so if you want to do one trial we will let you do it.

But if they are out of there I might as well do the trial as a placebo controlled trial and then I

know exactly how much impact I have.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: Thank you for your very interesting presentation. I was really interested in your list of immutable criteria and then I think you only gave us one thing that was mutable and that was the degree and level of informed consent.

I was wondering if you have any --

DR. SOMMER: I was flying back from Beijing at the time.

MR. CAPRON: But he gave us another one. He said, "Do not use 'best' if it is not available outside the trial."

DR. SCOTT-JONES: Okay. That is my flaw in note taking then.

DR. SOMMER: Okay.

DR. SCOTT-JONES: But I was really interested in this issue of informed consent and I was wondering if you had any suggestions about what might be done to help the process of informed consent and I was also wondering whether you have thought about the issue of parental consent given that you have done studies with children.

DR. SOMMER: Yes. Well, parental consent is obviously important. It is very hard to talk to an

infant and ask them whether or not they are willing to participate in a trial.

I think, and again I can only go by my personal, very practical experience, no theorizing here, this is what works in the field and what seems to make sense to me, the first level is we work hard at making sure we have a well-informed local IRB process. And it is not just for them to pass judgment on it but also you get them actively involved in the design and thinking through what is trying to be accomplished and what have you because remember you also want a reasonable feeling from the ministry, maybe of commerce and maybe of health and maybe of some other that if this works this may be something that they -- is reasonable within their context.

So that you have informed knowledgeable, local people to deal with in trying to think through what is appropriate within this culture and then you let them -- you encourage them to go down, spend time in the field, talk to the -- you know, get to know -- because often the people sitting in Delhi or Katmandu or Djakarta are having a -- they have less of a clue of what it is like out there in the rural area than you do because they never go out there even though they will tell you their ancestral village is sort of

in the middle but they have not been there in five generations.

You bring them out there. You have them meet with the local people and you let them guide you because ultimately they have to make the decision what makes sense within this particular culture, this level of literacy, this level of traditional belief, this level of religious conservatism and what have you, and if a guerilla does not come out of the mountains and go on the radio and tell everybody that you are an imperialist then you are lucky and you are doing what is most appropriate.

We were doing what was considered by everyone -- in the Philippines it is easy. It is a highly educated society. It is highly literate. We did get informed consent from everyone but the little kiddies but there was just one person who basically could stop the study cold by getting on the radio.

So I would use my local counterparts. So my job is to make sure I have thoughtful, well-informed, knowledgeable about the process local counterparts in a functioning body and then use them.

Sometimes politics gets involved there, too, and you find you have created a monster that you then have to just work with because it is their culture and

their monster and they have to work it out but you get personalities again and competing ministries and ethical belief systems but that is the nature of doing work in other cultures.

DR. SHAPIRO: Bette, and then Ruth.

DR. KRAMER: I would like you to talk a little bit more about the local IRB's that you set up and I am a little bit confused when you are talking about working say in India, is that IRB going to be in Delhi or is it going to be actually out in the communities where you are working? And then talk about, if you would -- when you talk about local membership, a representative membership from the local community, what does that look like? Does it -- are there representatives from the actual population that you will be testing or do you have to work with just those people who have a high level of understanding?

DR. SOMMER: Now that is a very good question.

India is a different kettle of fish. India has a highly sophisticated -- unfortunately, a highly politicized medical establishment, the Indian Council for Medical Research, and everything that goes on at a national level, although we have gotten away with doing things at a state level because they really are

so politicized, goes through the Indian Council for Medical Research and you do not even begin to start to tell them what to do. You are lucky if you get to say two words about the study design.

On the other hand, when we work at the local level in India we are able to avoid the Indian Council for Medical Research. Not because they are not smart people but just because it is such a highly politicized process. We work with the local government and local university, you know, and the local leadership to set up the IRB.

We do not always have -- as far as I can recall and I would have to check. I do not think we always have somebody actually from the local populous sitting on the IRB.

But in a way what happens is the study does not go if the local leadership does not agree to it and so the first thing that happens is the people working on the local IRB, and we working along side them, go out to the communities and, you know, this may be 450 villages and we gather together for several days and we pay the per diem for them to come. Nothing -- you know, just to a local place and work with the village leaders explaining the purpose, what is supposed to be done, and they will say, "This is no

good. We cannot do it that way. What about this? What about that?" And that will inform and change the process.

So rather than having an individual sit on the IRB, rather it is a dialogue that the nationals have -- Usually almost always involving a local institution that, you know, within the state or the province -- have with the leadership of the communities and then that process gets repeated within each village with somebody going along with the leader as he is or she is explaining it to the people in the village and responding to them. And often that changes the design and the process in which it goes forward so it is not the IRB approved it and here we go.

It is the IRB is one -- you know, it is the first step. Their review is a first step and then they review it with local people because you have to get local buy in.

DR. KRAMER: Just a follow-up question. Would that be different in Africa or it is the same process?

DR. SOMMER: Well, we do it the same way. It is sort of a standard routine we go through in every place.

DR. SHAPIRO: Ruth?

DR. MACKLIN: Yes, I would like to follow-up on Diane's question from your response with the informed consent. There is no question that one has to know something about the local customs, the religion, the literacy, all of those background information in trying to design an appropriate informed consent.

But in a place where research has not been done before or where it has rarely been done or where this is now a population or a group that has not been participants in research, asking -- one answer you are likely to get or I am -- this is a question but I am --

DR. SOMMER: You are assuming.

DR. MACKLIN: -- assuming that you are likely to get are answers about what is appropriate based on what takes place in the practice of medicine. Not what takes place in research but what takes place in the practice of medicine.

So responses like patients trust their doctors, doctors do not give too much information, they usually decide for the patient, they do not tell, you know, if they use placebos people would never accept a research study, they do not acknowledge

uncertainty, all of those kinds of things which maybe the local situation in the practice of medicine would misunderstand and misrepresent the research context.

So how would you respond, that is that what you would end up doing is lowering a standard of informed consent or of disclosure and informed consent in the research context by using as the model the answers that you get to these questions, the model of what is done in the practice of medicine.

DR. SOMMER: Well, that is real easy actually because in most of these cultures nobody has a doctor. There is no doctor-patient relationship. I mean the best they ever get to is stand in a long line in a clinic to see a nurse's aide who then gives them a pill. I mean, the whole context of your question is out of context of the places where we usually do these studies.

And even when you are doing it in urban areas where, in theory, there are some doctors, again the issues we are talking about are almost always societal public health issues which means a public health government response. Your study subjects are almost always people who have almost no access to traditional health care.

Now often in the course of our work we will

provide access to health just because we feel we have to do that even though it may go away when we go away so in the vitamin A trials in Nepal we have set up an eye clinic. I mean, how can we not -- they know we are ophthalmologists, some of us. How can we not treat eye disease when we are there?

I will give you an example -- you know, I mean, this is -- you are dealing with certainly very difficult issues. But let me tell you some of the contortions we go through to meet our own ethical standards. One example I think is worth a thousand words and I do not know how you will take this but let me give you one example.

There are two things we want to learn about vitamin A in childhood and that was, one, mortality, that is sort of the end result, and the other was morbidity. How much impact did it have on the frequency with which you get diarrhea or the frequency with which you get -- you know, on one hand we know, yes, you are more likely to die of diarrhea and you are more likely to die immediately. But how much more likely are you to get these and how much more severe are they likely to be and so forth?

Now the problem, of course, is in doing a morbidity study you have to examine the children

fairly frequently because, you know, they may get one diarrheal episode a week or two weeks so you have to see them every couple of days.

Well, if you nested the morbidity study within the mortality study you would be treating all the kids who got sick. If you treat all the kids who get sick nobody dies. If nobody dies you cannot tell whether vitamin A reduced mortality or not. So you play this game of I will do the morbidity study over here and I will watch those kids every other day. I do the mortality study over here. We have untrained people go out and give them vitamin A and they do not come back for a year because I do not want to know what goes on.

Now at the baseline when we give them the vitamin A if the kid obviously is vitamin A deficient we give them vitamin A and we drop them from the study because if we know a child is vitamin A deficient it would be unethical not to treat them. But what we do not see we do not know and so we deliberately set up this straw man, if you will, of we cannot look becasue if we look it becomes unethical to do the study.

That is the reality of the things we are doing and if we do not do the study then, of course, nobody gets any vitamin A anywhere.

DR. SHAPIRO: Bernie, then Alex, and let's keep the questions and answers short. We have to break very shortly.

DR. LO: I want to thank you for a very interesting presentation and discussion.

I wanted to sort of ask you a question that really pertained to the presentations that some of your colleagues are going to make later today who have actually tried to do field work looking at what are some of the issues that come up particularly with regard to informed consent.

One of the things that their preliminary work has shown is that in many of these countries basic conceptions of disease and pathophysiology are very different. So when people do not believe in a germ theory of a disease, who believe that you lose vitality if people take your blood, how do you explain -- are you able to explain basic things like venipuncture and antibiotics in a way that makes sense so that they can give something close to informed consent on an individual level?

DR. SOMMER: That is a very good question. I will take the chairman's point to heart and I will not tell you an interesting story about cultural beliefs of a highly intelligent, highly sophisticated

Swiss trained daughter of the Indonesian ambassador to Australia who was convinced that her epilepsy was because the local duquin (?) -- the local traditional doctor who her father insisted she go back to the village -- four generations -- I am going to tell you the story -- four generations earlier, just looking at her said the real problem was she did not take -- I had given her drugs.

She did not take the drugs. And she went back and a duquin said the real problem was that her father, who is a prominent politician, had this enemy and this enemy had sicced a spirit on him but they were -- they had the same birth day and the spirit got confused and was tackling -- attacking her. And it took about six months and lots of grand mal seizures before I could get her to go on appropriate treatment.

So we do not usually get into that. We -- because then you are fighting a belief system. We do not want to fight a belief system. We simply say we have this pill. We believe it is safe. We think it may reduce the recurrence of the following thing. We would like you to take it.

DR. LO: You do not even get into the --

DR. SOMMER: We do not even get into it because it is beyond a belief and cultural system.

Are you going to start arguing with somebody whether they are getting sick because of spirits or are they getting sick because of germs?

DR. SHAPIRO: Alex?

MR. CAPRON: I was going to say I assume you are telling me your pill works against spirits?

DR. SOMMER: I do not do that. That would be unethical.

(Laughter.)

MR. CAPRON: I wanted to follow-up on your second mutable principle about not using the best if it is not available outside the trial. And I took that to be -- and that is very much at the heart of what a lot of the debate is, very much. And I took that also to be behind the statement that was in your letter to Eric Meslin in which you found that the debate over the AZT trial was deeply polarizing because it was launched in an entirely unprofessional in many ways and unethical way by the individuals who did not have experience.

And I want to ask you whether you have a basis you think for generalizing about the views of people who do have experience? Your fellow researchers, your fellow faculty and deans of the schools of public health around the country, whether

you think you speak -- I mean, you were not purporting to speak for any of them but is this a topic which has -- on which there is a consensus within that community on this issue or not?

DR. SOMMER: Well, I --

MR. CAPRON: I am asking. I am not predisposing the answer is one way or the other.

DR. SOMMER: Right. Well, I cannot tell you. I mean, I have not polled anyone. I could poll them. I am president of the Association of Schools of Public Health at this moment so I sort of chair this meeting -- regular meeting of all the deans of the schools of public health and I could ask that question. But I know that during the discussions certainly most people who chatted with -- I did not hear anybody from the international research community who are actually actively involved in research supportive of the way in which things had been put forward and the way in which they had been polarized.

The issues that were raised were important issues and they could have yielded to a thoughtful objective discussion. But particularly with Marcia Angell equating it with Tuskegee was just unprofessional, unethical and that she is still around bothers me immensely.

MR. CAPRON: Well, I wonder if there is any way for the staff to take you up on the offer you just made --

DR. SOMMER: I would be happy to do that.

MR. CAPRON: -- in terms of framing -- I do not want the issue to be Marcia Angell's credibility or --

DR. SOMMER: No, no, no.

MR. CAPRON: -- whatever, but the issue of whether on this basic question people with a lot of experience -- I mean, we already have faced areas in which probably most of the researchers in the field disagree with the conclusion we came to about the way certain research issues should be handled, particularly on people with diminished capacity, that particular report. I am not asking you to do this because I then plan to --

DR. SOMMER: No, no, no. I understand what you are saying.

MR. CAPRON: But I really would like to know if there is a broad understanding of consensus on this point --

DR. SOMMER: Let me ask you to do one thing. Why don't you think about how you would like the question phrased --

MR. CAPRON: Yes. Exactly.

DR. SOMMER: -- and it takes me one e-mail -- I have one button I have to push that goes to every dean at every school of public health in the United States and I will have you back the answer in two days. So you think about exactly the question which you --

DR. LO: It is an exponential --

MR. CAPRON: It is exponential.

DR. SHAPIRO: The last question --

MR. CAPRON: Thank you very much.

DR. SHAPIRO: Diane, the last question.

DR. SCOTT-JONES: I have a question. Just in reflecting on the very useful information you have told us today, you have said that a number of the people who would be enrolled in these studies do not have any real medical care to speak of but you also at one point told us about some of the people with whom you work who are disconnected from the villages and would not know the village people.

So does that mean then that the people that you enroll in the studies are always the lowest income people in the country you go to and that the people -- they would not be like those people you described as the ones who were disconnected from the villages and

who might be more westernized? Is it not just that we are talking about international research but international research with the poorest of a particular country?

DR. SOMMER: What I am telling you from my experience it is primarily the poorest people because they are the ones who do not have access to doctors, who do not wash their faces every day because they do not have access to water, who have poor nutrition and that is why they are vitamin A deficient. My research has -- my overseas research as opposed to my domestic research, which is quite different, but my overseas research has primarily been concerned with the poorest people and so your characterization would be correct but it is with the poorest because it is their problems that we are trying to address.

DR. SCOTT-JONES: And then I have a follow-up question. You mentioned briefly that -- I think it was a medical society in one of the countries was politicized. And does that --

DR. SOMMER: It is not a society. It is the official Indian -- it is their equivalent to --

DR. SCOTT-JONES: IRB?

DR. SOMMER: -- the NIH. No. It is their equivalent to the NIH.

DR. SCOTT-JONES: NIH. And does that politicization have something to do with socioeconomic status differences? I was not quite clear what you would have meant?

DR. SOMMER: No, it has to do with if you knew India you would know it. It has to do with there are a lot of smart people but very few positions for them to occupy.

DR. SCOTT-JONES: Okay.

DR. SOMMER: So life starts out with trying to pull down whoever else is competing with you or at your level. It is an internal thing for them and it has nothing to do with us. You just get caught up -- you are just one of the things that they can use to beat somebody else over the head with.

DR. SCOTT-JONES: Okay.

DR. SOMMER: It is just a -- it is anybody who has worked in India medical research knows this well.

DR. SHAPIRO: Thank you very much. It has been a very good presentation and we really enjoyed it and very provocative in many ways. Thank you very much.

We will take a ten minute break and then we will only be about five minutes behind time because we

have an important panel coming up.

Thank you very much.

Around ten till we will get together.

(Whereupon, at 2:55 p.m., a break was taken.)

DR. SHAPIRO: Well, our colleagues will rue the day they did not get back in the room quickly enough because I want to proceed with our discussion.

As members can see we have quite a wonderful group of people with us that have been doing work on our behalf and are thinking on our behalf.

Ruth, should I turn this over to you? Do you have some order you have in mind here?

COMMISSIONERS' DISCUSSION WITH CONSULTANTS ON INTERNATIONAL RESEARCH PROJECT

DR. MACKLIN: Well, I actually thought -- well, we will ask for the presentations but it would be better if I do not moderate since I will then be going back and forth and it will not give the Commissioners as much of a chance because I lack self-control.

So if you or Eric or someone would do the moderating I think the order can start at that end and go to this end and then we should have -- the question is should we have questions of each presenter because remember the task is not so much to describe what you

have done because that is in the briefing book but to say where you think the research that you have been doing or will be doing or are in the process of doing or have completed best fits in to the outline as it currently exists?

DR. SHAPIRO: Well, what we will do is we will go as you suggest, from my right to my left, and I think we will try to have questions along with each person because I think that will be more focused. That relies on a certain amount of self-control and constraint on behalf of the Commissioners as well as our colleagues here but let's at least try it that way.

Jeremy, why don't you go first?

DR. SUGARMAN: Thanks.

You have seen a draft of our final report and I have already received some informal comments from several of the Commissioners that I think will be quite helpful in reshaping the next version.

One comment was to provide some more examples so that the discussion can be a little richer about how we got to the conclusions that we have offered.

Another was to provide the site visit guidelines that we have prepared as an appendix and we can certainly do that.

Another recommendation was to provide more thorough going mechanisms of resolving some of the issues at hand and I think we may have difficulty meeting that for the sense that the study was not designed necessarily to do that but it was to use the opportunities to visit and meet with these investigators and let their expertise shine in terms of the different recommendations they had for how human subjects research ought to be done when it is conducted internationally and collaboratively.

With that said I think we can all certainly look at the recommendations and see again if we can add more of the voices of the folks with whom we have spoke.

One of the overriding messages that I think has already come across from the last outline to this outline in how the report or our work can contribute to the work of the Commission as a whole relates to the fact that overall without a formal denominator in its numerical sense that there is a bulk of research that is conducted internationally that goes well, that this work is going on all the time, people figure out mechanisms that work well for all of the parties involved.

And that message, I think, is an important

message that we read the headlines which are driven by conflict, making situations, setting up opposites and polar opposites when, in fact, it seems as if the majority of research goes on, they are negotiated, there is compromise, and if that messages comes across, even though we again did not provide a systematic survey to look at the denominator and make that a formal claim, I think that is an important way it will contribute to the report and an understanding of the way that folks in these international settings conceive of this research.

In terms of particular areas, if the outline sticks in its current form, how could the findings that we have relate to that? Well, under the informed consent area I think it is easy to show how our work relates to some of the findings on informed consent. One of those relates to sort of larger meta issues and some are practical issues.

The meta issues, I believe the last time I spoke with the Commission I described an example regarding placebo use and how investigators in one country decided not to use placebos in a trial because they realized that they could not obtain consent to do that.

Now they recognized that we could call that

therapeutic misconception. They realized that it was an insurmountable task, felt an obligation to obtain informed consent in the way that we think of it here, realized the futility of doing so, and so opted for a different trial design.

Now that was a resolution that they came up with and so the way to think about that problem was not that they have got the same old problem of therapeutic misconception that doctors and investigators have here, it is that they really opted -- they made a moral choice to go ahead and use an alternative design sacrificing some kind of science. I think that nuanced understanding of our information would be helpful.

The second piece which came across quite clearly, and I think is going to be a repetitive theme throughout some of the other projects, are these procedural elements of consent, which just seem funny. They seem funny to cultures where the culture is not driven by paper and formal written accountability. They seem funny in cultures in which people do not receive any piece of paper even at the time of their birth or marriage.

And that some of the things that we require in our current regulatory apparatus, while they make

an awful lot of sense for an ability to audit and to track and for a society that revolves a bit more around paper, can not only get in the way and seem strange to participants, it can lead to selection bias in the sense that some people are afraid of paper and it can also actually cause harm to subjects.

Now there are provisions in the federal regulations that if the consent document is the only means of linking that to the subject and it is the only way that they could be linked and that link would cause harm, that is a very difficult decision for IRB's to make or do not seem to when they are conducting international research based on the limited experiences that we had.

So at least with the informed consent area we have some information that would be helpful.

In the justice area, and I think this is my aside and comment on the -- based on the discussions today -- I think there has been some -- in the discussions that have happened today there has been some confounding of issues of justice and issues of risk/benefit. And I think that as you work on this report a bit more some of the issues that are being considered under risk/benefit are actually some justice issues and I refer you to something that --

well, I mentioned actually the first time I spoke to the Commission along with Anna Mastrionni and Jeffrey Kahn about our work on our book on justice and research.

Madison Powers' chapter specifically addresses this area, which I think might be good reading for your next meeting when you discuss this, in that Madison outlines three areas following Wahlser (?). He looks at three areas of justice and how that has been applied to health care and research. Specifically in access to health care issues we often take an egalitarian approach to justice. In research ethics we often take a libertarian approach to justice setting up procedures for individuals to make choices. And in public health we often use the utilitarian approach to justice, weighing risks and benefits.

Now that worked all well and good until there were changing claims about justice nationally and we started to pay attention to why are people claiming for access to trials instead of protection from it. But in the international setting where public health mixes and the spheres of health care mix, as you have heard in many of the presentations today, it is no surprise that there are different claims about justice and some of those sound like risks and benefits.

I will not go into that in great detail but the reasons why I could not -- I was having trouble figuring out how I could stuff in some data into helping the risk and benefit chapter was that I think it is a little muddled right now and would benefit from some teasing apart and thinking through those design issues.

The justice issues -- I think a thorough going notion of justice, our work provides some data to inform that chapter in the sense of real conversations about claims from the parts of international collaborators to address questions that are important to us, and this is not again surprising but there are voices of people saying involve us from the beginning. These are both practical complaints and practical suggestions and I think we have some data to support that.

And finally in sort of moving forward with collaborative research I think one strong message that contributes to that final chapter is one based on accepting and trusting local investigators. They are experts. They do care deeply in many cases about the subjects that they are working with, the patients when they are patients and subjects when they are subjects.

And the questioning from the United States'

perspective of what they are doing is often interpreted as you do not trust us. And that even if we go in to negotiate or collaborate it is not built on a relationship of trust, which we know from other work is important throughout the research enterprise.

And finally that if we do trust folks we might be able to meet that standard of negotiation and compromise without compromising areas where we are not willing to compromise on our ethical standards.

So I hope that is the kind of comments you wanted and I would be happy to answer any questions, and I would very much welcome any comments you have about how we might refine our draft version. We are hoping to finish it in the next couple of weeks and would like any comments, either now or some time soon, of how to do that so we can meet your needs.

DR. SHAPIRO: Let me just ask a question on the trust issue because I certainly understand the feedback that you got and so on but I guess in this country we decided that when you have a natural conflict of interest trust is not good enough really to rely on. You have to help people do what is right. Therefore, we have reviews and so on and so forth. But he is a well-meaning person, let me stipulate that. Then how do you deal with that in these

countries? We do not accept trust here in that sense for this kind of work.

DR. SUGARMAN: I am not sure about the degree to which we accept trust or not in a research enterprise. The MPA System, Multiple Project Assurance System with institutions does in a sense rely on trust. The institutions negotiate in most cases with OPRR to be trusted to follow the requirements.

Now I am not speaking with lots of moral authority coming from Duke right now but I will say that there is a --

DR. SHAPIRO: The source of the question.

DR. SUGARMAN: -- negotiation -- the negotiation goes towards trusting folks and then auditing in some cases where that is not the case. The system would fall apart and require substantially more resources if there was not an element of trust that -- okay.

At the same time what does it mean to trust others and other investigators? We asked some folks when they raised this question is it different when you collaborate with the United States compared to when you collaborate with another nation? It was very interesting that some of the European governments

trust local authorities and local investigators a bit more. Now all these things could be tested in quantitative studies and in more -- in other designs to answer these questions. It was important that they drew distinctions in that way.

DR. SHAPIRO: Other questions?

Yes, Ruth, then Bernie, then Diane.

DR. MACKLIN: I would like to have a little more detail about the negotiation that you mentioned and particular -- I mean rather than -- negotiation rather than imposition or conflict. In particular, I want to know who are the parties, where do the differences lie and who are the parties in the negotiation? It is going to make a difference in our report whether it is a local or even national IRB in a country where a study is being done and an IRB in the United States or alternatively whether it is OPRR that is one of the negotiating parties or whether it is the researcher who has to negotiate with the Minister of Health in the country?

Who are the parties? I mean, what -- if you could give us just a little more about that and do you think different things have to be said about different parties in these negotiations?

DR. SUGARMAN: Yes. I think it is as usual a

tough question and I think what we heard that drove our recommendations along these lines were the need to negotiate first about simple things like the correct translation of a consent document.

There is a habit -- I sit on the Family Health International IRB and we have forms translated into whatever the local language is and then back translated and we check the back translation for accuracy. It is the best we can do. Sure enough we had examples uncovered in the field where the translation of the consent document was so culturally inappropriate and when they went back to the IRB's, many different IRB's in the United States to try to have that changed, they said, "No, that translates okay."

Well, there were things like slang and innuendo that were really insulting and I do not know the particular word and it was a word -- again I am trying to protect each of these places. It was a word in one language which the back translation, which I am sure was correct -- and it meant something about somebody's mother when it was used in the field and the IRB would not change it according to the requirements and they said, "Well, we just do not have to do this study."

These are the kind of stories that go a long way to saying just listen to us, we really do want to do this the right way.

Another example was related to consent form use and retaining a consent document, and there were at least two instances where those posed a danger to people and this involved a negotiation with the CDC on a project in which there were carbon copy forms which were just -- in the local cultural in which they were used just felt to be inappropriate, cumbersome and placing them at risk. But there was no negotiation or willingness to even come to the table to hear that from the perspective of the folks with whom we spoke.

So who would you speak to? The suggestions we received from the people with whom we spoke were the investigators, the folks who were likely to be like the subjects. We did not have an opportunity to speak with many sort of Ministers of Health but they may want to weigh in. Local IRB's, our IRB's would be a good starting spot.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: Jeremy, I want to thank you for what is really an enlightening and important piece of work.

I would really like to encourage -- I think this applies to the rest of you as well, I have spoken to some of you at breaks. I would really like to encourage you all to develop more of some of the examples and give us more detail. You sort of tantalize us but what I would like to see is the examples developed in sufficiently enough detail so that we can use them as best practice models because you raise a lot of issues here on what to do when someone does not believe in the germ theory of disease or has cultural taboos about giving blood or does not understand the use of placebos.

If you could say a little more -- both about the setting because I think the setting is important, both the study and the culture, but also how that was resolved in a satisfactory way because as I try and probe more about this with people I think a lot of people can see that there are problems and difficulties but you ask them can you explain to me an example of how that was handled well or how it was resolved well as a model for someone else to use as a starting point, I think that could be a real contribution we make.

So it is real easy to give either --

highlight problems or make -- sort of general recommendations, you know, be cultural appropriate and be culturally sensitive but to actually give us some examples.

Jeremy, you gave us a nice example where you decided not to do -- the researchers decided not to do the study. There must be other examples where you can say, well, here is a way of explaining it that is culturally appropriate and gets the gist of the western idea without sacrificing something crucial in the process.

DR. SUGARMAN: Well, thank you and I think the need to provide that is I think obvious to us now that we have got this first version out and we will provide more examples.

The only hesitation we have been having in developing the examples in as rich a detail as we would like is the protection of the people with whom we spoke and the countries from where they spoke.

I would hate for the story to tell in country X this is what they do.

DR. LO: You do not have to use the country. You can even change the details. I mean, to sort of protect people. But to put it in a context where people can say, well, this is an observational study

or it is a genetic study rather than a -- you know, a vitamin pill study.

DR. SUGARMAN: Okay. That is helpful. That helps clarify it.

DR. LO: Along the same lines if I may, on the last page where you give recommendations you say assessed formally whether there are any true cultural barriers. And again if you could give us some suggestions of how that is done and done well. What are some ways in which researchers really do try and assess where there are subjects -- where there are barriers to conducting the research. What would you suggest as sort of starting points? Again I think that could be very constructive in sort of helping researchers think through these issues.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: Jeremy, thanks for giving us data that we can think about and I just have a few questions about the process that you use to collect the data. I was wondering who did the interviewing in the eight sites. I imagine you did some or who were the people who did them?

DR. SUGARMAN: Sure. Let me remind you of our methods. What we proposed to do are intensive case studies and rather than -- you know, Nancy Kass'

group will show you some information about some small group conversations they had and then sort of formal interviews.

We used a variety of techniques to try to learn as much as we could about each of these places and I went on one of the first site visits. Judith Fortney went on one and Roberto Rivera went on another. Each of us having experience working internationally and had relationships with the people who would provide us with insights into each group.

We spent several days in those sites talking with anyone who would talk to us based on who this principal respondent told us to go speak with. And some of them were informal conversations, some of them were more formal conversations in which we used sites visit guidelines to cover areas about what happens when they do research internationally.

We then trained and Patty came down to help train the other folks doing the subsequent five site visits and they went out into the field to other locations and had similar experiences, a little bit more now with refined site guidelines, going ahead and trying to have the same kinds of conversations with folks.

As a result of those methods we learned an

awful lot. We learned a lot of things that we did not expect to learn. We learned about the broad enthusiasm for doing this and the fact that we were asking for their expertise was met with great surprise on their part and we were quite welcomed.

Roberto described a conversation that people would not stop. They made him come to dinner with him and kept him going for about a seven hour conversation with a group.

So people wanted to talk about this stuff.

As we did not do tape recordings, we did not -- we jotted field notes and that is why we do not have the same kind of language of transcribed examples to give you. We have flushed out stories and that was a way to get this -- there is not much empirical research out there and we wanted to make sure before we structured a questionnaire kind of study that we had adequate information to drive that.

Did that answer that, Diane?

DR. SCOTT-JONES: Yes. I just have a few other questions. So within each country is there one research site, one research group?

DR. SUGARMAN: We had a primary respondent in each country and -- who would then give us sort of the permission to go on and talk to other people who

aligned things up for us. The reason for that is if you look at how the anthropologist would do this, one would probably spend years in the field before being able to collect these types of data. So what we wanted to do is to try to provide a rapid answer by building on relationships of trust. These are people that collaborated either with Duke or with Family Health International who is a subcontractor to this study. So that there is -- that they knew that they could trust -- trust the person visiting to provide these sorts of information.

So we would start with one person at one place but we were often brought around the city. We were brought to different locations. It was --

DR. SCOTT-JONES: Okay. I am assuming that you have put more of these details in your report about exactly how you did it, right? We will get more details.

DR. SUGARMAN: I think the methods -- we can elaborate on the methods but again in order to provide some protection of the persons with whom we spoke, no, we will not. And I feel strongly about not saying we went to this hospital and this is the way this hospital did this or this is the way this doctor did that because I think we could really do a disservice

to folks in ways that we are not sure and I do not know what we would do with those data. I do not know how it would inform our conclusion.

DR. SCOTT-JONES: Okay. Well, I was only asking about details of method, not naming hospitals.

DR. SUGARMAN: Okay. Sure.

DR. SCOTT-JONES: And then my last question is that you have eight countries and they range alphabetically from Chile to the U.K., and I was wondering if you were going to say anything about countries because it would be a mistake on our part, I think, to lump all other countries into international research as if there is some monolith that, you know, to do international research in any country is the same as doing it in another. So would you be able to capitalize on the range of countries that you have represented?

DR. SUGARMAN: This is a -- I appreciate your comments and I think we can certainly add to our methods, and in our discussion of our methods I think we can highlight why we elected to do this study in this way.

I feel that tension and it is a sort of standard tension of now asking for something that when we obtained informed consent from the people with whom

we spoke we promised them in that consent process that these are the kinds of things we would not describe. We -- in terms of the individual that we would protect them as individuals and I want to make sure that we do that.

I do not know what kind of risks people face. I know that these are -- that there are political pressures to do research, that is their livelihood in some ways. It is the protection of their institutions. It is face saving in other places. And I feel this tension about providing rich details of what it looked like to sit in that particular clinic or hospital and describe for you what was going on but -- and then what does it mean if I was in a capital city compared to in a smaller city.

The more details I provide -- and I do not have to say that I was in an NBAC meeting but that I was at a meeting at a big hotel chain and there was -- you know, there was a major weather disturbance and, you know, I could provide you with enough facts that it could be too easily pieced together.

So I do not know how to strike that tension very well. From the comments I have been receiving I guess we need to do more in terms of flushing out the examples and I want to try to do it that way. And I

think we have tried to provide a limitation section showing that this does not generalize to the world and at the same time the reason you picked up exactly on why we alphabetized it, we just wanted to give in the most neutral way that these are some of the voices that are heard around the world.

It is not meant to be a thorough going study or evaluation. It is an exploratory descriptive study to begin a conversation in ways that have not happened previously. I do feel the tension there in every -- well, I cannot say pen stroke anymore but in every keyboard stroke.

DR. SHAPIRO: Trish and Larry, short questions, and then we are going to go on.

DR. BACKLAR: I am passing.

DR. SHAPIRO: That is what I call short.

DR. MIIKE: Just a comment on Diane's question to you. I think that it needs to be made clear what your study is about because so much of the discussion here is about these countries in which we -- the perception is that we are taking advantage of and certainly we are not taking advantage of countries like the U.K. or Japan. So your case studies need to make that real clear that it is not typically reflecting what most of the concern seems to be.

DR. SUGARMAN: Part of the reason we selected the countries was to try to strike a balance and there are tensions felt across these countries that are similar and when we talk about the themes that go across countries we try to make clear that this was something that happened in one country versus -- we tried to do it. Maybe it is too subtle and we may need to draw that out. But I think you are exactly right in interpreting that that way.

DR. SHAPIRO: Okay. Thank you very much and I am sure there will be questions we have as time goes on but let's give some of the others here a chance.

Patty?

DR. MARSHALL: The overall goal of my contribution to this initiative is to look at cultural context of informed consent and processes associated with informed consent in international research.

I have three specific aims.

First, I am in the process of completing a literature review on meanings and expressions of individual autonomy, particularly in relation to informed consent practices.

Second, I am nearly finished interviewing investigators, a small number of investigators who are conducting biomedical or behavioral research in

international settings. And these interviews get at challenges they face in obtaining institutional review for implementing the study and also the challenges they face in obtaining informed consent in the field.

I am nearly finished with those interviews.

Third, I have completed a case study of informed consent practices and institutional review processes associated with ongoing studies looking at genetic and environmental determinants of hypertension, breast cancer and diabetes type II in rural and urban Nigeria.

I think that my contribution to the project probably has most relevance to chapters 2 and chapters 5 of the outline. Chapter 2 addresses informed consent and disclosure practices and chapter 5 -- what did we call it -- it relates to the international collaborative research and some of the issues that come up there with the review process.

Bernie, this morning, one of your comments -- in one of your comments you called attention to the fact that some of the problems associated with cultural diversity, with cultural differences, they wind up being philosophical conundrums. I agree with you completely. I have a strong personal interest in the tension that exists between individual and social

agencies and their articulation in decisions that people make specifically in relation to research.

But all of that aside, I think if you rotate the question who has the authority to provide consent, who has the authority to make a decision here, and ask instead the question of how can we maximize the opportunities for respecting for persons, for respecting communities in the international research, then to move beyond that place of a philosophical conundrum.

I think that at that point then it is very possible to begin to make recommendations, to think about recommendations for opening up for expanding a moral space for negotiating informed consent in culturally diverse settings. I think that the data that all of us are collecting -- Jeremy, with your multicountry investigation and, Liza and Nancy Kass, with your survey and the focus groups that you are conducting, and my own case study and interviews and literature review, I think that the information that we are gathering does point us in the direction of specific recommendations.

Bernie, you were asking earlier about -- you want us to flush out in greater detail some of the examples that we have given you in our very

preliminary reports and we -- I think that that goes without saying. We can definitely do that.

Also I like your idea of focusing on what works. What we are hearing about what works. For example, in the genetic epidemiological studies the investigators with whom I have spoke are struggling with how to communicate very sophisticated scientific concepts, things like genotyping, candidate genes, when there are no words for these concepts in, for example, Uraba, but they are doing it. They have figured out a way to communicate with people who may not have a sophisticated understanding of the germ theory. They are talking about inheritability and so on and it is working for them.

They are devising ways to obtain consent beyond this process of community consent that I discussed in the small synopsis that you received.

For example, I was talking at lunch about this. In some cases, the hypertension -- the hypertension study is an example where researchers will meet with the potential subject and talk about the study, provide them with an information sheet, and then that individual will take the material home, discuss it with whoever they want. If they cannot read, usually there is someone in the neighborhood, if

not within their own household complex, that will be able to read. An appointment is made to go back to meet with that individual later and that is when the consent is formalized and so it is a process of consent and it is done to ensure greater protection of the individuals involved.

I will stop there.

DR. SHAPIRO: Thank you very much.

Ruth?

DR. MACKLIN: Yes. Patty, thank you and we will look forward to more detail as you continue.

My question pertains to the administrative issues as you describe here and referred to it briefly in your oral presentation, and what you said in your comments just now was challenges of researchers in obtaining institutional review.

DR. MARSHALL: Yes.

DR. MACKLIN: And in your -- in the written report you refer to the process of obtaining approval from ethical review committees, both the requirements of funding agencies in the United States and at local Nigerian institutions. So I think we -- if -- when you can provide it, it would be extremely -- or maybe you can tell us orally now, give us a few examples, because there are likely to be different difficulties,

different challenges at the local Nigerian institution from the U.S. funding agencies.

So if you could tell us maybe now if there is anything --

DR. MARSHALL: This is a very simple example. One of the investigators talked about his frustration dealing with Washington over what was required of him in relation to his local IRB. He did not have the resources within his department to produce nine copies of the protocol and he complained vigorously about the lack of support. He did not have the help and he did not have the money to effect this process successfully but it was required of -- it was required by Washington.

He also talked about his frustrations in trying to put together a consent that would satisfy Washington and simultaneously work for the community.

Finally sort of threw up his hands and said, "Here, I am satisfying you in Washington, fine. Now I need to make a plan for my community."

The local IRB would not necessarily have required nine copies of the entire protocol and a number of people were very frustrated with the details required with the informed consent, written informed

consent. People were concerned about communicating risks and were confused by why it is that here in the United States we feel so strongly about communicating to potential subjects things like, you know, you might die if you participate in this study for say a clinical protocol for cancer or something like that.

DR. MACKLIN: A follow-up quickly. I think your response just now gets to a point that we will probably have to address in some depth in the report or I suggest we might and that is the distinction between procedures and ethical standards.

DR. MARSHALL: Exactly.

DR. MACKLIN: Making nine copies is a procedure.

DR. MARSHALL: Exactly.

DR. MACKLIN: I mean, whether it is required or whether it is necessary, that is a procedure as I argue but others disagree as is signing a consent form. I mean, some of these are procedural differences and things are spelled out, both procedures and standards are spelled out in U.S. federal regulations.

However, disclosure of risks to a subject and if death is a probable or possible, that is a real possibility, not a remote or as I see it often

described by scientists a "theoretical" possibility rather than something that has been demonstrated because it is known from experience or from existing data then that goes to the question of the standard of disclosure and to change that, what must be disclosed simply because in the therapeutic context doctors do not tell patients that, really does lower the standard of disclosure in research.

So the question then becomes should the standards that are employed in any country, in that cultural context in the practice of medicine or what doctors usually disclose to patients be taken as the appropriate level of disclosure when what we are talking about is disclosure about -- in a research context?

DR. MARSHALL: Exactly. Exactly.

DR. SHAPIRO: Bernie?

DR. LO: Yes. Patty, I want to thank you. I think all of you are doing wonderful work and it is really helping us a lot think through these issues.

I want to follow-up on Ruth's comment actually. I have been particularly thinking about informed consent as I read these and not so much the procedures of consent but the substantive standards because all of you have identified what to me are sort

of red flag areas, things that we kind of take granted although our subjects may not understand but which really do not seem to make much sense in certain other cultures. Some of them have to do with disease beliefs like what is genetics, what is -- what causes infectious disease. Some of them have to do with research design. I mean, you have highlighted placebos and randomization are hard to convey. And some have to do with the nature of the doctor-patient relationship, whether you disclose information or not.

I agree with Ruth. I am less concerned about how many copies you xerox.

DR. MARSHALL: Exactly.

DR. LO: Than to sort of what -- how can you explain some of these concepts in a language and in a culture where they are not as familiar perhaps?

And I guess the second question really is should we be explaining in the same level to subjects in a developing country as we do here. So Ruth raised a question of how much discrepancy between clinical practice and research protocols do we want? And earlier when I asked Dr. Sommer the question his -- I mean, you know, we did not get into it in detail but, you know, what he -- how he said he would explain the studies he was doing, which admittedly are very

different studies than genetic research, you know, we would have to ask does that fit our standards, our image of what informed consent should be in a normative sense?

I think those are some of the questions I think we need to get at. Can we explain it in a way that makes sense and, if we cannot, does that mean we do not do the study?

That was your example, Jeremy.

Or do we somehow omit that part of it because it really is not that essential that they understand what genetics is as long as it has to do with a disease that your parents might have had and you may pass on to your children?

DR. MARSHALL: Exactly. Bernie, I think that your question is actually relevant for research being conducted in both international settings and here in the United States and specifically I am talking about our duty, our obligation to explain and make an attempt to explain concepts that are relevant to the research being conducted.

In Nigeria the investigators actually were -- although they were frustrated with this -- having to meet the requirements for informed consent the United States places on them, they were relieved. About

seven different investigators said to me how relieved they were that people understood this notion of inheritability so that it made their job easier in figuring out a way to communicate that.

I personally believe that we do have an obligation to make an attempt to explain to the best of our ability what is happening in the study. I think that it is not enough to say it would be too difficult to explain. It does not work.

DR. LO: Yes. I think what would be most helpful for us is if you could articulate for us how the investigators that you talked to addressed that issue, what are their concerns, how do they weigh it so that we can get a sense of how they think through that problem. That I think is another level for us to decide whether their approach is one that should be somehow adopted or incorporated into the recommendations we make.

DR. MARSHALL: Another thing is investigators I spoke to were reluctant to translate these concepts. Even though it was frustrating they had figured out a way to do it by talking about genes as the basic structure of who you are and what you inherit from your parents.

DR. SHAPIRO: Alex?

MR. CAPRON: I also want to thank Patty for her preliminary paper and for her presentation and I particularly would like to follow up on the point that you were just making about the relevance to the U.S. situation domestically of the same set of concerns.

And what I hear coming through is that there is a sense that on many of these things we can have examples of creative ways of explaining a technical issue like inheritance that turns out can be understood whether or not the words genetics or genome or whatever are used.

But all of this, Ruth, goes to the question of the information that is material to the individual and it is here that I suspect that we have as many problems unrecognized in much research that goes on in the United States of researchers and their colleagues and peers even if some of them are not officially from the institute, who assume that certain information will be material because it would be material to the decisions that they make and particularly as we move away from certain things which you philosophers call primary goods, such as, I think, life and health itself, which it may be that there is a small number of people for whom life and health are of no interest or value. They live entirely in a spiritual world and

they do not really care about their material existence.

But for most people if you are to talk about something that could have an adverse impact on their health and life you could be pretty sure that is going to be of interest to them. When we get to so many of these things, particularly on a genetic epidemiology study where the question is, well, what impact would it be for you to know something or for others to know if the others are your doctor or this research or members of your family or your community.

We come to it with presuppositions about what the relevance of that is and we domestically as well. We say, oh, well, these are the concerns. We have privacy concerns or whatever and there may be a whole different set of concerns that never would have occurred to us.

So it seems to me that what -- in terms of mechanisms -- we ought to be thinking about or emphasizing perhaps the importance -- and if your illustrations help that, so much the better -- the importance of realizing that we need to have some means of knowing what the -- what is material to the subjects.

And the question that Diane followed up with

Dr. Sommer about comes through here. If the researchers in the host country are themselves a member of an elite and if as to certain diseases, not all diseases, they are diseases of the poor, the illiterate, the uneducated, the disenfranchised, et cetera, even there, there is no reason to think that simply because you share a nationality and maybe an ethnicity with your subjects that you actually understand them.

But the emphasis that we could be thinking about is how do we try to improve? Never ensure perfection but try to improve the process of relevant information being provided to people because if someone pooh-pooh's the theoretical risk of death it is because doing this kind of research no one has ever died and it is irrelevant. But there are other things that might be relevant but how do we figure out what they are. I would hope that we could find some grist in your mill to push us in that direction.

And then the question for the sponsoring countries' academic IRB where the researcher is coming from, the U.S. collaborator is coming from, is what kind of documentation could the researcher in the other countries submit to them to explain why some things are in the consent form? Like we did a focus

group. Like we sat down with people who were among the population we might be going to and we talked to them about certain kinds of these problems.

And I refer you to an interesting discussion in this paper that Gayla Frank and her colleagues had in the Medical and Anthropology Quarterly about a year ago from some research that was done in our center and her concern was -- this was reporting a particular interview in our study with a Korean woman around the issues of advanced directives and dying. And the researchers themselves were concerned that even talking about these kinds of concerns in a community in which it is not good for a real patient and a real doctor to talk about them. It is sort of jinxing. And they talked to the subjects first and they said, "Can we talk about this?"

And they said, "Oh, yes, because the questions you are going to ask are my hypothetical opinion so I am willing to talk." It is not that I am not willing to think about the genre of questions but I would not expect in my own physician-patient relationship for my physician to say to me this is your diagnosis, the prognosis is very dire, what do you want us to do because that -- as one woman said, "It is not my choice. I am the patient."

DR. MARSHALL: Exactly.

MR. CAPRON: But you see what I am saying. The only way to find out that is to go through that kind of a process and find out what is relevant and how people are able to -- anyway you get the point.

DR. MARSHALL: Alex, I know exactly the -- I know what you are talking about by Gayla and others. One of the things that you made me think about right now is that, you know, there is information out there about cultural differences in relation to truth telling and disclosure of medical information and in some cases it is very relevant to the kinds of concerns that we have about disclosing in the context of informed consent the informed consent dialogue.

Thanks.

MR. CAPRON: And just one other comment back to Ruth on something that you said. I totally agree with the notion that we cannot lift ethical injunctions on people simply because medical practice is not to do things. After all, in the United States medical practice does not begin to rise to the level in many fields that a good IRB would insist upon for research. And we do not say, well, wait a second, we ought to waive that because most doctors do not bother to talk to their patients about this. We say we ought

to be educating the doctors to try to learn how to talk about it instead of lowering the expectations. So it is just as relevant here. I agree.

DR. SHAPIRO: Thank you.

Why don't we go on? We will come back. I hope you will be able to stay because I hope we will come back to the general discussion.

Liza?

DR. DAWSON: Okay. I will describe some of the work that has been done so far and then some that is forthcoming on Nancy Kass' project which I work on.

We have qualitative and quantitative data as you can see from the briefing book report. We included in the report a sample of the qualitative data. It is very preliminary. And we also included the survey instrument which will be our quantitative piece and the survey has not been sent out so we have no data on that.

I will start with a little bit of the qualitative data. We did some small meetings with researchers. We will be doing some one on one in-depth interviews but we have not started those yet. So the data so far is all from groups. And really the themes running through these small groups, as you can see from the report, address all of the major areas in

the outline from informed consent in the second chapter of the outline to the justice issues and the risk/benefit issues that are described in the next two chapters of the outline.

We had a lot of comments from researchers who were asked very open ended questions about what they perceive to be important ethical issues in their research and they generated a lot of substantive comments and interesting comments on their own without the need for much prompting.

Particularly they talked about the themes of risk/benefit, what justifies doing a study, what medical care should be provided to participants both during and after a study. They also talked about the larger sort of justice issues. Whose benefit is being considered? This has been brought up already today. Several researchers brought up the problem of whose benefit are we talking about when we describe risk/benefit. Is it the study participants themselves? Is it a larger community? To whom does the researcher have an obligation, a moral obligation? So these issues were very real and very -- discussed very intensively.

In addition, the outline discusses enhancing international collaboration and that was also a common

theme. People particularly talked about the role of local IRB's, the need for strong local IRB review, what could be ways that the United States, either regulations or practices, could enhance the review rather than impede it or make it more difficult.

So there is really a lot of material which addresses this wide range of topics and we did provide a preliminary report so I will not go into too many examples in the interest of time.

Then the themes and the concerns raised in those small groups were used to help design the survey instrument along with a lot of feedback from colleagues at Johns Hopkins and from Jeremy and from some other people who have helped us with their comments on the survey instrument.

The themes are the same in the survey. It is divided into sections. There is a section on consent. There are sections on IRB review, both for the U.S. and for the local review, which there may be more than one local review. And there is a section on ethical issues which covers a sort of sampling of different ethical issues that some of them relate to the "standard of care" problems. Some of them relate to problems which may be similar in the United States as they are in other countries about protecting interests

of research subjects and some of them are more particular to the international setting.

And we have a section on recommendations at the end of the survey which was derived largely from researcher comments. We tried to pick and choose some comments that seemed to capture ideas that were relevant to researchers and changes they felt would be productive either in the regulations, or in practices, or in policies and give them a scale of agree or disagree, you know, to express their opinions about these recommendations.

There are some areas -- you know, obviously we have organized the themes differently from the outline that we have seen for the NBAC report and some of the differences are just simply organizational and then there are also some differences in substance that are not major differences but there are a few subtopics that were brought up in meetings that were not brought up in the outline and vice versa.

For example, we did not hear people discuss what exactly were local regulations in other countries very much but we heard a lot more about local practices in other countries. And we heard a lot about the need for U.S. IRB's to have more understanding and experience of international

research, which could go under the heading of enhancing international collaborations, which I think was a point implied in the outline but could be made more detailed when we talk about what may be lacking in the U.S. review process.

So there is one -- and there is one theme that we did not put into the briefing book report because we have not collected very much data on it but it rather goes to the heart of some of the justice questions, which is we asked -- in one small group we asked the question why do you conduct your research in developing countries as opposed to in the U.S.?

And we did not ask that in every group so in the interest of sort of being fair to participants and collecting a reasonable amount of data we did not report on it yet but we plan to find out more about that. It also is a survey question and we expect that we will find a wide range of answers there which also may be interesting in looking at the sort of macro issues.

I will stop there.

DR. SHAPIRO: Thank you very much.

Any questions, members?

Ruth?

DR. MACKLIN: This is actually a question

addressed to everyone on the Commission -- everyone in addition to Liza. The themes that you developed and have reported so far in the qualitative study are the same ones that you are going to do in the quantitative study, right?

DR. DAWSON: Mm-hum.

DR. MACKLIN: The quantitative study then are providing data as opposed to, I guess, stories, narratives, examples, et cetera.

One of the reasons I think why people like to see quantitative studies is that they tell you the magnitude of the problem or how many people believe this or that or the other rather than just having illustrations and anecdotes.

Are the results of these quantitative studies that you are doing, and you have got a large number of respondents, and I guess this is to everybody, this is my naive ignorant question, are they likely to have some weight as a part of this report if the report wants to recommend changes that might be fairly significant changes? And by fairly significant I mean something that would involve going back to Alex's comments this morning, a change in the Common Rule or, if not that, a change in some of the procedures that are now undertaken either by local IRB's or by OPRR or

any other -- or by the funding agencies?

Is my question clear? In other words, if you have sufficient data that a lot of people responded in ways that would seem to call for a change in some of these practices -- and I guess I am not talking about the informed consent but a lot of the other issues -- would that carry -- be likely to carry weight?

I mean, Dean Sommer told us how many placebo controlled trials he had to do in order to convince people. Here we are having some studies on quantitative data that might show something that has really never been studied before and might demonstrate that the present system is not working very well in these international -- in the international collaborative context.

DR. SUGARMAN: I think what the quantitative data will give you from these are generalizability about the extent to which the findings, these sort of very rich findings from these qualitative studies, have sort of highlighted with rich stories and narratives because if we just happen to have talked to people who had a good story to tell you would not want to drive policy based on one good story or you might. If it is a really good story you might want to drive policy.

But I think in terms of policy the generalizability question is one that is going to be quite important to knowing whether the efforts into, you know, giving the whole system a remake is sort of warranted.

And it is to that issue of generalizability -- I am anxiously awaiting the findings of probably the first quantitative study to come out that is as systematic as that and it will probably help in that way but I do not think we are going to do this by vote. So I do not think it is going to say that just because 80 percent said this then we ought to have a different rule because we can outline lots of reasons when that sort of approach fails.

DR. DAWSON: Could I add a comment to that?

One of the few generalizations we were able to make from our small meetings is that the experiences of -- I am concurring with what you just said. The experiences of researchers are so diverse. I am sure everybody else has found that as well. Developing country conditions are so diverse, populations are different, the study designs, the study procedures, everything is -- there is such a wide variety.

In fact, I will just mention -- not to get

into huge detail but one feature of the survey that we thought about very carefully with help from some colleagues was we did not want to ask researchers, okay, generally when you do your research, you know, how is the local IRB because you cannot generalize. You cannot generalize about five different studies in, you know, three or four or five countries.

So what we did is ask people to describe a particular study and so what -- and we asked -- we had a reason -- you know, a criterion for how they would select what study to talk about and to think about. We asked them to describe one study in detail and then at the end we have some general questions about their attitudes and opinions.

So that way we hope to capture the diversity one respondent at a time so that we will not have necessarily an average response which says sometimes it is hard and sometimes it is easy or whatever. You know, every question would be a sometimes.

So I am sure there will be some points that everybody is in, you know, 90 percent agreement and then I bet a lot of the data will show really a huge range.

DR. MARSHALL: Right. Thank you, Liza.

I want to build on what Liza just started to

discuss.

Surveys are only as good as the qualifications around them, as the parameters around them. In other words, the information that this survey will collect will be relevant to the people who respond to it and relevant to their experience. Most of the respondents will probably be U.S. researchers. Correct?

DR. DAWSON: Well, for our part and then Noreen will discuss the international respondents.

DR. MARSHALL: And you do not know what the response rate will be. Hopefully, it will be -- I mean, that is a statistical issue but I do not think the policy necessarily needs to be built around response to a survey but there are limitations to both qualitative and quantitative methods and I think you have acknowledged some of them.

DR. DAWSON: Right. There will be some strengths and weaknesses.

DR. MARSHALL: There is so much diversity. Absolutely. There is so much diversity in the experiences that people have with these investigations. Earlier this afternoon Dr. Sommer was discussing his experience and perhaps some other people might have brought very different experiences

to the table, people involved in public health in India even or Africa and some other countries.

DR. SHAPIRO: Trish?

DR. BACKLAR: I am wondering if it might be a fatal flaw of the report, the fact that as I read through this I only see that there are three interviews with subjects and that no subjects are being interviewed. What do you think, Ruth? I only am concerned remembering our report -- capacity report and the issue of making sure that we listen to and heard the concerns not simply of the researchers but of the participants.

DR. MACKLIN: I think we should ask our panel of researchers and methodologists.

DR. BACKLAR: I am asking -- I am throwing it out.

DR. MARSHALL: I recognize that when you are referring to the three subjects that I interviewed in the -- in Nigeria and I recognized even in relation to those three individuals that they were selected for me by -- I do not have any illusions about, you know, particular biases. I mean, I was given --

DR. BACKLAR: Right. But I was actually concerned that there were only -- I see only three subjects who are subjects of research and I feel as

though that this is already becoming a very slanted review and as I listen to the discussions that we had this morning with researchers I am beginning to be a little hot under the collar about this as though I really do not know the story and as though we will be perceived, which I would not wish to be, as wishing to further research in developing countries. And we are listening to the researchers problems and we are going to fix it up for them.

DR. MARSHALL: One of the things that I might be able to do -- I will be back in Nigeria early next year and I could put together a focus group both in Ibadan and Igbo-ora (?) that would include people who have participated or are still participating in studies, the genetic epidemiological studies if you would be interested.

DR. SHAPIRO: I have quite a few people who want to speak on the Commission. I have Alex, Diane and then Bernie.

MR. CAPRON: I just wanted to highlight one thing that was in your report. The suggestion that a respondent spoke of the concept of a national IRB for the United States and then said, well, actually he or she did not really mean that because that would be too big a work load or something.

If you think about institutional review boards we are usually thinking about research that is going to be done in the neighborhood of -- at the institution that is doing the institutional review and the IRB has two purposes.

One is to reflect the community's views in some fashion, anything that might be peculiar to that institution or to the community in which it resides. And the other which is -- has both an up side and a down side- is the institutional responsibility for the research. That is to say that an institution does not want to find itself having been the sponsor of, the conductor of research that goes against or puts the institution in a bad light.

And if a researcher from Johns Hopkins is going off abroad to do research sponsored by CDC, both of those concerns might arise but the first seems very attenuated because it is no longer the population of Baltimore that is going to be the Johns Hopkins' researcher's subjects or people drawn to that campus from across the country if it is a trial that is drawing more broadly.

The second concern perhaps is still there, the president of Johns Hopkins does not want to wake up and find that the Sun has run an article about some

unethical research that was being done by a member of the faculty. But in a certain way what we are really more concerned with are the U.S. regulations that have certain expectations being complied with.

And it might be an issue for you to think about, Ruth. Would there be -- would it make more sense to say that the sponsoring agency ought to convene an IRB that would look at projects sponsored by it because in a certain way, whether it is CDC or some branch of the NIH or I suppose Merck or Pfizer, which probably do this already, they are perhaps better situated to do that U.S. based thing rather than having it go to the institution as it would otherwise and are there occasions when we should not be operating so much on the "I" in the IRB institutional review board but we really are talking about a national standard.

I just -- I thought it was an interesting suggestion that that person put forward and something worth thinking about.

DR. DAWSON: Could I just elaborate a little on the actual comments that --

MR. CAPRON: Yes.

DR. DAWSON: I did not put them all in, in detail, but in the group where that idea was brought

up the same concern was raised by another person that you just raised about the need for a local sort of understanding of the research in a locality but there were a couple of reasons this particular researcher suggested the national IRB concept.

One was the idea that research which was rejected by one IRB could not be approved by another IRB because there would be one national standard.

And -- well, really the same point stated another way is just inconsistency. Two different research protocols with similar concerns might be reviewed entirely differently by two different IRB's.

So --

MR. CAPRON: Well, we know that happens domestically.

DR. DAWSON: Right.

MR. CAPRON: And when people throw that at me and say, therefore, the IRB system is useless because, look, it comes to different results, I say, "Well, we do not know. Maybe the reason institution A rejected doing the research was based on factors which do not exist at institution -- the other institution and we should not be worried that one said yes and one said no. That is because they are institutional review

boards taking into account the values of their institution and the community in which they reside."

But in this case the local community is really the host country and its IRB at a local level or national level, whatever there is in that country is supposed to be doing some of that work on the population, what are the local values, et cetera, side, and so I just think we need to think about it and I welcome the fact that it was mentioned and brought out in your report.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I have a comment that I would like to make about the methodology of the three reports that we have read and heard about now and I would also like to go from that to a comment about how we might want to think about shaping up this report and my comment on methodology has to do with a difference among the three.

Patricia described her study site in great detail and seemed quite comfortable speaking about the site, naming it specifically when she talked about it, and it seems to me that that is the great value of qualitative research that it is richly contextualized so that you know a lot about that particular instance. You are giving up the generalizability but you are

gaining in a richly contextualized description.

But Jeremy's and Liza's projects disguised or omitted specific names so that we do not know the context and the reason that I think knowing the context is important is once again that international research covers a lot of stuff and Jeremy's sites alone run the gamut of societies that are very much like our's to societies that are not in many ways much like our's.

It seems to me in reflecting on our day's discussion so far that we have confounded international research with research done on people of color, people who are very much impoverished, and there could be another genre of international research that is done on affluent middle-income persons in other societies that are like our's and that kind of international research does go on.

So if in thinking about international research we are only thinking about studies of people of color in very poor countries then we probably should start out framing the research that way because it will lead us to think about different things and also there are likely to be commonalities as I think Larry pointed out earlier with research done in this country with people who are impoverished and are

people of color.

So I think it is very important for us not to lump international research into one bucket but to think about the varieties of international research that is occurring or that could occur.

DR. SUGARMAN: I think your points are actually -- I do not care.

DR. MARSHALL: Go ahead.

DR. SUGARMAN: I think your points are --

DR. SHAPIRO: Quickly.

DR. SUGARMAN: -- are well stated and very important to consider. Remember that each of these studies brings you something completely different and each study is constrained in the way it was constructed for a variety of things to bring you different voices and different pieces, and we would like to do all the things in any one study but we just cannot do it. We are going to try to give you as much as we can constrained by what the methods can give us in each case. At least, you know, we are going to endeavor to do that and I am sure that these groups will as well.

I can tell you that the conversation helps me recall other examples that were not dominant themes, and I can tell you that in one case I brought up in

the one country we went to where truth telling is not a habit with cancer diagnosis, we were concerned that this would be a big problem with informed consent because if we cannot say the word "cancer" how can we get informed consent for a cancer study. And it turns out actually that the folks that they use as research subjects are the wealthier folks who do not share that notion of truth telling, it turns out, and so it is the most wealthy and the highest SES folks who are engaged in research. Whereas, they feel it is inappropriate to do it for the same reasons as the placebo in that they cannot get consent.

So there is a lot of this going on in here and it is important that we highlight those issues as well and I appreciate your comments.

DR. SHAPIRO: Any other comments before we go to Bernie?

DR. DAWSON: Could I say something quickly? We did -- for the same reasons Jeremy talked about, we protected the confidentiality of our small group meeting participants so that their studies and experiences would not be identifiable. But one of the virtues of the survey is that it is -- because it is much more sort of anonymous -- I mean it is completely anonymous in terms of data that we can ask more

details about studies and in an individual survey we will have the country -- a description of the study, the population, what is their literacy level, you know, some different parameters that are relevant to what you are talking about. So we will have an idea of what the conditions really are for individual research projects so it is just a different arm.

DR. SHAPIRO: Bernie, the last question and then we are going to move on.

DR. LO: It is actually more a comment to follow on Trish's concern about our gathering a lot of information from researchers but not very much information from the perspectives of subjects of research in international studies. I share her concerns and I guess at this point the question is, is there some way of trying to get some of that information in ways that would be useful?

I mean, Jeremy, you had a lot of experience with the Radiation Commission going to institutions and sort of getting research subjects or potential research subjects on the spots that were not preselected.

But I think --

DR. BACKLAR: I do not think Jeremy was here when I was talking about this.

DR. LO: -- pointed out a real concern that --

DR. BACKLAR: I am concerned that there is no --

DR. LO: -- our view of what is pertinent and important and of concern to research subjects is all filtered through the researchers.

DR. SHAPIRO: All right. Why don't we move on?

Noreen?

DR. TEOH: Yes. Once again I am Noreen Teoh. I work with Dr. Adnan Hyder who would love to be here but unfortunately he has to be in Pakistan and he said, "Please let me know when the next meeting is." He really wants to be here.

As you may have already noticed from the title of our project, it is a sister project of what Liza and Nancy Kass are doing so I will not really repeat what you she has already said for the sake of time and also it is redundant but I will say again it is qualitative and quantitative. Qualitative through focus groups and in depth interviews. We have just barely started. We have just started one focus group and three interviews and we have just revealed some patterns that are emerging in the report that we have

written to help you along with what we are already seeing.

The quantitative side obviously will come mostly from the survey part.

What I do want to address were some interesting comments already made by the Commissioners and what you said, Diane, about lumping the international group as just one thing. What we are doing with these surveys is we are going to -- based on the numbers we are going to stratify the people we are going to send it out to. There will be 300 people on our survey list. Now I hope for the best in terms of percentage response but we are doing our best to stratify by region and we can tell from each survey -- on the first page it does say from which part of the world you are right. I think it is like Latin America, Caribbean, Africa or Asia or whatever. So that is one aspect and we did already notice that that was coming, what you were saying, so we have just begun an extensive literature review.

How much we will get out of the literature review I cannot tell you but we are doing our best to go forward because we realize the survey and the focus groups and the in depth interviews in themselves may not be sufficient maybe. So we just want to be very

clear that we do cover that basis as well because I think there is a lot of emerging information that is now available about this and that countries are having ethics issues coming up so I hope that kind of sort of will help answer your concerns because Adnan and myself are more in the international health arena in terms of our background and we are very attentive to that there are very big differences between regions and even more within countries. So that is one.

And I want to address Trish's comment about concern about not addressing the subjects themselves. First of all, I was delighted that we were invited by NBAC to even have this sister project, to even interview and to study the developing country researchers because I thought that that was a great step. Sort of like in the business world they talk about listening to your customer.

Although in this instance the customer is really the subject in the indigenous country. I thought this was a great -- one step forward that we at least – are finding out the experiences and attitudes of the people doing the research in the developing world and how they perceive U.S. IRB's and about ethical guidelines and their perceptions.

So I was attentive to what you were saying

and I had thought about that and I thought, my gosh, this will take us to the year 2002 if we were to include the subjects. I mean, you know, ideally I would have loved to. So I just want to make that comment.

Then I want to get back to Bernie's overall theme all day. If anything I learned today in terms of what I need to incorporate into our future focus group guidelines and in depth interviews in particular is to also come from what kind of solutions do you have because I am now reviewing our guidelines mentally.

I have not looked at it thoroughly since you have spoken this morning. To really look at how we have been even addressing the questions. The kind of questions we are asking are what is your experience? What is your opinion? What is your attitude about U.S. IRBs or other IRBs that you have experience with? Let's say the U.K. or the Swedish if that happens to be the case.

So I hear that as a recommendation and I do not -- I will take that on with Adnan and see how we can incorporate that because we are still very early in the game. We just started three months ago and we are just setting up business and any recommendations

that you have for us to implement before we go too far I appreciate that.

OT So I hope I have covered enough ground with what you have posed already to my colleagues so far.

Thank you.

DR. SHAPIRO: Thank you very much.

Bernie?

DR. LO: Again I wanted to thank you for what is going to be a terrific study and I like the way it is going to compliment what Liza and Nancy Kass are doing.

I want to ask you some questions about IRB's, page 7 of your document.

DR. TEOH: Right.

DR. LO: Because it struck me reading it that IRB's are one of the sort of real keystones of how we think research subjects are protected in this country and in the first paragraph you said that participants generally agree that review by local IRB is essential but then all the rest of it is problems.

DR. TEOH: Right.

DR. LO: And I guess two issues. One, do they generally think that local IRBs in the developing country is beneficial and, secondly, are the types of criticisms or shortcomings that you learned about any

different than what the situation is in this country? I mean, I would imagine if you went into research in this country and asked about IRBs you would get a lot of -- you would get, you know, a lot of --

DR. TEOH: Right.

DR. LO: -- paragraphs about this is wrong and this is wrong.

DR. TEOH: Right.

DR. LO: So I guess what I am trying to get a sense of is how useful are they in developing countries and is the situation there -- are they any more effective or less effective elsewhere in the world than they are here? That is a really hard thing to generalize.

DR. TEOH: Yes. Like who do you ask to compare that. You know, if I ask a developing country researcher if they did not have any experience in the U.S. how would they compare --

DR. LO: They all have to have had some interaction with a U.S. IRB to get approval --

DR. TEOH: Yes.

DR. LO: -- for these studies. So do they think we are more bureaucratic and they are kind of naive? Somehow tie it together.

DR. SUGARMAN: You should take the data from

our findings on IRBs and probably incorporate some items in your guidelines because we did find some things about the sort of cultural clash of what an IRB means. In some settings it is not appropriate to meet and discuss another investigator's work because if you did it you would be insulting that person and so it is not viewed in the same way. So the actual meeting caused personal -- the livelihood of the people on the IRB. So they created IRBs to meet the Common Rule but they would go around individually and the chair so they would never really meet.

So they did not quite get there but they tried and there were paperwork requirements and the like that were criticized. So if you could find -- get some more systematic data in that regard I think it would be very helpful. Some are substantive and others are just procedural about what was positive about the local IRB process.

DR. TEOH: Yes.

DR. LO: That would be useful.

DR. TEOH: That is great. Thank you.

DR. MACKLIN: And to add -- to build on that and add other things that seem not to be very well known about local IRBs in developing countries is what are their methods of procedure. I mean, one of the --

some of the things we learned is they do not have written procedures. Some go by consensus. Some listen to the chair because the chair rules all. I mean, all of these differences.

Who are the members? How are they selected? Not how many people on it. I was interested to hear -- and this goes actually -- I apologize to all of you because I read all of these and cannot remember everything that was in each person's report so my apologies but in one of the reports it was noted that the IRB members -- or there were questions about the numbers of the members. I lost this thought that I was going to -- but I guess the questions here are how do they operate and what is known about -- oh, I know what it was. It was how to find somebody representative?

In one of the reports it was, gee, there is a real problem because we do not know who is going to represent the community. Well, in this country the people who are the "community members" could hardly be called representative and especially if the community has different social groups, different racial or religious groups, there cannot be any one individual. So that is a kind of odd comment that suggests that the notion of what it is to have a community member or

a representative is perhaps not well understood in that context.

So if there is anything that we could learn about the operation, the way members are selected, more than just -- I mean, something systematic, I think that would help enormously.

On the Ethical Review Committee of the UNAIDS organization we see -- there is a requirement that the UNAIDS has that for approval there has to be local approval by the local ethical review committee. Our committee, the Ethical Review Committee of UNAIDS has absolutely no idea what those committees are, who is on them, whether there is really a committee or a single person who puts a stamp on it, that is the authorizing official at a university.

So if we can get some more information about that I think it would give us a richer picture not only of the details of operation but how similar or different are IRBs in the countries where the researchers come from to our own.

MR. CAPRON: Do you think you could set your wordprocessor when you are writing the report to insert in random places a parenthetical "of course the same is true domestically?"

(Laughter.)

DR. TEOH: Yes.

DR. MACKLIN: Well, domestically, though -- I mean, here is a very big difference in this area.

MR. CAPRON: I do not mean everything is the same.

DR. MACKLIN: Yes, I know. No, no, no.

MR. CAPRON: But actually how representative they are, how they are appointed and detailed. It may be buried in some assurance but it certainly is not uniform institution to institution.

DR. MACKLIN: Right. Those things are not.

MR. CAPRON: You could generalize.

DR. MACKLIN: But they need --

MR. CAPRON: Does the chair dominate or not, et cetera, et cetera.

DR. MACKLIN: Yes, right. So very different --

MR. CAPRON: Right. Yes. All those problems exist.

DR. SHAPIRO: This is a comment on the issue that you raised before whether this report is focused on poor people, people of color. Of course, a lot of the testimony here today has been on examples of exactly those kinds of societies but it was interesting to me when I read Ruth's outline one of

the things about it was it focused on places that were different from us because that is where we are more likely to run into different kinds of issues.

They could be different not because they have different diseases. They could be different because they have different cultures. They could be different because they have different risk/benefit ratios. So there is lots of ways they are different and I thought it was kind of helpful to look at it that way but I think we ought to give that some more attention as we go through but I think that is where additional problems besides the one we have at the moment like what do you call a research subject is a good example. Well, that is no different here than elsewhere in a lot of cases and so on. So it is an interesting issue.

Larry?

DR. MIIKE: The reason I raised that issue about we made it -- we better make it clear about where we are at because if you read the beginning of your talking outline it is heavily on developing countries and so the implication is not that it is international research across the board but this difference in economics. I mean -- and I think that that is where the main concern is.

DR. SCOTT-JONES: And I have another comment. Also I think the concerns are even stronger when the research being done in other countries is research that could reasonably be done here. The research presented by Al Sommer was research that could not reasonably be done in the U.S. because it focused on a condition that only existed in other countries.

There the ethical issues are not as problematic as they are say in the perinatal transmission of HIV because we have problems with that here in the U.S. and you could do studies of it here so it is -- and there are treatments available that carry a price that is more bearable here although not uniformly bearable in our society.

So the ethical issues are sharper in my view in those -- in that instance than in the kinds of research that Al described. So I think that we somehow need to make distinctions among international research and not just sort of treat it as one monolithic category.

DR. MIIKE: I agree.

DR. SHAPIRO: I think we ought to -- Elisa is sitting there patiently the last hour or so.

Why don't we turn to you and then we can see what questions there are for anyone?

DR. EISEMAN: Okay. Well, my project is quite different from all the projects you just heard about and actually arose from a question that was asked probably over a year ago by Alex, and that was what is the federal government spending on international research, and from that initial question it has grown from just what is the federal government spending into what is the private sector spending, pharmaceutical companies, biotech companies, as well as what is the private -- what are private foundations spending.

The information I gave you today mainly covers the federal funding because as I mentioned earlier those are the numbers that are easier to get my hands around but the intention is to fill out the information to include those other sectors.

To address Ruth's main question to us, where does this fit into the outline, that is a good question. I think Ruth and I both have been scratching our heads over how exactly will this information fit into the outline. I think a lot of it is background information and may end up in the introduction or chapter 1, but I think I wanted to tell you a little bit of the richness that is contained in this data, beyond just the bottom line

number of this is how much is being funded, that may actually fit throughout the report where we need facts about where is the research being done and what types of diseases are being studied.

The first thing I want to do also is qualify the data that I gave you. It is a draft and it is because even though the federal funding is easier to get my hands around there are certain agencies that are quite difficult to get information about. Two of the main agencies that we are severely lacking information about are the CDC and USAID, which are very big players. That does not mean we cannot get the information. It is just a little bit harder.

I talked to Majorie Spears today from CDC and she has volunteered graciously to help obtain more information about CDC. She told me briefly that there is well over -- or at least 100 studies that the CDC is involved in and, as you can see on the table I gave you, we have only captured one study. So obviously there is going to be a lot more information from CDC as well as USAID. We are trying to pursue that information.

But based on the information that we have so far -- like I said I wanted to try to let you see some of the richness that is contained in this data. For

example, within NIH at the National Institutes of Allergy and Infectious Disease there has been 49 awards given. Twenty-one of those awards deal with AIDS research, and one of the questions today was are we only looking at the very prevalent diseases like AIDS.

Well, in comparison, twenty-one awards are also involved in other infectious diseases, microbiological infectious diseases and stuff like that. Also at USAID some of the awards that I pulled out, over half of them were dealing with infectious diseases other than AIDS such as malaria, TB, sleeping sickness. So that type of information is contained within the data that we have been pulling.

Also the question of where is the research being done? Is it all being done in developing countries or is there also research being done in developed countries? The information that we have pulled so far shows that there is research being done in both places but it is quite interesting that there is twice the number of awards in developing countries as there are in developed countries as well as if --

DR. SHAPIRO: May I just ask a question about that? I am sorry to interrupt you.

When NIH makes a grant to a British

researcher at Cambridge University who is going to study something in India or somewhere, not in the U.K. How does that get classified in this scheme?

DR. EISEMAN: That gets classified the way I have classified it so far as where the research is being done.

DR. SHAPIRO: Does the data contain information, for example, on the number of subjects or whether they are clinical trials or other kinds of studies?

DR. EISEMAN: There is information contained in some of the data that I have pulled about the types of studies they are. I do think that it is going to be difficult to classify each one as to whether it is a clinical trial or a prevention trial because information about all the studies is not going to be available for that but I do have some information about that, for example, within NCI at NIH, the National Cancer Institute. Out of their 46 awards that we found, 29 of them are in cancer prevention so it is prevention studies and not clinical trials.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I just have a question for clarification about how our federal agencies can give awards. Harold, in your example you mentioned giving

an award to a researcher in Cambridge, England, for research done in India. My understanding is that awards must go to a U.S. university or U.S. institution. Is that wrong?

DR. SHAPIRO: That is not my understanding but I am not the one to ask.

DR. SCOTT-JONES: That is my understanding at NSF.

DR. KILLEN: Awards can go anywhere in the world.

(Simultaneous discussion.)

DR. SCOTT-JONES: At NSF, at least in my directorate, we only give them to U.S. researchers. The collaborator in the other country has to work with a U.S. researcher through the U.S. institution.

DR. EISEMAN: That is not necessarily true with all of them.

DR. SCOTT-JONES: Okay. Because we do not do research. We only support it and we give that support to U.S. institutions.

DR. MESLIN: There are research review requirements for NIH funds that will flow -- I do not know if Christina Moore is here and wants to give any more information on NIH. That was the only NIH person I see here but as a former NIH'er I can tell you that

research can flow elsewhere and both study sections and review requirements are in place to allow that to happen.

DR. EISEMAN: And that -- we have that information. So who the grant is going to, who the award is going to, as well as where the research is being done, and actually that leads to another area of richness that hopefully we are trying to pull out of this data is whether the research is done as a collaboration between researchers say in the United States and in another country or whether it is done as a researcher from the United States going to that country to do research. So there is different types of ways research can be done and we are hoping to be able to pull that information out as well to try to get some more richness to this information.

DR. SHAPIRO: We interrupted you. I am sorry. We will let you finish.

DR. EISEMAN: That is okay.

The only other thing I wanted to point to is some preliminary data that I gave you from the pharmaceutical industry. And I tried to make a note that that is total R&D spending. That is not just spending for human subjects research. But I think it gives some ideas of the types of spending that is

going on looking at R&D spending versus sales and I do not know exactly how to parse this data but I think that there is some interesting trends in the data.

For example, if you look at the top country -- the top region actually for R&D spending, which is Western Europe for the pharmaceutical industry, they are being funded about $2.5 billion dollars in 1997. And in comparison their sales were $21 billion dollars. That is about a tenfold increase or ten -- for each R&D dollar that is being spent they are getting a tenfold return on their dollar.

But then if you look at some place like Africa that is actually one of the lowest places for R&D funding for the pharmaceutical industry at $5.2 million their sales are $680 million dollars. And if you do the comparison there it is actually 130-fold difference.

So whether there is some information in there that we can pull out that may be research in Africa is very cheap and then when they go back and sell the pharmaceuticals that they have developed they are getting a lot of money in return or whether there is actually pharmaceuticals flowing back into these countries and there is some kind of distributive justice that can be buried in these numbers. Those

are the types of information that we are going to try and pull out of these numbers as well.

And that is basically what I just wanted to tell you today.

MR. CAPRON: Is the R&D money from what you have seen of it broken down between bench science and human trials because your NIH -- excuse me, your federal funds are human subjects research?

DR. EISEMAN: Strictly human subjects research and at this point --

MR. CAPRON: Which is what interests us.

DR. EISEMAN: Right. Exactly. And at this point the only information we have about the pharmaceutical industry is for total R&D but the intention is to get rid of the bench science and only focus on the human subjects research.

DR. SHAPIRO: Okay. Thank you very much.

I think now if there is any questions any Commissioners have either for the panelists who are here right and/or other thoughts that would be helpful to Ruth as we try to take the next steps in this project.

Larry?

DR. MIIKE: I just want to reiterate what Trish and I were talking about and Trish's main

concern is that we have made recommendations in our capacity report and in our biological report that changes the way that we want to deal with human subjects in the United States and I think there are some things that we need to be careful about that we are still in convergence with that when we talk about the international report, particularly about the human subjects protection or issues about community involvement, et cetera, in our other -- in the second report.

DR. BACKLAR: We discussed this during the break. I am sorry I did not bring it up here.

DR. SHAPIRO: It is appropriate to reinforce and not --

DR. BACKLAR: We do not want to come out disagreeing with one position on one side of it.

DR. SHAPIRO: Alex?

MR. CAPRON: I think Bernie attempted to get us to do this and I think we need to try to do it, which is to come back to the point that Trish made. There are certain reasons why we focused on researchers because part of the question as we framed it was are there from the viewpoint of people who do the research barriers to doing the research are there omissions that they have become aware of. It is

possible just by looking at research awards to figure out what the community of researchers is. It is obviously much harder to know what the community of subjects is. But there certainly is information to be gotten there.

When the President's Commission did its study of informed consent we looked at what physicians thought informed consent was but we did a very big study, the biggest in dollar terms of all the studies we did, on what the public thought and we did not -- we had the advantage there of not having to ask patients.

We wanted to know what the public thinks assuming that the average member of the public, him or herself or through a child or parent or family member, has been at some time to a physician and has some sense. And we got some fairly startling things about a lot of the cynicism on the part of the public about what informed consent was all about. Mostly it was a doctor’s protection mechanism in their view.

I think some creativity in perhaps some of the funds that will come with our renewal, I hope, might be spent in this endeavor and I think if they are not, at the very least if they are not, we ought to design a research project even if we say we cannot

carry it out in time or fund it, and suggest that this -- that before the recommendations that we come to are implemented that others who are carrying on and implementing our work ought to have some concern with this, and that might be the kind of thing which the Fogarty Center, which has a long-term interest in international research, has given some thought to or could be persuaded to give some thought to or other groups. The Rockefeller Foundation was mentioned as a historic funder of research abroad and it might also be persuaded that this is something that would be worth looking into.

And I do not know whether we could, in effect, ask Yankelovich (?) or Harris or somebody else to go to Uganda and do a public opinion poll. I bet in a lot of these developing countries there are mechanisms whereby a public opinion is sounded on things and in a sophisticated way, which is beyond just a yes/no survey of a telephone survey or something which would be irrelevant in many of these situations, it would be possible to get some answers and it would be potentially quite illuminating.

It was certainly illuminating to me to find out what the public thought about informed consent so I do not want us to all nod, as Trish says, this is an

important topic and then move on and eight months from now have no idea further about it and not even indicate what it would be to know more about it.

DR. MACKLIN: One difference -- I mean, we also should look at what the Radiation Committee studied, the Subject Interview Study, for some information but one difference that I would see in what you describe, Alex, that the President's Commission did, which was looking at taking -- finding out what the public thought since most people --

MR. CAPRON: Oh, I agree. You cannot do it that simply. You have to --

DR. MACKLIN: Yes, but most people in the public have been patients at one time or another.

MR. CAPRON: Right.

DR. MACKLIN: And, therefore, have that experience.

MR. CAPRON: Right.

DR. MACKLIN: Here it seems to me to find out what people in developing countries think about --

MR. CAPRON: No, no, people who participated in research.

DR. MACKLIN: -- people who have participated in research.

MR. CAPRON: No, no, no. Certainly. No.

That is why I said you cannot just do a public opinion poll. You have to go -- you would have to be able to go to sites where research was done and it -- I do not know, has any of the UNAIDS process involved -- I mean, you went and had interviews in those countries. You held meetings. To what extent were the people who were coming to talk subjects as opposed to researchers or government officials?

DR. MACKLIN: Well, these were mostly workshops. I mean, the ones that led up to --

MR. CAPRON: Okay.

DR. MACKLIN: -- the guidance document.

MR. CAPRON: Right.

DR. MACKLIN: Which will be published any day. Those were an array. They always included, as very many AIDS activities do, always included persons living with AIDS.

MR. CAPRON: Right.

DR. MACKLIN: And for the most part they are or have been research subjects, and they always include people from NGO's as they are called in other countries, nongovernmental organizations.

MR. CAPRON: Right.

DR. MACKLIN: Usually health advocacy organizations where the people who are the health

advocates, women's health advocates, AIDS health advocates, et cetera, know a great deal but the focus there was not really on the experiences of research subjects so there are places you can tap into and -- especially because there do exist health advocates and health advocacy groups in a lot of different countries and that might be a route to take.

DR. BACKLAR: Would it be possible to do a Radiation Committee type study that you did in a few places with subjects?

DR. SUGARMAN: Trish, I can tell you --

DR. BACKLAR: A descriptive opinion study.

DR. SUGARMAN: Trish, I can tell you from being the primary staff member responsible for designing and conducting that study and Ruth being a Commissioner for the Radiation Commission, I think that the outcome of the study was that the data were extraordinarily useful and very powerful and continue to be powerful and are the most systematic data we have.

The challenges inherent in doing such a project are enormous. There are -- it is expensive. It is time consuming. It is logistically quite difficult even in the United States. And I am intrigued by Alex's suggestion about proposing a

project but not doing it but in the sense that as you continue to deliberate about what might be useful to inform your deliberations you obviously want to get the data that are going to be helpful. Otherwise it does not make sense.

And you might want to think through doing what we did in a phased sense in that we started our study with focus groups the same way we started this project and now we are getting it. That is about all you might -- even with a stroke a good luck and a lot of money you could probably get those data in time for whatever your schedule is for this report and then use that to design a systematic study that might be done by another agency and I think that would go a long way because we would even need those sorts of data.

The issues of translation are going to be enormous. The issues of comparing site selection, respondent burden, local IRB review, all of the things that are going on. It is an enormous -- you will need another power source.

DR. BACKLAR: You already have a descriptive study in here where you were talking to researchers in a nice array of countries. Is it not possible to tap into them to get something like this done?

DR. SUGARMAN: Certainly. I mean, things are

possible. It would be to sort of find the subjects and --

DR. BACKLAR: To go back to where you have already been.

DR. SUGARMAN: Absolutely. If that is in the interest there are ways of doing this and we could think together about that. If that is where you go and want to go through that, I would be happy to be a part of that conversation. I think that there could be a lot to be learned but again you will have to do that -- to make those decisions in light of its costs and its tempo and given some of the important constraints that are placed on federally conducted research, how fast that is going to be able to occur is going to be dependent on a variety of factors beyond the Commission's control.

MR. CAPRON: I did not think we had OMB problems with focus groups.

DR. SUGARMAN: If we do --

DR. SCOTT-JONES: What? I am sorry. What?

MR. CAPRON: The OMB clearance concerns with focus groups I thought were not as severe as with research questionnaires.

DR. SUGARMAN: I believe if you -- yes, you would have to check with OMB.

DR. SCOTT-JONES: It is complicated.

MR. CAPRON: I mean, the OMB barriers we would be lucky to have a project designed and even approved by the time this report is done much less conducted and analyzed.

DR. MARSHALL: One of the differences between conducting focus groups with investigators in different countries in a way that I have done in Nigeria and that you have done with the six different groups and the state -- the eight state study, those were conducted in English.

When I have done work just even in Nigeria for this project, in some cases I have needed to have a translator, someone who speaks, in my case, one of the languages in Nigeria, Uraba, and it would be possible for me to go back and to put together a group -- a focus group of issues involved in these studies. They would be foreign language speakers and necessitate working through a translator. In this case it would just be very specific, though. It would not be -- you know, it would not be looking at an array of patients involved in different sorts of studies. Again it would just be one example.

DR. SHAPIRO: I just want to think through what we are going to learn. It is not really quite so

obvious to me as it seems to everybody else sitting around the table.

DR. MIIKE: Not to me.

DR. SHAPIRO: It is really of direct interest to us.

DR. SHAPIRO: We are not sort of guardians of those populations. That is their country's efforts. I am sure there is something we can learn. It is not at all obvious to me that there is something to learn so central to what we are doing to sort of exert some major effort. Maybe we want to think about it is all I am saying.

MR. CAPRON: Well, I mean, just to begin a conversation about what that might be. To what extent do people involved in research really look to their local researcher as their source of assurance that what they are doing is okay as opposed to situations in which there is a U.S. collaborator and being told this was reviewed by a United States agency as well and found to be okay? Is that an important source of assurance to people or not? Do they feel that the kinds of forms they have been presented with were helpful to them or not?

Because if it turns out that those forms are heavily driven by well-meaning but ineffectual U.S.

requirements and that we were to hear very uniformly -- I mean, a focus group is only going to give you a hint as to what you can found out. But if it were to turn out on a larger study something, yes, absolutely, these were much more useful than anything I ever hear from my doctor and I felt that I understood whether or not I wanted to go into it on that basis, or conversely, no, I regarded this as window dressing that was probably there for some requirement somebody had and I just signed it without thinking about it.

I mean if you got strong results -- see, the power of your results depend upon whether or not you get dichotomous results or not. If you get sort of an even mush across, no, you do not find out anything but that is true of any study.

DR. SHAPIRO: Larry?

DR. MIIKE: I am just thinking about how we started this meeting about the next schedule about how we are going to be dealing with the study. Then I am looking back at our biological materials report and we did do focus groups in the United States on that, and that took a long time and I am thinking about going back to Africa and places like that. I just do not see a convergence of that activity fitting what we have decided already about the timetable for this

report. And I am actually looking for ways to condense this study a little bit down but I always seem to be on that end when we get into discussion. You always want to enlarge things.

DR. SHAPIRO: Yes, I mean we should not make any big decisions yet.

Liza?

DR. DAWSON: I appreciate all the concerns about time and efficiency but I just wanted to point out something interesting about the concept of involving participants in the whole discussion, which is -- has been brought up, I think, by Diane over here and by other people, class differences between researchers in other countries and participants, and big cultural differences within countries, and the fact that a lot of researchers who collaborate with the U.S. may have a lot more in common with the U.S. researchers than with the study population, and we have heard that.

I am sure you have heard that from some of your respondents and we have heard that they need a translator and a intermediary between the local researchers and the local populations, and that there is a big divide there. So in a sense it is we are interested in protecting the interests of those

subjects and the local investigators are also maybe one or two steps removed from those people so not that it may be --

DR. MIIKE: You are also describing --

DR. DAWSON: -- it may be not feasible.

DR. MIIKE: -- the United States.

DR. DAWSON: Exactly. Exactly. But I think one of the things --

DR. MIIKE: I am not questioning the value. I am just questioning the timing and --

DR. DAWSON: Right.

DR. MIIKE: -- just where we are --

DR. DAWSON: Right. But I think it goes back to Diane's point about you cannot assume that everybody in another country is all the same, you cannot assume that all the different countries are the same, and so participants -- you know, people in Nigeria are not all the same.

DR. SCOTT-JONES: Exactly.

DR. DAWSON: And do not all have the same voice.

DR. SCOTT-JONES: Right.

DR. DAWSON: So I think that is something that is for the future.

DR. SCOTT-JONES: Exactly.

DR. BACKLAR: My concern -- my answer -- you said how your question is what good will be done by it.

DR. SHAPIRO: I was not sure, yes.

DR. BACKLAR: Okay. Then I cannot tell you what good because when you do research you are not -- you have a hypothesis but if you are in equipoise you do not know how it is going to come out. So I cannot give -- I cannot answer your question but let me say -- let me answer it in a negative. I am concerned that if it is not done the report itself will be of less value and I am thinking again of the Radiation Committee and what a difference it made to have the subject -- that descriptive study and how important and valuable it was, and did you know that that was what you were going to get? No.

DR. SUGARMAN: No.

DR. BACKLAR: Right. Of course.

DR. SUGARMAN: If it would be helpful we could certainly give a presentation or at least it is chapter 16 of the final report of the advisory committee which at minimum one way to go and I would be happy -- this is another one of the talks you can give in your sleep but I would not try to do that even if it is late in the day. But I would be happy or

Ruth Fadden can do this or any of the people that have been engaged in this process, Nancy Kass could give a talk of this. It would be helpful to the group and a couple of the Commissioners like Ruth Macklin could describe how that influenced her decision making, if that would help inform this Commission's decision making.

MR. CAPRON: Well, we can all read the chapter. What I would think would be helpful would be if you are willing, and the staff, to spend a little time looking at that and saying how might it be adopted -- adapted, excuse me, to this other context in the kind of phased basis that I was mentioning -- recognizing, Larry, we do not have time to do the whole study and we do not have the money and everything else. But not yet answering the chairman's question, well, exactly what do we know we are going to get. We do not know.

DR. SHAPIRO: Well, I think there is no question we would learn something if it was properly designed. We would learn more at the end than we did at the beginning. The question I have in my mind is really a rather more strategic one and that is what am I going to learn that is important given the focus of this report and what we consider to be the most

important parts of what we are doing. I just want to think that through. I do not know. I do not have an answer myself.

MR. CAPRON: What I always think about is sitting in your chair in front of a Senate committee and your report has been the subject of this committee hearing and the question is now I understand that your recommendation is that the following changes should be made in the regulations.

Why did you think those were important changes to make? Was it an ethical dictate that brought this to your mind? Well, no, it was not. It was more grounded in the real world? Yes, it was. Well, where did you go? Well, we went to researchers, both domestic and foreign, and asked them what problems they had with the regulations and some of those problems seemed very convincing to us and so we have made recommendations for alleviating those problems. Now that is perfectly reasonable.

And then the senator next to him is going to say, well, did you ask subjects what problems they had in their experience with this research and you say, no, we never did.

And it just seems to me that Trish is saying we make our conclusions less useful taking into the

universe, less convincing and subject to a criticism which we are not going to be able totally to evade -- avoid but we might at least identify that we recognize that that was an issue and this is an area for further thought by others in a follow on.

DR. SHAPIRO: I think we -- if what you are saying is we have to have good reasons for anything we recommend, I agree. You had a whole series of answers in your questions.

(Simultaneous discussion.)

MR. CAPRON: I am describing a process that we are going through.

DR. SHAPIRO: I understand.

MR. CAPRON: I mean, we had discussions around here as to part of the reasons we are looking at certain things is we know that there is friction on those issues. They are points of friction in the system. It does not run smoothly but we mostly know that because researchers and some sponsors of research complain that those points are friction points.

DR. SHAPIRO: Ruth?

DR. MACKLIN: Yes. I guess the question is what are the boundaries of the report. We did not think about -- and I did hope to get some responses from the Commissioners before our chairman closes us

out for the day because we really have to know whether --

DR. SHAPIRO: Five minutes.

DR. MACKLIN: -- well, we have to know whether to follow the next steps as indeed we have set them forth but as the present outline is constructed it is not addressing the question are subjects adequately protected, are subjects of research in other countries adequately protected.

The question -- and that -- and I share with Harold the concern about what we are going to learn unless we add that to what is now here because it is not in here. There are a lot of questions about process and procedures. There are a lot of questions about the smoothness of the research and there are surely questions, the justice questions, namely do people in the countries where the research has been conducted benefit from the research after it is completed.

But there is no part of this that actually focuses on the question of adequate protections. Are they harmed? Are they wronged? Except perhaps for the informed consent. We get something from the informed consent section of whether they are being wronged. So we would have to add something to the

additional outline thereby expanding it beyond what is now here and making it even more ambitious and in a way change the focus or at least add an important question.

So as many people around here have said, even today, it is a question of what our research questions are and what we want to find. We could always as in any report make a disclaimer and say surely information is needed about the responses and the perceptions of research subjects in other countries. This report did not try to do that but we think it would be valuable but in the time and under the constraints, et cetera, it was not here. So there are ways of putting boundaries on the report but I think we have to change a lot of -- actually the focus and add something if we were going to get into the question of how adequately are subjects protected.

DR. SHAPIRO: Bette?

DR. KRAMER: I would -- I do not see expanding it beyond that because I am not sure at the end of the day that we would be able to derive the information or we would be able to derive sufficient information to really be helpful.

One thing that occurs to me that we might do is to be back in touch with the people who have

presented to us, people like the two doctors that spoke this morning who are actually doing research themselves, supervising research, and asking them -- get some feedback from them as to whether or not there are ways, is it even possible -- is it even possible to do if we had the time, if we had the money, if we had the other resources? And possibly including that information in sections such as Ruth just referred to.

But I -- I do not see us expanding the report to encompass that at this point.

DR. SHAPIRO: Alex?

MR. CAPRON: Ruth, I do not think the question that you put is the question that Trish raised. It was not can we in this report say that research subjects participating in U.S. sponsored research abroad are adequately protected. We cannot say that for the United States. How could we say that for this much more heterogeneous set of research that is farther away from our every day observations?

I think it is a different set of questions and I think to a certain extent those questions are addressed in here. I mean, after all, one of the questions about variations in consent, should there be some difference, is there -- are there some points for

which it is not ethical imperialism to insist that they are part of the consent process and other ones where changes beyond just using different language to explain what genetics is or something are appropriate?

I mean, those kinds of concerns are ones on which we are going to get, if you look at these research documents, some interesting answers, I think, from researchers. The question is would you like some interesting answers from research subjects. Even the very notion of what you think is a benefit. I mean, is it a benefit if your country comes away with a better infrastructure but does not come away with the ability to buy the drug? I do not know.

I mean, ministers of research -- ministers of health in some countries say, yes, that is a benefit. We will take that. We think that is a good that you do in your research. It counts on the benefit side. Subjects may say we agree or they may say we disagree. I do not know what their answers to those kinds of questions are and I agree that it would take quite a bit of study to answer that but I do not think it is a question that is not addressed in this report.

It is addressed only from certain voices, however, our own perceptions of ethics and some empirical data we are going to have about what

researchers think. That is probably all we are going to have. I am not complaining that we have this earlier report out but if we know that there are other perceptions it seems to me we would write a better report if we identified the fact that we realize it, identified how one might go about it, any preliminary steps we have taken, any discussions we have had with others who also think it is an interesting issue who may be able to pick up that particular torch and carry it.

DR. SHAPIRO: Trish?

DR. BACKLAR: I think it is demeaning not to consider all the stakeholders. I am concerned about that and I just want to also use some recent experience having participated in producing the report on the capacity report. As I go around the country speaking to people who have mental disorders the big question I get over and over again, despite the fact that we invited people here to talk with us who did have mental disorders, is the prominent consumers in the field who are now -- who are also -- many of them actually are providers as well --felt that they were excluded from that discussion and their input was not listened to and they feel that it is extremely important in that particular group of people that if

you are going to do research on us, we should have a voice.

DR. MIIKE: That always happens.

DR. BACKLAR: I am not disagreeing.

DR. MIIKE: Even the people that knew about the meetings and came to the meetings, some of them will always raise --

DR. BACKLAR: You know something, I agree with you but actually I do think -- and I feel in some way responsible because I was involved with it and there were a group of people that I perhaps should have pushed more to bring. It was not that anybody stopped me. We -- I did not think about it.

DR. MIIKE: I think we are talking different things. What we are talking about here is international research in the country to country level. We are not talking at the lower level. The other thing is that if we begin to try to design a way to get that, my first thing would be to say why Nigeria. Why did we just pick five places in Nigeria? Why those particular tribes? I mean we would never -- we would not have an end to it and I still do not know what it would add to what we eventually come out with in terms of our recommendations and conclusions in our report. Basically I think the issue is that we

are talking at different levels of policy.

DR. SHAPIRO: Bernie, and then we are going to wind up.

DR. LO: Let me try and suggest a way to sort of resolve this situation. I mean, I think a lot of this is a time, resources, focus issue and I think it really is unrealistic for us to try and design a study, how to get this information, it is just not in our time frame and I do not think we have the resources unless Eric is sitting on a lot of money that no one else knows about.

I think it would be good to make an effort to say we do take it seriously so both in the report to highlight it but also I think we should make some effort to see if there is a way of bringing people in who have some information about that that is credible. So I think we should try and get information that is already gathered but just stop short of saying we are going to go out and collect it ourselves. We should, I think, try and formulate an argument for making a recommendation we think that is important that someone else do that to try and get the ball rolling.

So what we are trying to do is show our respect for the subjects of the research by expressing the importance of their perspective. We should do

that but not feel that we actually have to go do it.

NEXT STEPS

DR. SHAPIRO: Okay. Well, what we will do over the next couple of weeks is we will give this particular item some further thought and send a memo around to everyone to see what some proposals are and how you might feel about it.

All right. Let me just express my thanks to everyone who helped us so much today.

Ruth, thank you particularly.

Thank you as well.

It has really gotten us to a very good spot right now and I really thank you all for the work you have done on our behalf. We are very, very appreciative.

We will adjourn until -- do you have anything else?

DR. MESLIN: Yes. Just about tomorrow morning and your books.

Please take your things with you. The room is going to be cleaned so do not leave your materials.

MR. CAPRON: It is going to be redecorated actually.

(Simultaneous discussion.)

MR. CAPRON: They have been putting in a tile

floor in the lobby while we have been up here today. We have not done anything but they have got a tile floor in.

DR. MESLIN: Secondly, as you all know, Alta Charo is not here so she will not be leading the discussion tomorrow but we will begin at 8:00 a.m. sharp.

DR. SHAPIRO: I will not be here as far as I know.

DR. MESLIN: And we will discuss dinner momentarily.

(Whereupon, at 5:05 p.m., the proceedings were adjourned.)

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