37th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

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I N D E X

P R O C E E D I N G S

OPENING REMARKS

DR. SHAPIRO: Colleagues, I would like to call our meeting to order.

If you hear some conversation in the background, we are trying to get Alta on the -- who wants to participate by conference call. Let's just wait a second and see if we can get this conference call.

So if anyone hears -- we have had this before. If anyone hears a voice from beyond, this is Alta speaking.

Alta, welcome. Hope you feel better soon.

PROF. CHARO: Thank you very much.

DR. SHAPIRO: Welcome, all Commissioners. I wish you all once again a happy New Year. We have an important meeting today and tomorrow morning, of course. We hope in that process most importantly to make significant progress on some aspects of our international research project and to lay out and discuss our plans for our so-called comprehensive

project looking at the overall system of federal protections in this country and how it is operating. That will be principally tomorrow.

Although, as you know, from looking at your agenda Bob Levine, who you all know, is here and will be talking to us really on both aspects of that since he will be talking shortly on the issue of obligations of subjects, communities and so on, and later on talking about a topic which is more relevant for our work tomorrow and so we have really a lot to get done. I hope we can focus on some issues that will be helpful in advancing both of these reports.

So let's just turn directly to our business today and before I turn to Bob -- Ruth Faden should be joining us shortly -- let's turn first to Ruth and Alice for an update or an overview, I should say, of the work to date on the project.

Ruth?

Let me just say to all commissioners if you want to speak you press down this thing called "MIC on/off." It turns red and that means you are on so if

you are speaking just press that. When you finish speaking please press it again so it goes off.

Thank you.

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

OVERVIEW OF WORK TO DATE

RUTH MACKLIN, Ph.D.

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

DR. MACKLIN: Thank you, Harold.

Good morning, everybody.

We have a packed agenda for this meeting but also a lot of time for discussion with the commissioners, and again Alice and I are urging you to give us as much feedback as possible.

One small note about the program, we had invited a U.S. researcher named Christopher Plowe, who is the Founding Chairman of the American Society of Tropical Medicine and Hygiene, and he was planning to come but is unable to.

He works in Africa and does research on malaria but he had a skiing accident and had to have some surgery so he will not be with us at this meeting

but said he would join us for the February meeting so the panel -- the second panel of the morning is short by one person.

The memorandum that was sent to you and is in the briefing book essentially describes everything and I will just very quickly walk through it.

If you will recall, at the December meeting we circulated some outrageous propositions that we asked you to respond to and, indeed, you found them outrageous, and there was a lot of good discussion. Based on that discussion we prepared the document that is now a narrative document but embedded in it are findings and recommendations relating to the choice of a research design.

So the -- I forgot what tab that is at. Alice can help me. That is at -- the title is "Choosing a Research Design," 2D, and that is now a fleshed out version. It has different versions of those propositions that you saw in December, much more nuanced than the ones that we presented in December, and it provides the accompanying text, which is

intended to explain, if not also to justify the findings and the recommendations.

So we have set aside time this afternoon to discuss that. That will take place following the session on the oversight project and the break that follows that and we have set aside that time. So if you have not looked at it yet in detail, maybe during the lunch or some of the breaks you could again familiarize yourself with that because we would like feedback on that part.

Also in the briefing book is the -- a slightly revised findings and recommendations on informed consent. We are not going to discuss that at this meeting. We thank those of you who have responded in the past and others continue to respond. We have made some, as this memo says, we have made a few changes following some comments and suggestions from Bernie and Larry and Harold, and we will continue to work on that but it is premature to discuss it further since there is not much that is terribly new.

The main topic for this meeting has the

uninformative title "Potential Recommendations for Chapter Four," but the more informative title is "Obligations to Research Subjects, Communities and Countries." That is what the chapter will be entitled.

Once again we have prepared this in the form of relatively brief or desperately brief propositions and the discussion on these will form the basis for what we will write with accompanying text and explanation.

So that is basically what is there for our discussion and the panelists -- the two panels for this morning and the one speaker this afternoon will be introduced in due time.

DR. SHAPIRO: Thank you.

I would also like to point out that in the material, I think, at your places there is a brief one-page chapter by chapter description of this report, which you might want to review some time during today or tomorrow or subsequently to see what the overall structure looks like or remind you, I

should say, what the overall structure looks like. That is in this NBAC folder that we all have at our place so I do not want to particularly discuss that now but just to ask you all to look at it and to give any -- if you have any reflections or thoughts about it to either give them to Eric or directly to Ruth, whatever seems most appropriate.

Are there any other questions for Ruth before we turn to our guests today?

Okay. Well, thank you very much.

I will turn to Bob Levine, who is here. I think you all know him. I feel it is almost redundant to introduce him. As you all know, he is a professor of medicine and long time contributor and, indeed, pioneer in many areas of bioethics.

Bob, it is very great to have you here today. Thank you very much for giving us your time. Let me turn the microphone over to you.

PANEL I: OBLIGATIONS TO SUBJECTS, COMMUNITIES AND COUNTRIES

ROBERT J. LEVINE, M.D.,

DR. LEVINE: Thank you very much, Harold.

It is an honor and a privilege to be here and I thank you for this opportunity to present my views on some of these matters.

I think that I was going to be given a remote control for the projector unless you would prefer to do it from there.

In my brief presentation I am going to take up obligations to subjects, communities and countries. My initial focus will be on individual subjects and I hope you will bear with me on this because I hope to show that this is -- this will lead us into a consideration of obligations to communities and countries because I see it all as one seamless web.

Let's see if I get lucky with this machine.

(Slide.)

Yes.

I am going to begin by looking at the now notorious Article II.3 from the Declaration of Helsinki. This, I think, mistaken article has been

the grounding of much of the criticism that has been heard in the last two or three years of international research activities.

I believe that a focus on what is wrong with this article will lead us to an understanding of our obligations to research subjects, communities and countries.

First, I want to consider what is wrong with this article? What does it forbid?

(Slide.)

A literal -- a strict interpretation of this article -- I was going to say a literal interpretation but how else can one interpret words -- a strict interpretation of this article would forbid all new therapies for any condition for which there is an existing therapy.

The reason for this is that you cannot try out a new treatment on somebody who is getting the existing treatment or you will not know what is the cause of any observed response. This means then that we would not have been able to withhold belladonna

alkaloids in order to try out the now standard histamine 2 receptor antagonists.

It also means that the treatment that the development of antihypertensive drugs would have stopped with a demonstration of the efficacy of ganglionic blockade and physicians who are as old as I am can remember what a mess using ganglionic blockers was for the treatment of hypertension.

In fact, one might even argue that you could not develop ganglionic blockers because you would have to give everybody the rice diet.

(Slide.)

Another category of activities forbidden by Article II.3 is placebo controls in clinical trials in which there is virtually no risk from withholding the best proven therapy. Trials of new analgesics, hypnotics, anti-anxiety drugs, these are all routinely placebo controlled, and I do not think any knowledgeable person would ever insist that these be compared with the best proven standard therapy.

But to go beyond into a field where there is

some risk from withholding treatment, although a vanishingly small amount of risk given the conditions in which we try these drugs out, in the field of antihypertensives and in the field of hypoglycemic drugs, these are all generally placebo controlled.

I think an insistence of providing the best proven standard therapy would vastly decrease the efficiency and increase the expense of these trials, and in exchange for that you would get a negligible increment in safety for the research subjects.

(Slide.)

The third category is the one that, I believe, is most controversial in connection with international clinical trials. Article II.3 would forbid research designed to develop for use in resource poor countries relatively inexpensive therapies used in industrialized countries.

As an example as a case study of this I am going to speak briefly about the short duration AZT trials in developing countries. These were placebo controlled.

(Slide.)

But first I want to digress into why do we find this and other surprising requirements in the Declaration of Helsinki.

I think this is a verbatim quote from the text of the CIOMS 1993 document which points out that the Declaration of Helsinki does not provide guidance for controlled clinical trials. Rather it assures the freedom of the physician to use a new diagnostic or therapeutic measure if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

In other words, what the World Medical Association developed is a document which provides standards for what we in the United States call "compassionate use" of investigational new therapies and that is not at all what we need to provide guidance for the conduct of clinical trials.

Now to the case study I said I would offer.

(Slide.)

At the time the short duration AZT regimen

trials were begun the clear best proven therapeutic method, the standard in industrialized countries, was the so-called 076 regimen. Administration of this regimen produced a 67 percent reduction in the rate of transmission of HIV from mother to baby. The cost of this treatment was approximately $800 per women.

(Slide.)

Now why can't you use the 076 regimen in developing countries? Well, first, the cost is prohibitive. $800 buys only the chemicals, not one other thing. And to put this in perspective, the -- about the top annual per capita health expenditure in Sub-Sahara and African countries is about $10 per capita each year. So the chemicals for the 076 regimen cost 80 times the annual per capita health expenditure in these countries.

Also, the traditions of prenatal care in these countries is incompatible with the 076 regimen. Women simply do not seek out prenatal care early enough to begin the standard 076 regimen of AZT. Another point is that in the 076 regimen the AZT is

given intravenously during labor and in most of the countries in which the short duration trials were carried out intravenous administration of anything is available only in major hospitals in the major cities. This would not be a way to address the needs of the population at large.

Finally and perhaps most importantly, in these countries women breast feed their babies. They do this even if they know they are HIV infected. The reason is they are advised to do this by public health authorities. Why is this? Well, first, they have no formula to use as an alternative. Well, we could provide them with formula.

However, when you have formula you have got to mix it with water and the local water supply in these countries is probably even more deadly to newborn infants than HIV infected breast milk. The rate of transmission from breast feeding is about 14 percent but we know from Sub-Sahara and African countries that the rate of death from infant diarrhea is at least four million babies per year. I mean,

that is what is reported to the World Health Organization.

And for all these reasons we simply cannot use the 076 regimen in these countries. Therefore, it was necessary for these countries to try to discover an effective prevention of perinatal HIV transmission that, one, they could afford and, two, might work.

(Slide.)

Now, as we consider what the best proven therapy standard should be, we have to wonder whether we are referring to the best therapy available anywhere in the world or whether instead we are talking about the standard that prevails in the host country.

I think we can find the beginning of the analysis by looking at the CIOMS International Ethical Guidelines.

(Slide.)

In these guidelines we find these two standards which I believe are far greater, far more powerful defenses against exploitation of people in

resource poor countries than the ones we most typically talk about, things like informed consent.

What it calls for is that the research goals must be responsive to the health needs as well as to the priorities of the host community or country and, as a corollary to that, there is another standard, which says that any product developed will be made reasonably available to the inhabitants of the host country.

(Slide.)

Now I am going to leap ahead to some preliminary conclusions and I do not have time to provide the full argument for them. This can be found in the three articles that I sent to you that arrived here too late to be included in the briefing book and for that you have my apologies.

I conclude that the initiation of a research project is not the same as the establishment of an entitlement. I also conclude that the relevant standard is the one that prevails in the host country.

(Slide.)

What we are seeing in the international guideline development scene is the emergence of a new ethical standard. I am going to talk about it under the rubric "highest attainable and sustainable therapy standard." This name is likely to change with the passage of time and I want to tell you a little bit about what this means.

(Slide.)

What do we mean by "sustainable?" What we mean is that there is a reasonable expectation that the therapy could be continued in the host country after the extra resources of the research program are no longer available. It does no good to develop therapies that the host country cannot possibly continue.

As one commentator from Thailand put it eloquently, "You come in here and you build us a Rolls Royce and then you go away and we cannot even afford the gasoline."

(Slide.)

Why should it be sustainable? Because this is the only way to meet the two standards of CIOMS. This is the way to be responsive to the continuing health needs of the host country and it is only sustainable therapies that we can assume will be made reasonably available to the residents of the host country.

(Slide.)

What is the meaning of "highest attainable?" The meaning of this is that you cannot merely say, "Well, we are going to provide the therapy these people get anyway." This therapy could be woefully inadequate simply due to neglectful policies.

What we are expecting in the highest attainable portion of this standard is that one will do -- or that the sponsors and investigators and the officials in the host country will get together and do the best they can do.

One note of caution, though. If you go too far with this you can change the setting to the extent that the data developed from the clinical trial are no

longer relevant to the host country.

One example of this would be what would happen if in a field trial of an HIV preventive vaccine we provided post exposure prophylaxis to anyone who is exposed to HIV infection. That is a standard, more or less a standard, for health care workers in the United States now.

It is certainly not sustainable but if you were to provide this during a field trial of HIV preventive vaccine where the outcome measures are whether or not one develops disease, providing post-exposure prophylaxis would distort the data to the extent that you would have no idea as to what to expect when you use the vaccine in the country. It would, in effect, erase all of your outcome measures.

One final comment is that for those who argue that we should be providing the 076 regimen to the control group in clinical trials of new therapies to reduce perinatal HIV transmission, the arguments have been very skimpy. What they have neglected to reflect or accommodate is it is not merely the matter of

buying $800 per woman for buying the chemicals.

You would also -- in order to make these chemicals work -- you would also have to change the pattern of prenatal -- seeking prenatal medical attention in these countries. You would also have to make facilities for intravenous administration of AZT or of anything available throughout the country.

You would also have to clean up the water supply in the country so that you could provide a meaningful alternative to breast feeding. I have not seen anyone who has attacked the placebo control trials address the implications of that.

Now, in conclusion, I want to say that it is necessary to acknowledge that there are great imbalances in the distribution of wealth across the nations of the world. There are huge imbalances. The resource-poor countries cannot possibly afford what we in the industrialized countries consider standard medical therapy.

The resource poor countries must be enabled to develop treatments and preventions that they can

afford and also treatments and preventions that are responsive to the conditions in their country.

We should try very hard to refrain from developing guidelines that would obstruct the efforts of investigators and sponsors in industrialized countries from helping the resource-poor countries in their quest for affordable and effective and safe therapies and preventions.

Thank you very much.

DR. SHAPIRO: Bob, thank you very much and let me welcome Professor Faden.

You came in at exactly the right time despite the traffic. I apologize for exposing you to that today.

But I want to save most questions for later because I want to turn to Professor Faden in a moment but if there are some questions that are short, we could take them now. And let me remind anybody who wants to speak, you have to press this button and get a red signal on your microphone.

Larry?

DR. MIIKE: I just wanted to ask you, Dr. Levine, the last point that you made about if you were to give best available therapy to the control group in the AZT trials you would have to change the whole health system. But isn't the point that you could do that for the control group itself without -- because you sort of leap from providing best available care to the control group to best available care to the whole population.

DR. LEVINE: Thank you for that opportunity to clarify. Yes, of course, we could provide the best available therapy for the control group. This would then present us with a variety of new problems. The only new problem that I mentioned so far is that by doing that you would render the data utterly irrelevant to the needs and priorities of the host country.

They do not need to know whether the short duration regimen is better than the 076 regimen. What they really need to know is whether it is better than what they already have and what they already have is

no antiretroviral therapy.

Another couple of points that I did not mention is that if you provide the 076 regimen to anybody in the clinical trial and if you think -- well, this would present, I should think, overwhelming pressures for people to enroll in the clinical trial. They are going to get something that they could not get anywhere in the resource-poor part of the world simply by enrolling in the clinical trial. This is one of the reasons that I presented with that argument my -- one of my conclusions that establishment of a research program is not the same as the establishment of an entitlement.

Thank you.

DR. SHAPIRO: Let me take one more question now and we will take the other questions later.

Alex?

PROF. CAPRON: There is clearly a fundamental tension here and I wondered whether you have any advice for us about the mechanism by which decisions could be reached which would have the greatest

likelihood of being ethically justifiable because the argument can be given as to what the trade-off is between having something which is realistic for the country involved without opening the door to such a strong incentive to export dangerous research to countries where the existing health system is so inadequate that people could conduct the research there very cheaply and have that incentive, and where the likelihood that people would desperately sign up for even the most remote chance of having some benefit makes consent so doubtful.

So I wonder if you have any sense of what kinds of mechanisms would be most likely to counteract those dangers and yield results which people of good conscience could say are likely to have avoided that trap while also avoiding the trap of developing therapies that have no point for the country and which are in another way almost as bad.

DR. LEVINE: Thank you, Alex. That is a question that calls for something other than a brief answer. I will begin by saying that I have no way to

assure that all of those important goals will be accomplished. I think, though, that one way to avoid exporting research that is too dangerous to be conducted in the United States but which is oriented towards developing products for marketing in the industrialized countries is the standard that already exists in CIOMS.

You have to have something that is responsive to the health needs of that country. It has to be responsive to the priorities that have been established by proper officials within that country and at the end of the day you have to make it reasonably available.

This distinguishes it from the early studies where we would do many Phase I studies in developing countries because it was cheap and because you were not hassled by the regulatory apparatus that is more typical of the industrialized countries.

Apart from that, I think all you can do is to state your criteria for justification and state your procedures for seeing to it that all research is

justified according to these criteria. The criteria specified in CIOMS, which as you know is undergoing revision right now, are that we have something like IRB's -- we call it Research Ethics Committees -- in the country of the sponsor as well as in the host country.

Part of the obligation of launching a research activity in a host country is that you would contribute to the capacity of that country to carry out its own ethical review and its own scientific review as well as its own science in the future.

Now when you resort to a procedural fix -- I should say this to a lawyer -- what you do is you present your standards and you get together a group of people who seem likely to be able to achieve the purposes of the standards and then they give you a decision and that decision is made available publicly.

If anybody decided to exploit people in these countries in a big way, I think the decision would be subject to scrutiny, to criticism. Just like the

current IRB situation in the United States, there is nothing that gives us a guarantee that one IRB will not make a really inane decision but once the decision gets out there before the public we expect that there would be criticism of such a decision.

PROF. CAPRON: Can I just have a brief follow-up?

I -- the first part of your answer suggested to me that you were looking for something that was more transparent than the present IRB system. I mean, the present IRB's do not now in any significant way communicate with the public and what goes on in IRB's is --they meet behind closed doors. Their results are not at least at my university publicly posted or whatever in any way. The individual researcher knows the protocol has been approved and I suppose if someone had some inquiry they could address it to the chair of the IRB or something but it is not a very transparent system, in fact.

And I took your first answer to be something that was more transparent where a process goes on and

was I correct in understanding that, that you would like this to be -- or do you think that there are too many problems with that? I am not trying to put words in your mouth. That is what I thought I was hearing you say.

DR. LEVINE: Well, in part, I think this reflects a difference in our perceptions. The actual process of IRB review and approval or disapproval is not carried out in public at most institutions. What is made publicly available is the result.

The results of the research are published in journals and they are available to the public and in the course of the public's studying the results of the research they would be able to detect most or many ethical improprieties and criticize them.

I mean, the paradigm case was Beecher's studies of what he ended up calling "questionably ethical research" that was published in standard -- actually in the leading medical and scientific journals.

Another point is that in the mid-1970's while

the National Commission was debating whether or not IRB's should carry out their activities in public, several IRB's -- well, many IRB's and state universities were required by state law to open up their meetings to the public.

I cannot really comment on that experience. I can comment, though, on the experience at one private university and that is Yale. We opened our meetings to the public and early on we had visitors from across the continent. We had philosophers. We had legislators. We had journalists. And after about a year we had nobody because they found that we were not discussing Tuskegee or Willowbrook every evening. Much of what we were discussing was brutally dull and they could not find any stories for their newspapers in it.

What can I -- right now I think it is -- the only time I have a visitor at a meeting is that -- is when a colleague from some other institution is visiting me anyhow and says do you mind if I sit in on your meeting.

The first meeting in February we are going to have a whole -- we are going to have about half of the newly established Research Ethics Committee from St. Petersburg State University in Russia sit in on one of our meetings but this is an attempt to demonstrate how committee meetings are carried out. I think they already know that they are dull.

Thank you.

DR. SHAPIRO: Thank you.

I want to turn now to Professor Faden, who is Professor of Biomedical Ethics and Executive Director of the Bioethics Institute at Johns Hopkins.

Welcome. Thank you very much for coming today. We look forward to your remarks.

RUTH R. FADEN, Ph.D., M.P.H.,

THE BIOETHICS INSTITUTE, THE JOHNS HOPKINS

DR. FADEN: Thank you. I want to apologize for being late. It is very frustrating to me. Many of you know I live in Montgomery County and I commute sometimes to Baltimore and sometimes to D.C. and it always is very distressing when the commute to D.C. is

longer than the commute to Baltimore. This was one of those days and I should know better because I have done it so many times. I allotted an hour-and-a-half and it did not do it so, thankfully, Bob was here on time and that is one of the advantages of having speakers from out of town. They usually get in the night before when they have a 9:00 o'clock session.

Thank you, Bob.

My apologies to the Commission.

I am afraid that my comments are going to be a little frustrating because -- well, maybe not to everybody. Hearing the tail end of Bob's, I have tailored -- I have tailored my comments to more theoretical considerations and I am happy to entertain very practical -- my views about very practical dimensions of how we should be thinking about these problems in the discussion with the Commission but my comments are structured around some more general questions in research ethics that underlie, I think, some of the controversy in terms of international research ethics.

I was asked to talk about the obligations of researchers to subjects and sponsors to subjects, and then of sponsors to others, and I thought -- I did not know how much thought went into the forming of the question but I thought it was interesting that there was no researchers to others. It was researchers to subjects, sponsors to subjects, and then sponsors to others. I would like to return to that in a little bit.

For right now I want to not make a distinction between the obligations of researchers to subjects and sponsors to subjects and we can go back to that later but generally talk about obligations to subjects initially and then switch to where it is or how it is that we get obligations to others other than subjects.

In terms of the kinds of obligations we generally talk about, we talk about obligations with respect to questions of human dignity and obligations with respect to welfare and justice.

I am assuming that most of the focus of the

discussion at this point is residing more on issues of welfare and justice but I want to just say a couple of comments about obligations with respect to dignity. This is the beyond consent part of the obligation.

I am very concerned and I know that others here around the Commission table share my concern about questions of voice and standing in the context of all research but particularly with respect to international research ethics. I am very concerned about how it is that we recognize and respect the dignity of potential subjects in terms of questions of both political authority and political legitimacy, basic human rights questions, as well as questions of power and oppression in the context of social structures and cultural practices.

I think that my own experience in research ethics is that we have absolutely no capacity for thinking about these issues and no structures for dealing with them. It is essentially impossible for the IRB at -- I will speak for my place -- the IRB at the School of Public Health at Hopkins or for the IRB

at the School of Medicine at Hopkins to make political human rights judgments about the legitimacy of particular political authorities at medical establishments. It has become a matter of deep frustration as we have had, for example, requests to do research in countries like Burma. How are we to understand what that would mean in terms of the obligations of the IRB or even in terms of more basic questions of research ethics?

We also are always and continuously struggling with questions of how to integrate what are presented as deeply rooted cultural practices and I am looking, of course, at Ruth Macklin who has written so much on this question but we continue to struggle with how to understand the claims about embedded differentials in power and counter claims about oppression and violations of human rights.

These, I think, are very basic problems in understanding obligations we owe to subjects that get often quite lost in larger debates about placebo controlled clinical trials that kind of are captured

at the national -- in the international attention. Put that to the side for a moment, not that it should be put to the side but put on the table and go on in the short amount of time that I have.

In terms of talking about obligations to subjects that reside in either kind of a welfarist or justice construction, most of, I think, us in research ethics have historically focused on kind of outcomes, the outcomes of the research, how it will turn out in the end, and a kind of minimalist requirement that we have had in place for forever was at the very least the subject should not be made worse off by virtue of their participation in the research. That is the pattern of outcomes should not disturbed by virtue of -- at the very least by virtue of the researcher being present and the person functioning as a subject.

There are at least two kinds of justifications for why we owe something more to subjects of research than merely not making them worse off.

One is an argument that has to do with the

fact that there is surely some burden associated with participating in research. Otherwise we would not be worried about the activity in quite the way that we are and if there is, indeed, some burden that is imposed on research subjects.

And by this I mean something more than the imposition of risk of which -- that would constitute part of the burden but there is some sort of burden associated and that burden is undertaken on the part of the research subject at least, in part, so as to benefit the rest of us then surely there ought to be some sort of compensation for that burden and one way of interpreting that compensation is if the person should be left better off by virtue of participation in the research.

We can have a whole discussion of what that would mean but it would lead towards some sort of an understanding that says something is owed to the research subject that is greater than merely not leaving them worse than when we found them or leaving them the same as when we found them.

There is another line of argument which I am very attracted to that is more relational that could serve as a structure for grounding why we owe something more to the research subject and it has to do with recognizing that there is some moral significance to relationships and to even something as simple as proximity, that there is something about the fact that when a person is a research subject that it transforms the relation of either the investigator, the researcher and/or the sponsor, and I would love to talk with this group about how you would see this, to the subject. That is we can have all kinds of accounts of what generally we owe, each of us, or what this nation owes to other nations with respect to the tremendous global inequalities that Bob has already referenced to the fact that many people live in the basis kind of poverty and we live in very extravagant affluence.

However, we think about that, when we have a personal relationship we stand in relation to that person in some respect, does it change? Audit -- does

it change? Does it change in ways that are relevant to the research context?

I hear that view expressed often from people who are working as investigators and as research workers and even as sponsors of research, particularly after a site visit rather than before a site visit. You cannot leave the place the way you found it. Once you have been there it changes something and it is not merely a psychological phenomenon I would argue. I think it changes the moral landscape, the fact that you stand in relation to someone now in a way in which previously you stood only to a group.

Now let's assume that we had resolved something about what is owed to research subjects such that we got some kind of consensus and, hopefully, your deliberations will provide guidance here as to what it is, in fact, either the sponsor, the researcher or the two together owe to the research subject.

What I want to submit to you is that would not solve the problem of exploitation because

the problem of exploitation is situated in a wider social and political context.

What I mean by that is, let's say we could construct a situation in which we provided benefits, whether they were Western Standard of Care or not, okay, benefits to research subjects that seemed from the perspective of the subjects and from the perspective of the investigators and the sponsors, and from the perspective of research committees and political institutions seemed to be a fair and appropriate compensation for the burdens of research or an appropriate response to the relational demands of the researcher-subject situation or the sponsor-subject situation.

You could still step back and say but this still constitutes exploitation because the background conditions of the research subjects are so disadvantaged that even in constructing a compensatory or relational response you have still taken unfair advantage of the situations in which these people sit.

Of course everything turns on what

constitutes unfair advantage.

I came to this frustrating -- and looking at some of the work that Tom Beecham and I had done years ago trying to unpack exploitation and look at the question of welcome versus unwelcome offers, and at that point years ago we had gone down a path in which we suggested, well, if an offer was welcomed by a person, even a person in disadvantaged background conditions, then perhaps you could construct an argument that that was not exploitive because the person welcomed the offer even if their background situations are disadvantaging.

And over the years I have come to think that that response is inadequate because you can imagine many circumstances, indeed, where people would welcome the opportunity to be research subjects that we would consider to be problematic at best.

So now the problem becomes why is it problematic. I have had extensive discussions particularly with our students at the School of Public Health and at the School of Medicine who do research

in developing countries or who are from themselves in developing countries, and I use the Nike factory example.

We all start with, well, okay, it would be terrible to go into the Gambia, for example, where, in fact, there is a tremendous research enterprise and offer them all kinds of incentives so that they would set up research -- clinical research facilities in the Gambia and, you know, it would be great. It would be fabulous.

It would put money into the economy and there would be hospitals built, but the products that would be developed and the interventions that would be treated are very unlikely to end up ever having practical widespread use in that part of the Africa. The students immediately respond, "Well, that would be awful. That would be terrible." And then I go to the Nike shoe factory.

Well, okay, so what if it is the Nike shoe factory that comes in and the conditions are far worse? You can spin out -- we do not have the time

today. You can sort of all spin it out and the students are always struck by this problem.

Well, it would be really bad but I guess we would not want to -- especially people from Africa concerned about development and economic growth in the future do not want to stop the Nike shoe factory coming in with some constraints. You know, we set out minimum labor conditions that are far worse than they are in the United States but far better than exist in many countries in the world. And we set up minimum wages which are pitiful compared to the United States but far better than generally exist, and working conditions, and so on.

And for some reason ultimately most of my students will end up saying, "Okay. The Nike shoe factory is just different from having a bunch of people come in and stick needles in them and draw samples from them and cut them up. It is just different." I even hold the mortality rates constant, everything is held constant.

And so what I throw out for consideration is

that there, is something special about the enterprise of research involving human subjects that has to do with really foundational concerns about the uses of the human body and the human spirit that differentiate it from the kinds of understandings of what would even constitute nonexploited international labor practices in kind of reasonable market conditions.

And these kinds of questions have almost nothing to do with the questions of whether owed to particular research subjects but have an awful lot to do with understanding the ethics of international research.

Now there is another part of this which is if global inequities are at the root of all of the problems we are having in research ethics -- well, it is global inequities that are at the root of all of the problems that we are having in terms of understanding the world generally, including things like a Nike shoe factory in the Gambia versus a research -- clinical research facility say that Ciba-Geigy wants to set up in the Gambia and kind of what

is the difference.

Finally, I want to ask a question and the question is where do we get this obligation to communities when we talk about the ethics of research involving human subjects in terms of international research but obviously in terms of domestic research as well.

If you take the classical paradigm of research in -- within one country and -- I do not know, let's make it a clinical trial and a person is selected from a pool of people because of their relevant medical characteristics, the person agrees, and blah, blah, blah, and the research is reviewed and so on. We do not generally have a discussion of what is owed back to that person's community.

We do not think even about whether that person stands in relation to a community. We talk about the research subject. Part of why we are having so much trouble with this is that our whole traditions of research ethics have been situated in a relationship or an understanding which is focused on

the subject as an individual, the human subject as an individual, and we have not really considered until very recently whether any obligations accrue to the communities from which subjects come.

Now we did have deep concerns that have a long history about exploitation in the sense of selecting subjects from particularly vulnerable communities. Certainly that is right. There has been that tradition for a very long time but here what I am talking about is let's assume that otherwise the research is not exploitive. We then generally do not talk about obligations to the communities from which the individuals' sit.

Now I am not saying that that is right. I am just saying that it is kind of an interesting observation that we have kind of turned this around and one of the things that has occurred to me a lot lately is that obligations to individual subjects may stand in conflict with obligations to communities.

This I have heard very much from my colleagues who do work in the developing world where

they would be happy to construct a situation in which the duties to the particular research subjects were quite high. There is the obligations in terms of providing medical care during the course of the trial or for some period afterwards to the people who were their research subjects was quite high.

They would be quite comfortable. In fact, they would prefer it because of the human relational demands I made reference to earlier. They would actually feel more comfortable in a situation in which they could provide very high quality medical care to the people who are their subjects during the course of the trial or even for some period afterwards because they have a relationship to them and they would prefer that.

But from the perspective of constructing what would constitute a fair deal you could see a situation in which someone might want to propose, particularly from the perspective of the health authorities of a nation, a deal cut in which there is a lower level of benefit provided to a wider community, that is to say

we extend the benefits not only to the research subject but to the community from which the research subjects come at the expense of the research subjects who now receive less than they would have previously gotten and how would we think about that.

I will stop there. Thank you.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: Thank you very much for those very thoughtful remarks.

Let me turn to the Commissioners for questions either for Professor Faden or Professor Levine. Let me turn to members of the commission.

Alex?

PROF. CAPRON: One of the points that Bob mentioned which is a standard part of the litany these days is building up the capacity of the country and I suppose that that -- both from the scientific and the ethical side is an example of that kind of conflict that you were just referring to because building up that capacity may very well have benefits for the country and its whole population but the immediate

benefits are going to flow to the elite of the country, the people who are, in addition to already being professionally qualified as scientists or physicians, to have more facilities available to them, to have more opportunity to increase their knowledge, and their ability to do research who are already the educated people who will be the super structure of that ethical review process and so forth.

And again I ask you is there any process? Bob made some passing reference to this being, I suppose, a lawyer's approach but it does seem to me that we understand the dilemma here and it seems to me that no analysis of the dilemma is going to make it disappear.

The tensions that exist are going to be there and so we are going to have to say in the end what is a process which is most likely to overcome that.

Stepping then from the context of the process for reviewing an individual research project to the broader one of setting this framework, is there a process which you believe is likely to yield results

which are, in fact, ethically defensible and which are likely to be accepted as such in terms of this balancing which you nicely pointed out to us of the western -- the traditional orientation towards obligations to subjects versus this more amorphus concern of obligations to community and country?

DR. FADEN: I agree with you that we have to come up with procedures that we at least think have a reasonable likelihood of giving us outcomes we can accept as ethically tolerable. I do not agree with you that more analysis might not help us figure out better what the process should look like.

PROF. CAPRON: I did not mean to say that we should not --

DR. FADEN: Okay.

PROF. CAPRON: -- analyze. I just have a sense that that -- the tensions that we are talking about --

DR. FADEN: Yes.

PROF. CAPRON: -- are inevitable and, I mean, I agree with Bob's comment. When the pill, the

contraceptive pill, was first tested in Puerto Rico there was no thought that this was -- the question of unwanted pregnancies was unique to Puerto Rico nor that that would be the major market for --

DR. FADEN: Right.

PROF. CAPRON: -- the pills once developed. Right? I mean, so I mean you can -- there are certain categories of research but there are things where we say, "Look, we are dealing with malarial research or something."

DR. FADEN: Sure.

PROF. CAPRON: Or pandemic HIV --

DR. FADEN: Right.

PROF. CAPRON: -- where there are countries -- but there are going to be some things that come out of it. You know, are we going to be inclined to take the research over there? If the short arm or the short regimen, whatever it is called, the short regimen of the --

DR. _____: Short duration.

PROF. CAPRON: -- short duration AZT thing

had worked spectacularly, we would never have said, well, we cannot now use it in the United States or Western Europe having discovered that it is --

DR. FADEN: As good as, yes.

PROF. CAPRON: -- has excellent outcomes and costs a tenth as much. But the thought was, well, we have something that works --

DR. FADEN: Right.

PROF. CAPRON: -- here and we have got to go do something there because what we do for ourselves will not work there.

DR. FADEN: Let me suggest at least the beginning of an answer to the procedural questions. I am not sure how to do this any better than anybody else is and some people, I think, have been ahead of me on thinking through the practical procedural parts by far but it seems to me at minimum that we need some way of distinguishing both in terms of guidelines and procedurally between the sort of structurally okay background conditions for proceeding and the particulars of a specific research project.

Right now we bundle the two. That is part of the frustration, I think. We combine the procedural safeguards, guidelines that ought to be in place to address whether doing business in the Gambia or Burma or Thailand or Finland is okay or what needs to happen to make it okay, including capacity building questions, including questions of addressing human rights.

A whole range of issues that really have nothing to do with the particulars of a special -- this particular trial that we are talking about. We need some structure and procedure that addresses that and then a related structure that goes proposed research project by proposed research project.

Now whether that can be -- you know, how to arrange that into what the appropriate fora are, I have got some thoughts but they are very inchoate. I would imagine that Bob has more developed ones that go a little bit further.

You need, I think, both more developed guidance than we have now about the conditions under

which it is okay to do collaborative research and you want to then test context by context so it gets complicated but it is -- because in some countries you cannot even do this at the national level. You may have to do it by the province or I mean think about a country of the size of -- well, it matters a lot what country you are talking about.

So you come up with guidance that -- guidelines and standards and so on that will help around these -- what I have been doing is trying to come up with a distinction between the structural considerations, the structural and political considerations, and the traditional research ethics questions.

I am repeating myself here, Alex. I actually do not have any very particular things to say about having set this up but what I do know is the IRB system is not capable of handling this, that it has to be internationalized, that it has to be set in the host country or in collections of host countries, and that we need to really radically alter how we work

this through to help the investigators here in the states as well.

DR. SHAPIRO: Bob, do you have something you wanted to say on this issue?

DR. LEVINE: Thank you.

First, let me just say I did not say -- I did not mean to imply that setting up procedural safeguards was a lawyer's approach. I was saying that setting up procedural safeguards is something that I really probably did not need to explain to a lawyer but the procedural safeguards that have been established in the U.S. and internationally, a lot more than lawyers participated in their development.

But I want to comment on the community issue. Ruth Faden quite accurately points out that it is not part of our tradition to consider obligations to the community. There are several reasons for that.

I think it has a lot to do with the fact that in developing guidelines and regulations for research involving human subjects almost all of the focus until the mid 1970's was on principles that we might call

respect for persons and beneficence, or autonomy, or well-being, you know.

But it was in the mid 1970's that we began to take seriously ideas of justice and social justice. You see the beginnings of a development of a responsibility to the collective in the National Commission's recommendations for research involving prisoners.

They said, "You cannot do research in the prison unless you do all of these things. You have got to make it possible for them to have telephone access, for them to have medical attention, for them to have private rooms or solitary confinement or whatever."

But this is the beginning. It is a very rudimentary beginning. You see it developed much more fully in the children's report. You are not allowed to use children for research unless there is a reasonable expectation that the fruits of the research will be of benefit to a class of people called "children."

Then we were reminded even more sternly in connection with the development of the HIV pandemic. Early on we began to realize that doing things that seemed to assist individuals might inflict grievous harms on collectives. For example, in the early 1980's saying that one of the risk factors for HIV is that you might be from Haiti. We wiped out the Haitian tourist industry overnight. This served as a very strong wake up call.

Rather than continue my soliloquy I also want to say that now that we are sensitized to looking at problems associated with dealings with individuals embedded in communities then we go into the developing world and we find something that vanished from the United States probably towards the end of the 19th Century and that is real communities.

These are people -- Robert Bella's definition. They live in situations where the boundaries between public and private life are blurred. The doctor is not simply somebody in a white jacket who you see for a half hour once a year to get

a check-up. The doctor is also a member of your religious organization, marches side by side in the parade, somebody who has a spouse, children and so on. That is what a community is.

And as I referred to Robert Bella, he quite aptly points out that in the United States, particularly since World War II, the notion of community has vanished and what we now have is lifestyle enclaves where there are very, very thin sets of superficial rules and nothing binding people -- you know, like residential suburbs but you do not really know the other people in the suburb.

In any event, I think now that we are finding something that could properly be called communities in the resource-poor countries it is having a great effect on shaping our considerations and how to deal responsibly with them.

Thanks.

DR. SHAPIRO: Thank you.

Jim?

DR. CHILDRESS: Thank you, Ruth and Bob, very

much.

I am going to raise a two-part question. One that is more to Ruth and one that is more to Bob. In a way I think it is a version of the same question.

Let me just start with Ruth.

Ruth, you have focused on the relational model and setting in relation, and emphasized that as one thinks through that it has to do not only with psychological factors but also from your standpoint with moral significance as well.

And yet it is hard as we are thinking about obligations to know sort of how to specify that concern or sense for thinking about what researchers or sponsors should do because you really state it much more in terms of that sort of felt obligation as a result of the standing in relation.

So my question to you given that perspective is how one might go about giving more specificity to obligations is really in the context of setting out the kinds of standards that we think should govern at least U.S. participation in or conduct of research?

Okay. So that is my view.

Now let me put it to Bob the other way.

Bob essentially is focused much more on the kind of minimalist rules that set a kind of floor, a foundation for our work, but what I am not clear from Bob's standpoint is whether, for example, if we in the U.S. are thinking about sponsoring or conducting research, we might have some sense that this is really getting too close to exploitation even though it does not really violate the standards that have been agreed to internationally.

So I guess I would be interested in both of you thinking from your own presentations today about how you might relate those two dimensions.

DR. SHAPIRO: Ruth?

DR. FADEN: I think your question, Jim, very much resonates with my struggles on trying to sort of get clear on when I am thinking about obligations in the context of concerns about exploitation and when I am thinking about obligations in the context of considerations about the subjects who are the people

before us.

The latter is easier. Okay. The latter is easier and there, I think, in terms of specifying the nature of the obligation, I think at minimum, you throw away the standard that says it is okay as long as we do not leave people worse off. That is not adequate. Okay.

That -- so that gets gone and that I think is useful because at least in my exchanges with people when -- around these issues there are folks who hold out that that would be a minimalist but sometimes sufficient standard for considering the research ethically acceptable.

So you have got to do something more than merely leave them no worse off than they were before they became your research subject. Then how do you specify the obligation further and there, of course, they start to get a little lost but I would at the very least begin to construct it in the context of the nature of the research project itself and some research projects lend themselves to more available

answers than others.

For example -- and this happens all the time, and I know Bob can speak to this as much as -- better than I can actually, and that is there is often a very felt sense that basic primary medical care needs to be provided during the course of the trial.

Now sometimes that is both a humane response and a self-serving response because you want to keep people basically going during the course of the trial but quite apart from the combination of motivations that lie behind it. There is very often a genuine felt sense that basic medical care needs to be provided now -- basic primary medical care needs to be provided.

Now immediately we get into the standard of care debate that I am sure you have had ad nauseam in this group and we can begin to have those struggles as well but let's just start from saying that at very minimum you get rid of the no worse off than they would have been otherwise.

And then you move up to something that speaks

to some understanding of basic primary medical care during the course of the trial that might also include adequate nutrition, which is sometimes a consideration, and once again it is sometimes self-serving because you want the subjects to be well nourished.

It may also include certain obligations with respect to health education that is important to the basic well-being of the population that is the research subject pool and it may also include things like child care assistance and transportation, and things of that sort.

But I am not doing justice to a complicated question. I want to go to the flip over for a second before I get -- hear Bob's response.

On the exploitation question, I do not think we know enough to know how to guide people as to how to think about whether something is an instance of exploitation or not to say merely that it has to be a research project that fits with the national priorities and that it -- and the reasonable

availability standard, I think, does not get us far enough towards helping people think through whether something constitutes an instance of exploitation.

I do not have any brilliant suggestions so far. I have been working on it as to how to make that more specific or to provide it with more guidance but I know that one of the more telling considerations has to do with questions of timing and that is when there could be an expectation that whatever it is that might be the benefits of the trial would be available in the context of that particular country.

But my own thinking has gone much more recently in the direction of attempts to set up procedures that have to do with good faith agreements and understandings between the relevant parties before the work proceeds that specify what would constitute an acceptable nonexploitive context sufficiently detailed -- with sufficient detail so that you would know if you had failed.

My big concern is that we end up with sort of guidance of people say, oh, yes, this looks well, and

then the guidance is so ambiguous, so unspecific that afterwards truly reasonable people could disagree about whether the standards had been met or exploitation had occurred.

Somehow we need to have agreements in place in advance that are the kind that lend themselves to an interpretation afterwards as to whether they have been satisfied or not.

PROF. CHARO: Excuse me.

DR. SHAPIRO: Alta, we will get to you in just a second. Okay?

DR. FADEN: Hi, Alta.

DR. SHAPIRO: Bob, and then Alta, who seems to be getting anxious, and Bernie and Arturo and then Ruth wants to say something also.

DR. LEVINE: As I understand the question to me, it has to do with whether or not you could follow all the rules and still be exploiting people and that is -- is that it, Jim?

DR. CHILDRESS: That is part of it and that is whether we might have a sense of self-imposed

obligation or ideals that would lead us to say, well, just following those rules we have agreed to internationally would not be sufficient for our understanding of what would be appropriate moral participation in international research.

DR. LEVINE: I think we have to recognize the limitations of guidelines. I mean, you can specify certain types of behaviors that you hope people, in general, will adopt and adhere to but I have yet to see a coherent set of guidelines that says, "And while you are following all these rules it would behoove you to be decent people." Virtues do not fit well into regulations but one -- I think an awful lot of what Ruth is talking about has -- when she talks about such things as good faith agreements, we do hope that the researchers will be people of good faith but we cannot regulate that and we have to be alert to the possibility that some are not.

I think, also, we have to keep in mind as we develop all of our guidelines to protect people in developing countries from exploitation that this came

out loud and clear in the 1993 version of the CIOMS International Ethical Guidelines.

What came out even more loud and clear later was the people from the resource poor countries that say, "Where do you get off treating us so paternalistically? We have read your guidelines and we are alarmed by the fact that the guidelines for dealing with us are remarkably similar to the guidelines you developed for dealing with children. Maybe we are in the best position to determine what sorts of research can be done in our countries and under what circumstances."

I agree with Ruth that -- Ruth Faden that CIOMS does not go far enough. That is unmistakeably true and in recognition of that we are engaged in revising it to go a little further although I expect we still will not go far enough.

Ruth is concerned about a standard that says do not leave people worse off than you found them. It is an important criticism. That should not be the substantive standard for justification of research.

The statement in CIOMS that you should not leave people worse off than you found them is embedded in a document that says there are certain ways that you must leave people better off. You have to contribute to capacity building. You have to do this and that and the other thing, and incidently do not leave them worse off.

What did they have in mind? Well, one thing they had in mind was, as Ruth put it, you set up a program during the conduct of research to provide health care for the population you are drawing on for research subjects and when you set up this program that the resources that the host community previously put into health care are deployed elsewhere. The researchers are taking care of our health care.

And then at the end of the project the researchers go home, the health care facility, you know, begins to look like a Walmart in a shopping mall that is abandoned, and they have no resources at all for health care. That is one of the things that sponsors are exhorted to keep in mind when they are

admonished not to leave people worse off.

One final point, and that is the issue of good-faith agreements. All of the obligations for sponsors in the CIOMS document are stated in the form of prima facia rules that here is what you ought to do unless you can find an ethical reason to do something else and in the document it says because there can be uncertainties or differences in people's expectations it is necessary before you begin the project to reach agreements as to how you are going to interpret this standard or that standard.

This has become greatly strengthened in the U.N. AIDS guidance document. I am assuming now that it looks somewhat similar to what it looked like last time I saw it. They talk about what I think is a very valuable, not merely community consultation but community collaboration where everybody is involved in developing everything from the scientific design to the obligations for capacity building right from the earliest phases of development of the program.

Thank you.

DR. FADEN: May I --

DR. SHAPIRO: Ruth, yes, if it is short. We have got a lot of commissioners who want to speak.

DR. FADEN: Let me just -- two things really quickly. I do not want to sort of offend Bob by knocking the leaving people no worse off in the following historical sense: It is very important to recognize the history as he has indicated it and, indeed, there have been unfortunately situations in which people and communities have been left worse off.

The problem is that in emphasizing do not leave people worse off it sometimes stops there and I was not referring one way or the other to how to interpret CIOMS but rather to the recognition that that has now been burned in people's minds in many respects in the international context to the extent where it seems to take care of everything as long as we do not leave people worse off when we leave the country, leave them somehow with their infrastructure devastated.

What I am trying to do, and then just let me just articulate this one more second and then I will take the comments, what I am trying to do is find a way to think through how to separate questions of capacity building and infrastructure and human rights at a general level. The duties that fall into that category really cannot be worked out research project by research project.

I mean, if I had more time I would talk about if you want to sort of think through what the ethics of rich countries doing research with poor countries really require. It requires some transfer of resources from rich countries to poor countries that has to occur in a coherent and coordinated sense that is separate from the review of the particulars of this research trial and that clinical trial, and that drug study.

And I think part of our problem in not being able to move forward in the ethics of international research is we have not unbundled, we have not recognized that you cannot solve the structural parts

of the moral problem by a review process that goes project by project so that is what I was trying to articulate.

DR. SHAPIRO: Thank you.

I now have an even longer list of Commissioners who want to speak so I will ask everyone, if they can, to keep their remarks as short as possible.

Alta, let me turn to you from far away.

PROF. CHARO: Okay. Harold, I am sorry. It is hard to let you know I wanted to get put on the list without interrupting people.

Very short questions, one for each.

Bob, with regard to the placebo control trials, the example that you gave of the 076 trials is one in which the "best available" therapy or standard therapy was unworkable in that country but one can imagine situations where you want to test a new intervention as against a standard approach that is available but scientifically it is more efficient to test the new approach against a placebo.

Are you suggesting that in general the interests of scientific efficiency should permit such placebo control trials in these resource poor countries under exactly the same kinds of rules that we use here in the United States or in other developed countries or is there some kind of middle ground here about when placebos are appropriate and when the denial of standard therapy is appropriate?

DR. LEVINE: Should I answer and then she will ask Ruth a question?

DR. SHAPIRO: Yes, please answer that.

DR. LEVINE: Alta, thank you. If I could have planted a question I could not do better. I think that the relevant standard for any clinical trial is the standard that is called "clinical equipoise." However, I think the standard of clinical equipoise properly applies only in trials where there is a chance of injury to the research subject if the research subject is deprived of standard therapy.

That is why I am able to defend the standard in developed countries and industrialized countries of

doing placebo controlled trials of analgesics, of antianxiety drugs and so on.

So I would say that if you are working in a resource poor country and there is a standard therapy available in that country and you want to do a clinical trial that you could not justify the use of placebo on grounds merely of efficiency. You would have to measure up to the same standards that apply in an industrialized country and that is you can use the placebo control if this does not expose the control group to more than negligible risk of enduring injury.

PROF. CHARO: Thank you.

DR. LEVINE: Thank you very much.

PROF. CHARO: And second, and I appreciate your patience with me, Ruth, on the question of the definitions and understandings of exploitation, I am sure you are familiar with the writings of Wertheimer and others who have suggested that an important element to this is to evaluate the justness of the background conditions that create this power imbalance.

In other words, a slave owner who says, "I will stop beating you if you will perform some terrible task" is exploiting a slave even if that terrible task is better than the beatings because the background condition is one that is fundamentally unjust and was, in fact, created by the very slave owner who is now using that as leverage to create a situation where a deal that, you know, is in the short-term better for the slave is nonetheless viewed as unjust.

So it strikes me that it is very hard to describe our notions of what is fundamentally exploitative and, therefore, ought to be avoided at all costs or at least ought to be minimized to the extent possible without actually addressing the degree to which those of us who are fortunate enough to live in the industrialized world want to take on some notion of moral responsibility for a wrong and that wrong being the phenomenal inequity in financial and health resources across the world.

If we think about it as something that is

fundamentally unjust or partly our own responsibility, it would make for a very strong argument that we should be doing as little research in these settings as possible even if it is in the short-term advantage of the participants or even of the country.

DR. FADEN: Alta, let me --

DR. SHAPIRO: Do you want to press your button?

DR. FADEN: I am sorry. I forgot to press the red button. Okay.

The two pieces in that way of analyzing exploitation, I think, the way you have said it -- the way Wertheimer sets it up, the way it is set up generally just make the moral life complicated but complicated in a way we cannot avoid. I guess where I am going on these issues is to the first part as you set it up. Are the background conditions unfair? Yes. Okay.

So then where all of the problem lies is on the second question if you use your slave owner example. Do we stand in some way like the slave

owner? Do we have any responsibility for the incredible maldistribution of wealth and power in the world? And I do not see how the answer cannot be yes but let's assume if you set it up and said, "Well, no, no, this is not my responsibility. We are just trying to do a research project," it seems to me that is to ignore some of the most basic moral truths of the way in which the world is set up at the moment.

What I do not buy is your conclusion, okay, that the response should be that we ought, therefore, not to do any research in the developing world because to do any would be obviously exploitive since the background conditions are unjust and since we bear some moral responsibility for them we, therefore -- I mean, the logic of that does not work for me and this is why it does not work for me.

There -- to not do research in the developing world would be in a sense to perpetuate and to widen the gap in inequality between the wealthy and the poor, between the advantaged and the disadvantaged in the world. That is what makes this whole thing so

idiomatic (sic). If it was simple, if we could simply say, "Yes, the background conditions are unjust; yes, we bear a responsibility. Therefore we should not take advantage of them," the answer is, yes, it is done. We just do not do any research in the Third World. We do not get involved in any way. We may have other obligations but we certainly do not do that but, in fact, to pull out would be only to widen the gap in, for example, life expectancy and quality of life and health between the poor and the rich which we ought not to do.

So now the problem becomes how do you construct conditions under which it is ethically acceptable given the fact that the background conditions are unjust and we bear responsibility for them --

PROF. CHARO: Ruth --

DR. FADEN: -- to proceed.

PROF. CHARO: -- I am sorry, Ruth, but I really did not mean to suggest that you never do research in these countries but what it really was

leading to was a kind of skepticism with which all these research proposals are approached. Many of the conditions that Bob Levine was outlining begin to address how one would answer that skeptical approach.

That is you start by saying, "Why in the world are you doing it there? Prove to me why you have to do it there. Prove to me why you have to do it this way and only if you can prove that to me are we going to approve this." So it is not that you never do it but that you do it with skepticism.

DR. FADEN: That is, of course, right. That is, of course, right but I would say that that is not sufficient. I think that if we are really going to address the problem of how to proceed morally given the whole analysis as you have laid it out there has to be -- and this is the part that is the most difficult politically to go forward with -- there has to be transfer of resources. There has to be a way to begin to address at least for those elements of the structures of governments and societies that bear most directly on research involving human subjects and on

narrowing the gap in health and burden of disease around the world there has to just be more transfer of resources in addition to a careful scrutiny research project by research project.

PROF. CHARO: Thank you.

DR. FADEN: Now whether that comes from the private sector or the public sector or some combination those are very, very large questions but to pretend as if we are not supposed to speak to those issues because that is technically not part of the paradigm for research involving human subjects is, I think, utterly inappropriate.

DR. SHAPIRO: Ruth, that is the Ruth up here?

DR. MACKLIN: Yes. I want to thank you both for the presentations and I have a brief question for each but I did want to also thank Ruth Faden for pointing out that the question which we framed did not make the distinction between researchers and sponsors and their obligations, and that may partly be because there was an assumption, possibly wrong, that researchers themselves would not have the resources to

be able to provide something following the trial but sponsors surely could so perhaps it was ill-framed and we failed to make the distinction.

My question to -- let me ask Bob first just in this order. You endorsed or appeared to endorse the CIOMS provision that suggests that the successful products or results of the research should be made reasonably available and, indeed, you used that -- following the research you used that as one of the justifying conditions for doing the research.

Could you give us your view of what -- elucidate briefly how you see reasonably to be understood in that sentence?

And I will just ask Ruth because my question is brief also.

You referred at several points to human rights. When you were talking about the background conditions you referred to exploitation, et cetera. You referred to human rights. Are you in speaking of human rights talking in the somewhat narrow but literally correct sense of the human rights that

appear and exist in the human rights instruments around the world or did you mean more broadly the way people tend to throw the terms around these days?

And if you meant it in the narrow because you already nodded that you did, it would help us perhaps not at this meeting but maybe if you are willing to do a little more work for us to point to the specific instruments and the provisions in them that you think are relevant to the human rights questions.

DR. SHAPIRO: Thank you.

Bob?

DR. LEVINE: What do we mean by "reasonably available?" I do not know. I should stop there but I want to say that those who know me well know that I will not.

I think this is going to be a judgment that will have to be worked out contextually but let me give you a scenario that Ruth Macklin and I and Alex Capron sat through, and that is what happens when you have a vaccine development program which is carried out in multiple countries, and you might do the Phase

I studies in two or three countries, and you might do the Phase II studies somewhere else, and you might do the Phase III studies somewhere else, and at the end of the day your vaccine does not work.

And then let's say you discover another vaccine and you try it out and repeat the scenario in three separate sets of countries and this time the vaccine works.

To whom must this vaccine be made reasonably available? Just the people who participated in the successful one or all of the people that participated in the full program of development nationwide or what about the countries that were not invited to participate in this?

Let's say you carry it out in the Gambia but you do not carry it out in Cote d'Ivoire or some other place in the neighborhood. Why should the citizens of Cote d'Ivoire be punished because they were not selected for participation in the trial?

And when I say I do not know the answer to your question, that is just one of the reasons that I

do not know. Thank you.

DR. SHAPIRO: Ruth, do you have any further comment on --

DR. MACKLIN: No.

DR. SHAPIRO: Okay. Thank you.

Bernie?

DR. LO: I want to thank both Bob and Ruth for their really useful presentations and I would like to ask Ruth if she would be so kind as to write up her remarks and let us read them. There is a lot for thought there. I know they are preliminary but I think it would help us to --

DR. _____: We get a transcript.

DR. LO: Well, I mean, I have read transcripts and somehow they do not quite seem to catch the intellectual --

DR. FADEN: Bernie, I will make you a deal. You give me the transcript and I will work on it.

DR. LO: Okay.

DR. FADEN: How would that be?

DR. LO: Okay.

DR. CASSELL: It is just as hard as starting from scratch.

(Laughter.)

DR. LO: But let me --

PROF. CAPRON: You can revise and extend your remarks.

DR. LO: -- both of you have been helpful in sort of giving us an appreciation of how even more complex it was when we first started thinking about it and I think you have both pointed out the sort of paradoxes and contradictions, and inherent tensions in what we are trying to do.

I want to sort of pursue that with this notion of what do we owe subjects leaving aside the communities for a while because one of the things that seems to happen is that there are lots of different strands that go into that and one strand is the obligation researchers feel as physicians to do less than they would be doing if they were jetted back to their home clinic in the U.S.

Another has to do with sort of a humanitarian

response to, you know, inequity, suffering, poverty, whatever. It seems to me what you do as part of the clinical trial to the control group has implications for whether the trial is interpretable as being relevant to the problems of the host country.

I mean, you could give interventions to the control group that would help them but it would change their quality of care so substantially that the results would no longer apply to the conditions -- the baseline conditions in the host country.

And, you know, I think there is an argument to be made that that is exploitation in the sense that you have not answered the question that would help them and that does not seem to me to satisfy, Ruth, the relational drive to do something for the people you have come in contact with and interacted with.

I wonder is there merit to thinking about trying to do the -- to fulfill your relational obligations in other ways? And it may be education, public health, things like that, building infrastructure. But to try and separate that out from

providing clinical care, which may sabotage the very scientific merit of answering a question that will make a difference in the host country.

DR. FADEN: Bernie, your point is well taken and, in fact, we have -- I have worked with colleagues on exactly that kind of tension and, of course, we have this history in the United States as well.

You know well the controversy years back about whether to provide safe sex education in the context of HIV vaccine development trials where we were struggling between on the one hand we ought to be advising people and they are our subjects especially -- we have a special relationship with them and we ought to make sure that they understand about safe sex practices but on the other hand if we slow down the rate at which they are going to acquire the infection as a consequence will be able to attend and understand whether it is the vaccine or the behavioral practices.

DR. LO: But the difference in efficiency versus making the results --

DR. FADEN: No, I understand. I am just -- I

understand that, in fact, the implications for the trial and the interpretability of the results would be different but some people argue that you might, in fact, have such a change in behavioral practices that it would look like the vaccine was protective or the people -- if, in fact, the groups somehow responded differently to the education.

But, yes, that is why I think it is very problematic in terms of interpreting what exactly -- when Jim asked me the question about specifying what it would mean to leave people somehow -- something beyond no worse off than when they started and in some contexts it may be that the way that has to be expressed so as to have meaningful and useful results to the country in which the work is being done is to extend care understood more broadly than in medical care at the same time.

And I know you have heard this from investigators or physicians as well, I have heard you say it, it is very hard in the context of basic primary care not to provide it even if the background

conditions are that, in fact, basic primary care is not widely available and that may have something to do with that other question that I was raising or that other precondition, you know, ought we really to be going in and doing research in contexts in which even the most basic primary medical care is not available. And should we not first at least have transfer of resources sufficient to ensure that that is the case.

So there are other responses to that like in the way Alta phrased it, do we have to go where, in fact, not even basic primary medical care is something that is -- can be considered available enough that it would not mess up the trial to make sure that during the course of the study everybody gets it.

DR. LO: Thank you.

DR. SHAPIRO: Arturo?

DR. BRITO: I, too, have some questions that -- the same type of question Ruth Macklin asked you, Bob, about reasonably available in the readings and the question that Ruth had raised before has given me some trouble but thank you for being so candid in

saying that you also have difficulty in how you define that.

This question is related to that but it is really for Ruth Faden. In theory, I agree about the minimalist view about no worse off and how inadequate that is. When we are talking about making things available or what is offered to the individuals, not the communities now, I would be concerned about at what point -- and see what your thoughts are on this -- at what point does it become coercive in and of itself to promise something to individuals in a resource poor country.

DR. FADEN: I think there is probably -- for every tough question in this area -- a point where you hit that double edge sword and this is one of them. One response that I often make to that challenge is the odds are that however you set it up, in many contexts there is not going to be a good reason to refuse. That is to say in many research projects, in fact it is a nonissue because even if you do not do a whole lot it is kind of attractive to be in the

research project.

So you start with that recognition which is why for so long now I think people have argued that focusing on individual consent will take you not very far towards addressing the moral problems that these kinds of research projects raise. That is not a sort of conceptual or theoretical response to your problem. You certainly could bump up against it.

What I am saying is you are usually already there. You almost always start out in a context in which unless the trial is very noxious or the people are very callous there are good reasons to participate in the research project from the perspective of the self-interest of the individual subject in many cases already.

DR. SHAPIRO: Thank you.

Let me turn to Eric now. Eric?

DR. CASSELL: I must say that as a clinician I always thought the best case of all was one where you could not figure out the answer what was wrong with somebody and I am not much clearer so I think the

lack of clarity alone makes me come to a conclusion. I do not know very much about most of the countries in which this kind of work is done but I do know one foreign country in which research would have been just as problematic as it is as say in Cote d'Ivoire and that is the 1950's United States.

If we were in 19 -- in whatever this is called, "ought-ought," and going back 50 years and saying, "Well, how would you do research in that community when the standard of care was this and so forth."

Well, we would have a lot of trouble with it and, in fact, people did have a lot of trouble with it and the ideals that were set forth did not seem to work very well and yet they were ideals and they were held out. And then gradually a system was developed so that the population became understood, both research and investigators understood what the ideals were.

And then we finally got to where we are now over a 50 year period so that when we go into another

country and expect to use our standards of research in that other country we get to -- it just does not work and I am pushed more and more to what Bob Levine says about depending on the people in the country where the research is being done.

And also understanding that they, too, will be educated over the course of this just as this strange country of 1950's United States became educated if I am told how great the inequities are, how fundamental injustice is present in those countries and that the fat cats who are making out in this research. Well, I come from a country that cannot provide medical care for one quarter of its population so I am not too moved by lack of justice in other countries being a reason for us not to do things but I do see this as somehow whatever we do has to set in motion the solution down the line.

I cannot hear the two of you come to anything where nobody knows more than the two of you. Coming -- well, that is okay. Maybe somebody does but I do not know their name.

(Laughter.)

DR. CASSELL: And the two of you cannot come to an ideal that -- you know, that you find no exceptions to so if that is the case that is the answer. What, in fact, do you do in the face of such uncertainty and what we mostly do in clinical settings is try to do no harm for the period of time when we know nothing and set in motion something that will get time to pass and build knowledge?

DR. SHAPIRO: Thank you.

DR. LEVINE: May I respond very briefly?

DR. SHAPIRO: Very briefly.

DR. LEVINE: I want to take exception to only one word and that is "ideals." I do not think that guidelines, regulations, ethical codes are a good vehicle for expressing ideals. Many of the documents developed in the past express ideals that we hope will aspire to and perhaps achieve in Eric's 50 year span. However, your guidelines have to be practical statements of what you expect people to do today. If they are put as ideals everyone knows you cannot do it

so it licenses the investigators to pick and choose which ones of your guidelines they want to follow.

Thank you.

DR. SHAPIRO: Thank you.

Diane?

DR. SCOTT-JONES: I have a question for Bob and a question for Ruth.

Bob, you shared with us an anecdote about a person from a developing country who found our international regulations to be paternalistic and your comment prompted me to think about how much we are missing the voices of the people in the developing countries.

In our next meeting we are scheduled to have a researcher from Haiti and a researcher from Brazil to speak before us. I was wondering if you have thoughts about how we might become more aware of the views of people from Sub-Saharan Africa and other parts of the developing world. How could we do that efficiently and effectively?

DR. LEVINE: Efficiently and effectively.

One of the problems we have is that Africans are just like us. Many of them have their own political agendas. One thing we found early in this international business was that very often we got people coming to us to advise us on the development of guidelines that were themselves entirely too westernized.

I have sat through a lecture from a man from Nigeria we tried to persuade us that the standards in Lagos are about the same as they are in London with regard to informed consent.

You have available to you a wonderful resource called Ruth Macklin who has spent a lot of time figuring out who can speak credibly from these countries and I would defer to her. I also have my own little address book of favorites but these overlap to some extent.

DR. SCOTT-JONES: Okay.

DR. SHAPIRO: Thank you.

Diane?

DR. SCOTT-JONES: My question for Ruth is

similar to the question that Alta raised.

I was wondering, Ruth, if you think there are instances in which a developing country is simply too poor to justify research being conducted there when a more humane response from the developed world would be to work on the food supply, the water supply, vaccines for children and other aspects of well-being in those countries.

DR. FADEN: Depending on how you set your horizons, near-term or long-term, it may always be the case that the more humane response from the wealthy nations would be to spend resources right now on indicators of illness and disease. It might always be the case to take the way you have set it up that if you were to look at least in terms of short-term considerations that the more you -- your main response would be to transfer the dollars in the form in which the countries could use the resources to reduce the dramatic differentials in life expectancy that exists there relative to here.

So that, I think, is a problem. It is a part

of the deep problem of the whole structure. Now that takes a short-term horizon. You will immediately -- this again depends on your sort of -- how you think about what justice requires and whether you take account of obligations looking towards the future and if you are in -- if you take those obligations seriously and if you also are concerned about ultimately -- I have to be careful here or I will start to use the buying more disability adjusted life years form of analysis.

But if you are, in fact, thinking in those terms as I do in a lot of the work that I do now, you might end up buying more lives over time by investing in the right kinds of research that could result in the right kinds of interventions for even the poorest nation.

So I think it is even more problematic than you have tagged it. It is not only the poorest of the poor countries that raise this problem of whether we ought to better spend whatever money we want to transfer.

It is also more complicated, however, by the fact that when we do invest resources in research in the developing world it is sometimes, as Alex has pointed out, for a global set of considerations. That is where the health benefits are expected to benefit everybody. Okay. Not only the people in poor nations but the people in wealthy nations.

In some cases it is with an eye towards benefitting primarily or perhaps only exclusively, given the target diseases, the people who live in the poorest nations.

And another part of this mix, which is something that is so complicated to address with respect to the ethics of international research, is looking at the portfolio. How much of what we spend in the north and west, we spend on research focusing on illnesses and diseases and causes of health burden that we have that are terrible pressing concerns in the poor and south nations of the world.

DR. SHAPIRO: Thank you.

Laurie, do you have a question?

DR. FLYNN: Yes. I want to ask you to think for a moment about community in just a little different context. Not so much the physical community, the location, but community in the sense that many of us in health advocacy think of it. Those who have shared a particular health experience or challenge or those who are struggling with a specific illness.

In this nation we have a history of not for profit organizations that have taken a lively and in many ways effective role in shaping research agendas and challenging research paradigms and in being a sustainable advocacy voice and, indeed, are in many ways part of the consultation process that goes on as we think about these issues.

I am wondering if there has been any experience in this kind of participation of those who are most directly involved with illnesses and risks in the developing nations and whether that might present a potential strategy as we think about strengthening the ethical infrastructure and the ability to continue

to monitor the justice and social goods that we believe we are fostering as we move into these countries with complicated research projects.

DR. FADEN: Is that for -- that is for both of us?

DR. FLYNN: Yes. Either -- I did not know whether you could both comment or --

DR. LEVINE: Well, I did not mean to imply that the idea of community, as Laurie puts it, as understood widely in the United States is not an important thing. It is just different from what the term "community" was intended to mean originally. It is collectives of people who have common interests. I think they are extremely important in the United States in providing sound advice on shaping public policy.

I am not aware that we have any well developed advocacy organizations in most of the resource poor countries right now. If anyone is aware of such -- of something that let's say is the equivalent of NAMI in Sub-Sahara and Africa I would

like to hear about it.

Thank you.

DR. SHAPIRO: Ruth, do you have a comment?

DR. FADEN: I do not think I have a base for being able to comment on that. I just do not know.

DR. FLYNN: I guess if I could just -- if I could ask and then follow-up with Bob. I am not aware that there are such organizations around any set of illnesses, including AIDS and others. My question --

(Simultaneous discussion.)

PROF. CAPRON: In AIDS there is.

DR. FLYNN: Yes, but again I realize -- but I am not sure how legitimate they are the voice of the individuals in some of these nations. But even granting that that may have happened, is there a sense that that kind of involvement across some of these other areas is coming, is being seen as another way to strengthen the balance from the concerns about ethical designs and ethical conduct. I am struck by how little we hear about this and I have checked with colleagues representing other chronic and life-

threatening illness and they just are not aware of any recognition of the role these organizations can play over time.

DR. LEVINE: I can tell you that there -- certainly the people who are participating in developing these international documents are aware of the importance of such things in the industrialized countries and I trust you all know that there are strong voices throughout Europe on a variety of these special diseases that link them, or interests in specific diseases that link them.

I think the way I see in the international documents, and now I have to exclude Helsinki, but in the U.N. AIDS guidance document and in CIOMS you see something that used to be called community consultation but it is changing its name as well. That takes into account involving all of the important voices in the area in which the research is to be carried out and one of those -- and it specifies people who are interested in the disease, people who are potential -- in the potential target population

for the developing new product and so on. This then would embrace the advocacy groups for these specific programs.

DR. SHAPIRO: Ruth, do you have --

DR. FADEN: No.

DR. SHAPIRO: Larry, did you have another question? This will be the last question.

DR. MIIKE: Dr. Faden, I am sure you do not mean it in the sense that I am going to start off with so I would really like to -- and maybe you can provide some comments later on but one of the problems I always have when we are faced with difficult problems is people rephrase it as an even more difficult problem so you cannot do anything about it.

And that is sort of the sense I get when you talk about, well, you know, here we are talking about clinical research in developing countries and part of your answer is that, oh, we have got to really increase our foreign aid budget or change the whole structure of the country if we can even get serious about clinical research in these countries.

I am sure that is not what you mean and I would -- no, I mean, yes, but -- but it gets us nowhere in terms of -- you know, you cannot say, okay, we are going to put foreign aid monies into the NIH budget and they are going to go ahead and do it. That is a totally impractical solution.

So I would be more interested and perhaps you cannot give it to me now but later on about what do you mean when you talk about increasing resources to these countries in a sense about linking it to some -- in some practical means to the objectives around which we are discussing it?

DR. FADEN: The criticism is fair and I have been accused of that before and it is fair. I mean, the way -- but the response cannot be shall we throw our hands up and we cannot -- I think what I -- the only part of your characterization of my remarks that I would take exception to was the chronology that I would hold up research in the developing countries until we have the kind of redistribution that I think needs to be in place.

It is just that it cannot -- it has to work together but here is what I think is more practical about what I am kind of -- what I am -- you know, in an inchoate way trying to propose that it is certainly not realistic to look at NIH or look at Novartis or look at the European -- INSERM (phonetic) in France or whatever organization, private or public, and say, "Okay. You now bear the burden of transferring huge amounts of resources so that we can bring the standard of living of people in the poorest countries up at least to something that we do not have to be so incredibly ashamed is currently the case." But it is, I think, reasonable to address the question of the ethics of international research in structural questions in this respect.

I think we can look at -- and I am repeating myself here -- the fact that the infrastructure sorts of responsibilities with respect to both scientific infrastructure, health infrastructure, not for the -- not in the grand sense but relative to clinical and biomedical and public health research, and with

respect to ethical and social review.

Those obligations to have the transfer of resources, and that is not just money, it is also in terms of other kinds of resources, educational and otherwise, that has to be thought through and it has to be thought through and delivered not research project by research project.

Okay. Maybe it is region of the world by region of the world. Maybe it is nation by nation and there is some move in that direction if you look at what the Fogarty Center at NIH, for example, is doing in terms of beginning to invest in the training of investigators abroad in research ethics. That is one little example. It is not tied to a particular research project but you could, in fact, redirect resources both from the private sector and public sector thinking of this as -- you know, it is the same infrastructure, whether it is a particular HIV clinical AIDS trial or it is, in fact, looking at schistosomiasis.

Basically you want to make sure that the

country has the infrastructure to be able to deal with both the ethics and the science of the project and that -- those kinds of transfer of payments need to be happening now.

DR. MIIKE: I guess then the rough analogy would be like how NIH would fund clinical centers.

DR. FADEN: Yes.

DR. MIIKE: Right.

DR. FADEN: Yes. We need to be developing models that are something like that that begin to recognize that the problem is more complicated than, okay, we got this research project, we got to look at the ethics of that research project, and we have got to decide whether it is ethically acceptable or not. It is just not that simple.

DR. SHAPIRO: Thank you.

First, I really have two things. I want to not ask a question since we do not have time for it although I have many on my mind but I want to first of all thank both Ruth and Bob. Your help here this morning has been great as well as stimulating and very

informative, and I want to thank you both for taking time out of your busy schedule.

I would like to make, however, two comments. One is that virtually all the discussion this morning has concerned international research in imagining a resource rich versus a resource poor country and just from the perspective of the commission I think that some time during our deliberations and the report -- it is something I have talked to Ruth about -- we really have to parse this out.

There are issues that concern our relationships with countries who are every bit as well off in every way we can think about as we are and that is one set of issues. There is an additional set and much more complicated set of arrangements when one deals with resource poor countries for all the reasons that have been very well articulated here this morning, but I think in our report if we can distinguish these it will be helpful and I think it will be helpful, in thinking through our recommendations as well.

Ruth, you hit on a particular subject which has puzzled me for a very long time and I was really very interested in the way you articulated it, and that is in terms I will use how one's moral space and psychological space interact and impact each other.

I think that is a really tremendously interesting issue. I had never really thought about it in this connection so I am very grateful to you for raising that. It is a really quite important issue in general and we will see whether something comes here. I was very grateful to you for having brought that issue here this morning.

So once again thank you both.

We are a little behind schedule so I will ask if we can try to take a ten minute break and reassemble at 11:00 o'clock and I want to apologize to Messrs. Griffin and Glantz that we are running a little bit late this morning but thank you both very much for being here.

DR. FADEN: Thank you.

(Whereupon, a break was taken from 10:49 a.m.

until 11:00 a.m.)

DR. SHAPIRO: All right.

Eric has -- we are going to change our agenda because one of the people who was going to be here speaking to us this morning is still on a plane because of the snow in Boston but, Eric, do you want to just indicate how we will rearrange our schedule?

DR. MESLIN: Sure. So far we have heard no indication that there are public -- members of the public who wish to comment during the comment period scheduled for 1:15.

If that is incorrect, please let our staff know at the table, but assuming that that is correct, Len Glantz from Boston University is en route at this point so we have decided to have him appear immediately after the lunch break because he, in fact, has to turn around and get back on a plane and go back to Boston.

And we will then proceed with the schedule accordingly so we will just shift everything as needed. If there is no public comment our schedule

will be right on time. If the public comment is necessary it will occur right after Professor Glantz.

DR. SHAPIRO: Thank you very much.

I now want to welcome Dr. Paul Griffin here this morning. He is here from WHO and I think it is also true that he had some other business here in Washington. In any case we welcome you with the hospitality of someone who has come all the way from Geneva to speak to us and we are very grateful of you taking some time here today.

He has broad experience especially in the reproductive health area but will speak to us on issues that he has encountered in his experience with prior agreements and other such arrangements for sponsoring research trials in other countries.

Dr. Griffin, welcome. It is very nice to have you here today.

PANEL II: PRIOR AGREEMENTS

DAVID GRIFFIN, REPRODUCTIVE HEALTH RESEARCH, WORLD HEALTH ORGANIZATION

DR. GRIFFIN: Thank you very much and I would

like to thank the commission for giving me this opportunity to share with you a little bit of our experience in this area.

I feel a little bit anxious being the only person on this panel and coming from a country which is renowned for its snow and skiing. I hope it is not a bad omen that the other two members are delayed because of snow and skiing accidents respectively but anyway I will press on.

Ruth Macklin asked me a little while back if I could come to the commissions meeting today to address the issue of WHO's experience in the area of prior agreements with participants in research in the context of ensuring availability of resulting products. I am going to confess that I am going to steer a little bit away from that particular issue because as far as I am aware we do not actually make explicit, documented, legally-binding prior agreements of that type. Although, of course, that intent is implicit and often explicit in everything that we do.

What I thought might be useful for the

commission, and I apologize if the first few overheads are very simple and obvious to you all, and in some respects cover some of the issues that have already been addressed this morning. I think it might be useful to put in -- to help us see it in the context of WHO's positions and responsibilities.

(Slide)

One of the things we have to consider is the definitions of the study population from the WHO context, and as we have heard already this morning one definition is clearly and obviously the individuals and community that actually took a part in the study but also, of course, our target, of course, is the population that is in need of the intended intervention, whatever that may be, and I do not think we must overlook the broader objectives of the research.

If I can have the next overhead.

(Slide.)

Just to remind you what WHO's position and mandate is, it is an intergovernmental technical

agency in the United Nations system. It currently consists of 191 member states and countries and, of course, it is responsible for health issues and addressing the needs of those member states that are brought to WHO for attention.

So it has a global rather than a local, national perspective and, of course, the majority of these member states, and as a consequence the vast majority of the populations of them, are in the developing world.

(Slide.)

Now what is WHO's primary objectives in collaborative research and development activities and they are summarized in these three basic principles here, which is to ensure the general availability to the public of the resulting product. A kind of obvious statement but that is nevertheless what guides us in our work.

(Slide.)

And then secondary to that but perhaps more important is to ensure the availability of the product

to the public sector in developing countries on preferential terms. I will come back to the issue of preferential terms later on to indicate how we achieved that particular objective.

We also, to a much lesser degree, sometimes receive royalties which we invest in the public interest either to offset the cost of products or to fund further research to meet the needs of developing countries primarily.

(Slide.)

And the very fundamental mechanisms used by WHO to achieve these objectives are to encourage and facilitate new product research and development by processes I will come to in a moment, and also improving access to the products by a variety of financial and health service mechanisms.

(Slide.)

And linked with this is also the issue of building up national self-reliance in research and development and sometimes in manufacturing which has also been addressed today.

(Slide.)

I think it is also worth remembering that there are a number of types of research, and as a consequence, a number of types of resulting products and I have summarized them perhaps rather simplistically on this slide to indicate that we carry out, and research can be carried out on social -- in the social science area, which largely produces information on knowledge and attitudes and perceptions and behavior that impact on health.

And the products that result from this type of research can be broadly described as improved education and improved public health policies. And they are relatively quick and should be easy to implement in the sense that they do not require major financial or capital infrastructure.

They can have major impact on the health of individuals in the community, and as a consequence of that, some can have major effects on social/political change through affecting policy.

The products of biomedical research are the

things that more readily spring to mind which are the drugs and devices that result from biomedical research. These are the things which people usually think of when they talk about products and I will come back to this later on.

There are also products of operations in service research which can be translated into organizational information, if you like, which could be used to improve the efficiency and effectiveness of health services. These, too can be relatively quick and easy to implement and of course it does have resource implications both in terms of financial and personnel investments.

And then there are products of epidemiological research which can impact in a sense on all of the above and can be relatively easily implemented in terms of information and change practices which can have an immediate and wide impact on public health.

(Slide.)

So if we summarize these types of products,

they are information, drugs and devices, change practices and improved services. Of these I want to now spend a little time on the drugs and devices issues. I think that is one that is of most interest to this group.

(Slide.)

And there are essentially two main situations that arise in the collaborative research and development activities between WHO and the private sector. These involve inventions that belong to a company in the development and assessment of which WHO expresses an interest and/or is invited to collaborate by the company where it is thought that the resulting product could have major impact on public health particularly in the developing world.

But there are also inventions belonging to WHO which are a consequence of the fact that 10 or 15 years ago WHO took a much more aggressive stance in terms of applying for patents on the research or the inventions coming out of the research that it was funding.

This gives us a much stronger bargaining position, for instance, with which we can collaborate with an industrial partner, which is needed, of course, for the final stages of development and licensing and manufacturing of any products. So these are essentially the two main situations in which WHO and the private sector collaborate.

(Slide.)

And the respective inputs of the two are getting summarized very simplistically here. WHO provides scientific, technical and limited financial input and also the design and conduct of the studies, whereas industry provides again scientific, technical and major financial inputs and of course provides the downstream formulation, manufacture and helps with regulatory issues for registering the products.

Now WHO makes a very small financial contribution in comparison to industry but I think we are able to maximize the impact of this small investment through the process of seeding projects and acting as catalysts to get funds from private and

public sources to expand the research.

(Slide.)

Just to give you a couple of examples of areas of successful collaboration, there are many others but these are perhaps ones that you may be more familiar with. There are two very large research and development programs in WHO.

One concerned with tropical diseases and one concerned with -- primarily with fertility regulation although more recently it is expanded to include a broader spectrum of reproductive health. There are examples of successful collaboration with industry in the development of drugs against three of the six main tropical diseases that program is concerned with and some with the other three. I have listed some of the examples also of how successful collaboration has been with the industry in the development of new and improved contraceptives.

Now these, I must stress, are just examples. There are many others in other areas of WHO's work but I did not want to burden you with too much detail

today, but they all have the same objective obviously in ensuring the availability of the products to our constituents.

(Slide.)

Now what mechanisms do we use to ensure the availability? These are again summarized here. Any or all of these could be used for any product. The technical assistance is a two-way street between the private and public sectors and developing and developed countries.

We can use the mechanism of technology transfer which is largely to the public sector in developing countries from the private sector. For instance, in the provision of know how and often assistance with the building of manufacturing facilities.

There are licensing agreements from WHO for its own products, if I can refer to them as such, to industry to ensure that the public sector rights to the products are safeguarded.

There are a variety of preferential pricing

procedures that are used using a variety of cost-plus, profit and royalty subsidization, bulk purchase, these kinds of mechanisms to ensure that the products can be made available at the lowest possible cost in the developing countries.

And occasionally, relatively rarely, we also have straight forward donations from some companies, or products that may have been developed for other purposes but which are found to be useful for developing country health applications. And we have had one or two examples where that product has actually been donated free of charge.

So this is a very summary overview of the way in which we try to ensure that any resulting product, whether it be a tangible drug or device or change in behavior or services or operations, are translated and made available to the populations in most need in the developing countries.

It goes part and parcel with the whole process of international development. As I mentioned earlier, the issue of infrastructure development both

in terms of research and in terms of ethical practices and in terms of eventual product manufacture in the developing countries.

I apologize for the very superficial nature of this presentation but I thought it might be useful for the commission to see the sort of general framework within which we operate and try to achieve the objectives that I think are the subject of this session.

Thank you.

DR. SHAPIRO: Thank you very much and thank you very much for your presentation. Let me just ask one question just to begin with. You referred a number of times to WHO policy to try to make products available to the public sector on a preferential basis and you explained what you meant by a preferential basis.

I am interested in what you mean by the public sector in these countries and -- well, let me just ask the question that way.

DR. GRIFFIN: Well, the public sector is -- I

cannot recall the precise definition, but it is essentially the population that benefits from nonprofit health provision so it is the -- it could be that it is the nonprofit agencies, the government agencies in the countries because our -- we operate through the Ministries of Health and the governments of the countries and usually the poorer segments of the population that depend on the public health system for their health care.

There is a rapidly enlarging, in many developing countries, private sector as a consequence of the expanding middle class, and these definitions do get a little bit blurred.

DR. SHAPIRO: Thank you.

Larry?

DR. MIIKE: Could you tell us a bit about how your organization's policy is set and what is the structure like? In other words, you are an organization of multinations. How is it decided which areas to go into, when to collaborate with a pharmaceutical company, why a particular country, and

who makes those kinds of decisions

DR. GRIFFIN: Well, the ultimate authority is the World Health Assembly which meets each year in May in Geneva and is represented by all of the 191 member states, so you can imagine it is quite a large meeting. They each send a delegation of anything from two to six or eight people.

And it is there that the state of the world's health, if you like, is reviewed, and the health needs of the world is reviewed each year, and from that review essentially the priorities are identified for where the organization should be more -- would be most effective in working. Obviously we cannot do everything that needs to be done but our focus is primarily on the needs of the developing countries.

But the health priorities and the research needs are essentially identified at that stage, but they are largely also selected as a consequence of the detailed reports of the Secretariat that WHO provides to the assembly for discussion, and these are based on surveys of the health situation in different

countries.

DR. MIIKE: What I had in mind was really can you just quickly walk me through a particular research project? How it got generated? Why they decided to go where with what product, et cetera? I mean, who makes those -- is that a staff technical discussion and it is a pro forma approval by the General Assembly? I mean, how are these priorities set and how do they actually get set into motion and how do they get implemented?

DR. GRIFFIN: Well, perhaps I can give you an example from the program I know best, to use to WHO speak, which is the Human Reproduction Program in which I work. And as I mentioned, the primary focus of the program until quite recently was the development of new methods of fertility regulation and the process essentially is to look at all of the possible options, the research opportunities based on the knowledge of the field, and then to -- and at the same time to involve inputs from the developing countries in terms of their needs in the perspective

of their capabilities of providing new methods through the existing infrastructure and so on.

And the priorities are then selected on the basis of a variety of criteria. It is obviously expressed need and priority and preference from the developing country perspective.

Feasibility of development, possibility perhaps of private sector interest in collaborating in their development because there is a limit that WHO can do in terms of how far it can take new method development.

And we then convene -- I mean, this is not done in a sequence. This is all done in a -- as part of a much broader structure but then there would be a steering committee of experts in that particular field of clinicians, scientists, health service providers, community representatives, who would sit down and discuss the details of the research strategy in that particular area, and from that would flow the individual research projects and then once you have the individual research projects, of course, you then

make sure that it consists of all the appropriate scientific, technical and ethical components that are required to conduct the research.

We try as early on as possible to involve people from the countries in which the research is likely to be conducted and the countries are obviously those which have expressed the need and preference for that approach, but again, as has been mentioned earlier this morning, much of the early stages of clinical research, the Phase I and to some extent the Phase II stages of clinical research when you are testing the safety and efficacy of the new intervention, we try to do as much as possible in developed countries for a variety of reasons but then as quickly as possible involve the developing countries in the later stages of development to ensure that the work, once it gets to that stage, is carried out in a relevant population.

DR. SHAPIRO: Thank you.

Bernie?

DR. LO: I would like to ask you a question

relating to the suggested guidelines that a precondition for doing research in developing countries is that an arrangement be worked out before starting the research to make the intervention, if it is proved efficacious, "reasonably available" in the host country.

I have heard researchers complain about this guideline saying that it is impractical. It would slow up research and that drug manufacturers would not agree to that. I wanted to ask your view based on your experience and the experience of others trying to do international research how practical is that requirement?

Is it an ideal that we should strive toward but probably may not achieve much, or is that something that with good negotiating is likely to be worked out in practice in this day and age? I do not have a feel for how that works out in actual practice.

DR. GRIFFIN: Well, the requirement is mandatory essentially in all our negotiations with

industry in the two primary situations I described of them coming to ask or us going to them. One of the very first things that is put on the table for discussion, but perhaps not for negotiation, is the fact that they must insist on making the product available to the public sector in developing countries at the lowest possible cost.

And, as I mentioned, there are a variety of mechanisms that we can use to achieve that objective and that is essentially nonnegotiable. That is a mandatory requirement of the collaboration with the private sector. Sometimes, and I would like to think rather rarely, it leads to a rapid end to the discussions.

My personal experience has been that all of the major and small pharmaceutical companies, for instance, that we have negotiated with in the past have all agreed quite readily to this concept.

How you implement it and ensure that that obligation is met is much more problematic in the sense that you may end up with a product which even at

cost price or at a subsidized price is still unaffordable because of the nature of the product.

You heard an example this morning of the HIV therapy.

One way around that is to effect transfer of technology which is another requirement that, you know, if the company cannot meet our objective of providing the product at an affordable cost in the developing countries they must agree to provide technology transfer with safeguards to ensure that local manufacture is possible which should perhaps reduce the cost to a point where it is affordable.

But, as I say, my personal experience and I think the experience of my other colleagues in WHO who are involved in these kinds of negotiations, is that whether it is altruism or profit motive, I do not know, but the vast majority of the companies are quite happy to accept this requirement.

DR. LO: If I could just ask one quick follow-up. And is it your view that even if it were not a requirement, as it is for WHO, if the research

were sponsored outside of WHO auspices, is it your sense that drug companies would probably be willing if this was -- the negotiations were handled wisely to agree to similar sorts of provisions?

DR. GRIFFIN: I would be reluctant to speculate on the minds of the governing bodies of the pharmaceutical industry but I think there are examples of good old-fashioned altruism coming through occasionally.

DR. LO: Let me ask it another way. Is there something specific about WHO or the type of research or the diseases you deal with that make it more likely a drug company will agree to the provisions with you as opposed to HIV studies where they can use the -- they would have the same drug available for market in the developing world at much higher prices for example?

DR. GRIFFIN: Right. Well, I think the industry, the private industry, does see some advantages with working with WHO. I mean, they often see some disadvantages. I mean, the protracted time

frame, the rather extensive requirements and regulations that we impose on them.

But I think the advantages they see is the international recognition, the credibility of the organization, the neutrality of the organization, and the fact that we are an intergovernmental agency. We have direct access to the Ministers of Health, the regulatory authorities, to the whole of the R&D and eventual product introduction and use infrastructure that I think they can see some advantages to that. Although, I think it is fair to say also that some of them do see the cumbersome bureaucracy and the extensive requirements as a limitation as well.

DR. SHAPIRO: Thank you.

Alta, are you coughing or do you have something you would like to ask?

PROF. CHARO: No, no, I am fine.

DR. SHAPIRO: You are fine. Thank you.

Let me ask a question. I am interested in the -- you identified four subsets of -- four classes of research that WHO was involved in. One of which is

biomedical and that is the one that you focused on. The others were social science or kind of organizational or operation services and epidemiological. That is at least how I recall the four categories.

Could you give me some sense of how WHO's efforts is distributed amongst those, is most of the effort in biomedical, is most of it in epidemiological, is there -- just give me a feel for how that might be distributed in your judgment.

DR. GRIFFIN: I cannot give you any precise proportions and I think it varies from one program to another and from one health area to another because not all of WHO is concerned with addressing diseases. There is also sections that deal with health service development and so on but how much research they are conducting I really could not say as a proportion of their overall work load.

I can only talk again in the context of the specific program within which I work, the Reproductive Health Program, and largely because of its history and

tradition of working in fertility regulation I would think approximately 50 percent of its R&D budget is still going into biomedical research and perhaps 25 percent into social sciences, and the remainder is split roughly between the other two areas but that is very much a program specific picture and it may well be different in other programs.

DR. SHAPIRO: If I could ask another question, in the area of biomedical research when it comes to doing trials in which -- I guess we will take the case where WHO owns this process and it may and may not have partners at the stage of clinical trials. What kind of -- which of the many different kinds of ethical guidelines that we see offered around does WHO feel itself bound by? Is it the Helsinki Declaration? Is it CIOMS? Is it some other combination? Do you have your own? How would you characterize that kind of -- that issue from WHO's perspective?

DR. GRIFFIN: Well, again within our program, and I think it is true, also, of the other programs, the other research programs in WHO, we use as our

guiding principle the Helsinki Declaration and the CIOMS guidelines. But we have also developed a number of guidelines, again, specific to our particular needs in reproductive health.

For instance, guidelines on research involving adolescents, research in reproductive health involving adolescents, and research in reproductive health which requires or may require partner notification, and these kinds of things that are specific to our particular research interests, and we do have within our program a scientific and ethical review group of which Ruth Macklin is one of the major members, which has the responsibility as functioning essentially as a departmental IRB for reviewing research proposals that come through either -- sent to us by investigators or solicited from investigators and they have to pass through that review process.

DR. SHAPIRO: Let me ask -- if you do not mind, let me ask a follow-up question on that and I am trying to formulate this question in a way that would give me some sense of whether a set of ethical

guidelines, which do guide your work, both the CIOMS, Helsinki and your own additional guidelines in reproductive health. Do you find that there are situations where you would like to do a trial but find yourself unable to do it because you just cannot satisfy these guidelines because of -- I do not really want to know about particular countries. I am not asking for a specific example, but just trying to get a sense of in what way these guidelines really, if at all, constrain the work that you might otherwise do.

DR. GRIFFIN: I am not aware that they actually constrain. They facilitate the discussion process. There have been a number of situations, and it is constantly arising in the works of the scientific and ethical group, that new ethical issues are raised as a consequence of the research that is being proposed which we have not had to address in the past, and these guidelines provide a framework within which we can formulate and discuss the issue, and hopefully resolve any dissent amongst the members.

I am desperately trying to recall if there

have been any situations recently that provide an example of the kind of situation you are raising where we were unable to resolve a fundamental ethical issue that prevented a study from being carried out.

Ruth?

I am looking at Ruth hoping that she has a better memory than me but I cannot think of any illuminating example of that.

DR. SHAPIRO: Ruth, maybe --

DR. MACKLIN: Actually I cannot either. Not when we are thinking of the -- or referring to the Helsinki Declaration or the CIOMS guidelines. There are circumstances that occasionally arise when one of these other guidelines that David just mentioned, for example, the partner notification or the spousal agreement.

Now since the guidelines essentially in principle reject the idea of spousal agreement -- I mean, this is in -- usually in contraceptive fertility regulation for women and the guidelines presume against such spousal regulation. The committee puts a

stipulation, that is the Ethical Review Committee, the Scientific and Ethical Review Group, puts a stipulation on the acceptability of the research and this information is then sent back to the investigators. I mean, the way the review process works is there is -- there are certain categories of review.

One is approval, without any need for anything else. Then there is a recommendation for approval with amendments which are held to be binding amendments, approval with clarification of something that is unclear, deferment or disapproval.

So this would be in the category of an amendment that there not be spousal agreement if it does not fit with those guidelines.

Occasionally something else comes up that a member of the committee raises that does not fit into any guidelines but becomes an ethical issue.

For example, there was a suspicion at one point -- I do not remember the details, the scientific details, but a suspicion of some -- at one point that

some tissue that was being collected for research was actually coming from executed prisoners and the committee if I recall correctly would not approve -- wanted a clarification of where they were getting the tissue from and would not approve the research without having the answer to that question. So, I mean, there are specific questions that may arise that do not even find their way into the guidelines.

But having said that, let me add -- and I mean, I guess David would agree, but it is no different from what it is with research carried out here in the United States. This committee looks at guidelines, its own guidelines and pieces of paper and representations, and sends back approval based upon a paper representation from the researcher that the researcher will do what is stated or what is stipulated, and it is no different in this country.

I mean, the question of looking -- going and doing a site visit or making a surprise visit in the research context to see whether or not that is going on -- I mean, I do not think that happens there, but

it surely does not happen here, so I mean the implementation is a different question from what the committee might require.

DR. SHAPIRO: At one stage in your presentation you referred to attempts at -- or at least a requirement of some kind or an aim of some type regarding the general availability of a potential product or device of some kind.

I took that to mean that if the trial were successful that the product or device would be available sort of on a -- I do not know, we all use these terms "reasonably available basis." I understood it is preferential to the public sector. I understood that, but by "general availability," could you say a word about that? What that -- what I am supposed to be thinking about in that respect?

DR. GRIFFIN: Well, again it is to reflect the fact that we are the operating arm, if you like, of 191 different countries and our responsibility, therefore, is to make sure the product is available in all of those countries and the others.

I do not know -- I cannot recall how many are left out of the total number in the world so that we are not being restrictive in terms of the populations that will receive the product. We want to make sure it is generally available and that is what we mean by the word "general" in that context.

Within that "general availability" comes up the issue of ensuring that in the resource-poor countries it is available at an affordable price, which may be considerably different, several magnitudes different, to the cost in the private sector in a developed country for instance.

DR. SHAPIRO: Sorry to be asking so many questions but one final question I have, and that is a question of whether WHO does conduct research at least from time-to-time in developing countries. I understand you -- excuse me, developed countries. Most of your efforts are in developing countries. If so, how would you characterize that work?

DR. GRIFFIN: In terms of preclinical or clinical research?

DR. SHAPIRO: I was thinking of clinical.

DR. GRIFFIN: Clinical. Although again in our area, in the area of the human reproduction program, the reproductive health program, a substantial number of the early stages of the clinical research, the Phase I safety studies and Phase II preliminary efficacy studies are carried out -- I would say perhaps in the majority of cases in the developed countries for a number of logistic and political reasons.

Logistics being, generally speaking, a greater degree of control over the work and perhaps greater reliance in the information, although that sounds a bit patronizing, but also because we do not want to be accused of using developing country populations as guinea pigs at the early stage of clinical investigation and -- but obviously as soon as we have evidence of safety and preliminary efficacy, we try to involve, and they demand to be involved as much as possible, the mixture of developed and developing country centers.

DR. SHAPIRO: Thank you.

Any other questions from members of the commission for Mr. Griffin?

PROF. CHARO: One quick one if I may.

DR. SHAPIRO: Alta?

PROF. CHARO: When you talk about making these products reasonably available, one mechanism is through reduced price. For how many years is that availability assured, generally?

DR. GRIFFIN: It is again the subject of negotiation. We -- there is no fixed time limit. The only thing that is conditional on the time is the fact that at the end of the agreed period of time the company concerned must agree to provide technology transfer to enable the country or countries concerned to continue either to manufacture the product themselves or through a sublicensing arrangement to have somebody else manufacture it for them. So, we try to maintain the availability for as long as foreseeable.

PROF. CHARO: Thanks.

DR. SHAPIRO: Yes, Bette?

MS. KRAMER: Thank you for your presentation.

I do not know if you were in the audience when Dr. Levine spoke earlier. He raised an interesting question, and that is if a vaccine is initially tested in three different countries and subsequently fails and then another version of it is later tested in three different countries and succeeds, which countries then would be -- to which countries would there be an obligation to provide the vaccine on a lower -- at a lower price basis to make it more readily available? Do you all ever come up against that question?

DR. GRIFFIN: We do not distinguish between them. The principle of preferential pricing extends to all developing countries, the public sector of all developing countries which have a need for the product irrespective of whether they took part in any studies, even whether the study they did take part in was successful or not.

MS. KRAMER: So irrespective of whether or

not they took part or were invited to take part. Thank you.

DR. SHAPIRO: Ruth?

DR. MACKLIN: Yes, David, you referred to a broader obligation. I mean, in addition to the specific one of making products or research results available, and this comes up from time-to-time and we heard it earlier this morning, the obligation on the part of sponsors and particularly from the industrialized countries to engage in some form of capacity building so that at the end of the research it is not only that there may not be a product there but there is not even the capability of being able to deliver a product that might be made available but the capability.

Could you say a word about any efforts or activities that WHO does or any commitment it has in this area of capacity building?

DR. GRIFFIN: Well, it is a major function of WHO's work. There are a number of programs outside of our's which are engaged in resource strengthening per

se. That is the sole raison d'etre, is to build up national capabilities ranging from strengthening medical schools all the way through to manufacturing.

A significant proportion of our work within our program, one third in fact of our total budget, and I think it is true, also, of the Tropical Diseases Program, is specifically designated for building up national capability with a view to developing national self-reliance in research and development in these areas, both in the social sciences and biomedical sciences and strengthening ethical capabilities.

DR. SHAPIRO: Thank you. Any further questions by commissioners?

Well, once again, let me thank you very much. I hope there is no snow or skiing accidents as you return to Geneva and we very much appreciate you taking a little extra time to be here today. Thank you very much.

DR. GRIFFIN: Thank you. It was a pleasure.

DR. SHAPIRO: Let me suggest, unless there is any particular question that anyone has now, that we

-- I guess -- is there anyone in the audience -- we have no one signed up for public comment but does anyone in the audience want to speak to the commission at this point?

I guess not. Then let me make a suggestion. Let me make a suggestion that we break now for lunch. It is a little before 12:00. And that we reassemble at 1:00 o'clock. This will give our next guest, who is Mr. Glantz, a chance to -- a better chance to make his return flight to Boston and so on.

So let's break now and then reassemble at 1:00 o'clock as promptly as possible. Thank you very much.

(Whereupon, a luncheon recess was taken from 11:52 a.m. until 1:11 p.m.)

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

DR. SHAPIRO: Alta, later on we are going to have Eric diagnose you from afar.

PROF. CHARO: I am sorry. What?

DR. SHAPIRO: Later on today we are going to ask Dr. Cassell to diagnose you from afar.

(Laughter.)

DR. SHAPIRO: All right, colleagues. I would like to begin our afternoon session. Let me, first of all, begin by welcoming Professor Glantz here this afternoon, who tried his very best to be here this morning and was delayed only by an unexpectedly difficult snow storm in Boston.

I told Professor Glantz that I appreciated him sticking it out and coming down to which he told me there was nothing he could do on the tarmac. They would not let him back -- would not let him back to the gate and we have all experienced that.

So welcome and thank you very, very much for coming.

Mr. Glantz is -- Professor Glantz is an

Associate Dean of the School of Public Health at Boston University and Professor of Public Health especially focused in the area of law, and with a lot of experience in the areas that we are talking about.

As you know, Professor Glantz was going to be part of this morning's panel dealing with prior agreements and arrangements as we go ahead to set up research projects in other countries.

So, welcome and we look forward to your remarks.

LEONARD GLANTZ, J.D., BOSTON UNIVERSITY SCHOOL OF PUBLIC HEALTH

PROF. GLANTZ: Thank you very much.

DR. SHAPIRO: You have to press the button there and the red light goes on.

PROF. GLANTZ: There it is.

DR. SHAPIRO: There it is. Thank you.

PROF. GLANTZ: Okay. Anyway I wanted to say that I cannot tell you how pleased I am to be here, particularly considering the alternative that I was facing. It is much nicer than watching the snow fall

around your airplane and de-icing it and all that stuff.

I was supposed to be here on a panel called "Prior Agreements" and I just want to start by saying that I do not want to get too hung up on the term "agreements" which has occurred in the past when talking about this issue.

It has a sort of legal ring to it and coming from a lawyer, in particular, I am concerned about taking -- making it sound too much like a legalistic approach. I think it really in this context has more ethical strength than legal strength.

I want -- the underlying issue, the essential issue, is how can we better assure that products are developed as a result of research conducted with populations in developing countries and that those products are made available to those populations. The prior agreements are early planning or a means to attain that goal of getting products to those populations.

Here briefly are the three propositions that

I would start with and then I will talk briefly about them.

The first is that prior to research being approved, not just research in developing countries, there must be a showing that the potential benefits to the population outweigh the risks. I think that is a readily acceptable concept.

Second, in order to demonstrate the potential benefits of research in developing countries outweigh risks, the researchers' responsible for the research must demonstrate that if the proposed research is successful the products of that research will be made available in the country in which the research was conducted.

The only way to do that, I think, is to identify a committed source of funding for the purchase or manufacture of the product and for the distribution of that product.

The third proposition is that research that is done in developing countries that will benefit developed countries or private industry but not the

population of developing countries is exploitative and violates basic principles of justice.

The very justification for conducting research in developing countries is that less expensive interventions are required because interventions that are known to be effective are simply too expensive to be made available in those countries. The AIDS trials in Africa are the paradigm for this.

At the time those trials was conducted it was known, or I should say at the time the trials were proposed, it was known that the 076 regimen worked to substantially reduce transmission of HIV from mother to infant. The argument for research to develop a shorter and less expensive regimen was entirely an economic argument that poor countries could not afford the effective 076 regimen so something more affordable had to be done.

So in instances such as this, what needs to be solved is not primarily a scientific or medical issue. What needs to be solved is an economic

problem. The question should have been is there some dose of this drug that will be effective and that will actually be made available to the population at risk?

This can only be determined if it is known how much the new regimen would cost and if there is some entity available who is willing to pay that price. If the new regimen continues to be unavailable because it, too, is too expensive then its effectiveness is irrelevant. This makes the research that determines its effectiveness similarly irrelevant, nonbeneficial, and I would argue, therefore, not justifiable.

So, for example, it has been determined that $50 worth of drugs used in the 076 regimen appears to reduce the transmission of HIV from mother to child but the question is why was $50 worth of this drug chosen for research purposes. If $50 would also end up being too expensive then that knowledge is just as useless to the developing world as the data that existed for the 076 trial itself and this, of course, is what happened.

The fact that it is known that short-course AZT administration can reduce maternal to infant transmission of HIV has really not provided any benefit to the developing world.

The point is that prior to conducting research there must be a demonstration that potential benefits outweigh the risks, that is the general proposition. In the absence of showing that a success -- that if successful the intervention will be made available, one cannot conclude that there will be any benefit and, therefore, I do not see how it could be determined that the benefits outweigh the risk.

Furthermore, in the absence of such a showing I do not see how it can be demonstrated that the subjects were equitably selected assuming that equity includes notions of fairness and justice.

So both the existence of a favorable risk-benefit ratio and the equitable selection of subjects are preconditions to the approval of research under any research ethics standards.

So in order to meet these criteria it seems

to me at the outset that the investigators need to have an economic hypothesis since they are dealing with trying to solve an economic problem. The hypothesis would be, we believe that a drug given in a particular dose, in dose X, will cure the condition but again we have to come back and ask why did you choose dose X.

The answer will need to be because we reasonably believe, based on sound scientific information, it will be effective, and based on sound economic information that it can be realistically made available.

So I was recently discussing this issue with a colleague who asked me about AIDS vaccine research and how this might apply to that circumstance and she had said to me that the company that would manufacture the vaccine said that it could not say how much it would cost and, therefore, could not meet the standard that I am proposing and I would have a few answers to that issue.

One is that I do not find it believable. I

simply do not think that people go into that -- industry is sophisticated, the pharmaceutical industry developed goods -- without having any idea of what it would cost, that they might be creating something which certainly is just unaffordable to anybody.

I do not -- I understand that industry might not be able to say it is going to cost $27.55 but we could ask the question so do you think it will cost more than the hepatitis vaccine that was developed in Senegal and is not available in Senegal? Would it cost less than the hepatitis vaccine? Is there some reason to believe the manufacturing practices or development costs would be different?

So it is just hard for me to believe they do not have some kind of a business plan before taking this on.

I also think, by the way, in the absence of this information we do not have any reason to believe that the vaccine would be made available to impoverished countries. I think the burden of proof in regard to the ultimate utility of the product

should be on those proposing the research.

Finally, I would say that the scientific and epidemiologic reasons for selecting countries with serious epidemics is not sufficient justification for doing the research in those countries. The fact if one wants a large at risk population in order to efficiently test a vaccine is not the answer but the problem.

From a justice or equity perspective, the worse outcome is to develop a vaccine in the developing world because it has the horrible economic conditions that makes it ideal for testing and then to have the vaccine available only in wealthy countries because it is so expensive.

It seems to me this is the problem of exploitation, but there may be a variety of ways to resolve this issue without just a promise of funds, and I know that someone from the International AIDS Vaccine Initiative will be here this afternoon to talk about it and I think that that organization is trying to accomplish some of these things.

So it may be, for example, that a manufacturer of a vaccine might be willing to say we will give a free license to the country to manufacture the vaccine on its own and if the country is able to say, yes, we are capable of manufacturing the vaccine and will plan to distribute it, that in a sense resolves the problem that we are discussing.

But what is happening with IAVI, and again I think it will be worthwhile talking to Dr. Berkley about it more this afternoon, is there a better way to sort of deal with this issue than perhaps it has been dealt with in the past?

So in one of their newsletters, the newsletter dated October 1st, 1999, there is an interview with a Dr. Bhamarapravati, who was involved in the AIDS Vaccine Trials in Thailand. He was asked in this interview whether there was any discussion about making the vaccine available widely in Thailand and here is what he says:

He says, "Yes, for the first time in any vaccine trial in the world the manufacturer gave us a

letter of intent to work with Thailand in making the vaccine if it proves to be effective. So VAXGEN will reach an agreement with the Thai governmental pharmaceutical organization which manufactures EPI vaccines to have it produced in a dosage form at a reasonable cost."

Further, there could be an agreement to produce a vaccine locally. Of course, a letter of intent is not real -- is not yet a real agreement. There is still a lot to be done but the letter has had a lot of visibility among authorities. It is true that a letter of intent is not a real agreement.

It would be interesting to know how close they came and why it would stop there. We have the manufacturer. We have the country that is involved and I am not sure what the difficulty would be in working out that agreement at that point.

So let me say that the goal ultimately should not be to do research in developing countries. That is really not the goal.

The goal should be to do research in those

countries that can realistically be expected to reduce or eliminate the serious health problems that confront those countries and that that determination, I think, needs to be made prior to doing the research and the approach that I am proposing to you I hope would sort of further that goal.

Let me stop there.

DR. SHAPIRO: Thank you very much. Thank you very much, indeed, for those remarks.

Questions from members of the commission?

Bernie?

DR. LO: I want to thank you very much for coming and sort of being heroic in your efforts to overcome Mother Nature.

I have a question that sort of has to do with the type of study we have in mind, that as I hear you talk it seems to me that the studies that this would be most applicable to are definitive studies that give you the answer that, yes, this vaccine, which we are really going to use at this dose, will be made available for a particular price. There is a lot of

sort of work that is short of those definitive trials where I could understand various funding agencies saying, well, we are not ready to commit on that.

It is really more of a proof of concept idea that if you can show us that, for example, a shorter course of AZT works almost as well in some sense as the longer course, what we will commit to is doing more research to try and find a regimen that really is affordable.

PROF. GLANTZ: Right.

DR. LO: But we do not feel comfortable going to something that is affordable right now because it might either be ineffective or dangerous or something so it seems to me there are intermediate stages of research where I am not sure it would be quite so easy to get what you are calling an agreement. I was wondering if you could comment on the sort of things that are not the end stage clinical trial but the more --

PROF. GLANTZ: Sure, and I think that is an important point. I think that the question has to do

then with why are you doing that research in a developing country, that if you are -- where you are dealing with sort of the initial research issue. I think it requires a justification for doing it there.

DR. LO: Let me -- you know, I may not be able to think of the right example right now but suppose you have evidence that an 076 regimen works in the U.S. and people say we -- it would be great to have something that prevented vertical transmission and was affordable, how can we do it, and people said, well, there is a couple of approaches. We are not quite sure which one works yet. We should try and start to develop those programs of research knowing that our ultimate goal if it all works out is that there will be a regimen that is effective or at least effective enough and inexpensive enough that it will confer the sort of benefit you are talking about.

PROF. GLANTZ: Right.

DR. LO: But we need some intermediate steps to get there.

PROF. GLANTZ: Well, I think that it is the

inexpensive enough and that when people -- I think even the proposal at the beginning to say that this will lead to something which is inexpensive enough, I still think that that statement requires justification, and I am not sure what that justification would mean.

So we could ask, for example, and I do not know how you might come out on this, should the full 076 regimen had been used in Sub-Saharan African countries just to see whether or not it has any effect at all, whether or not that -- you know, those kinds of drugs have an effect on the types of AIDS that one might find there.

You know, I am not sure what the justification would be even for sort of a basic science -- notion of basic science to try out an $800 drug in Sub-Saharan African countries.

I mean, I guess if I had a better -- if I had more concrete example I might be able to think of --

DR. LO: I mean, the $50 regimen. I mean, I could imagine an IRB saying why subject someone to a

dose of AZT that may be totally ineffective, that it is just speculation it is going to work. Let's try a slightly longer regimen knowing that it is still not affordable in that country but it is the first step towards then a second study or a third study which will end up with an inexpensive enough regimen for that country.

Now one argument is do it in a country that can afford the $50 rather than --

PROF. GLANTZ: Yes.

DR. LO: -- you know, their other -- I am just -- I guess I am -- my concern has to do with trying to apply to a concrete situation ideas like, you know, agreement and economically feasible because as you said at the beginning exactly how you interpret that is -- how you apply it is important.

For instance, when you say you need to identify a committed source of funding, that is much different than saying an agreement to have a licensure agreement so that the host country can make it at cost with technology transfer.

PROF. GLANTZ: Well, I think -- but that is why it would be interesting this afternoon to find out what those agreements with other countries might look like.

So it will be interesting to know even what Thailand might have had in mind that I think is -- they would say in disagreement if VAXGEN had said there were circumstances -- there were no circumstances under which the people of the country will not receive this drug because here are the various alternative schemes that we have considered, and those schemes would be concrete. Concrete schemes.

And one of them might be that you have drug manufacturers in Thailand to stand prepared to give the drug in Thai -- the Thai government prepared to distribute it. Then the money almost does not matter as long as you have a system or considering a system in place to make -- to distribute this new found beneficial substance.

DR. SHAPIRO: Alex?

PROF. CAPRON: I wonder what we should do to avoid some of the unintended perverse effects of certain kinds of rules, particularly those that look to the country as the relevant unit.

What I have in mind is on the one hand we want to avoid a situation in which you kind of have a race to the bottom, that countries in order to have the potential long term benefit of being able to have access to specially priced medicines or the scientific technology transfer, things that are supposed to go along with research, offer up their populations under conditions or for research designs that other countries are reluctant to undertake.

Another and somewhat different problem would be countries wanting to hold off participating in research because they want the research to be far enough evolved that it is likely that something good is going to come from it and in many of these areas the early studies are much less likely to yield an effective treatment. The later studies more so. So you want to hold your country back and then put it

forward at the right time as a research site so that there is very likely to be a benefit.

Laurie Flynn pointed out this morning when you were not here in talking to Bob Levine about some of the issues of community that in some ways the people see themselves in communities that are quite separate from political jurisdictions and particularly in the area of diseases are likely to look more broadly across regions or countries, I suppose around the world, that identify with other people as being in the same community of sufferers from a particular condition.

But if we follow that too far then the drug companies are going to be told, well, once you research in the community of people with HIV you now owe to all people in that community who come in all shapes, sizes and colors with all different nationalities access to this new treatment, and they are going to say, well, it was one thing to say that the Thai's can get it cheap but Americans who suffer from this or Americans who want to, suffering from it,

whatever, ought to pay whatever price we can extract from the American market.

So how do we deal with these -- that if you start erecting these agreements and so forth, you have these different unfortunate incentives that you build in. What is the relevance of political jurisdictions here and so forth? What kinds of assumptions are built in? Can you explore a little bit of that?

PROF. GLANTZ: Well, I have a lot of sympathy for the argument that country lines are arbitrary, that diseases and conditions, social conditions as well as medical conditions cross lines. I do not think there is anything you can do about it though.

I think that for convenience sake that those country lines have come to exist and when one looks at the various requirements and research codes, international research codes, there were discussions of, you know, community approval, country approval, Ministry of Health approval. I think they sort of assumed that the unit -- the negotiating unit will be a country.

Although I think there is again a really good argument that that does not really solve the relevant problem. The relevant problems are people who are poor with diseases and they cannot afford the treatment, that that should be the unit of analysis, but I am not sure that there is any way to get around it.

I would certainly, you know, like to see a commitment to the poor of the world to make useful products available.

In terms of the rush to the bottom issue, or countries wanting to hold off -- the rush to the bottom issue of countries being willing to have less stringent ethical standards, for example, has to do with review in this country, and we are talking about research being done by developed countries, particularly the United States and other places.

And I think that we have to apply strict research criteria and ethical criteria to research in other countries. The fact that another country said this is okay with us is not satisfactory. I think it

is a necessary condition, obviously, but not a sufficient condition.

In terms of countries wanting to hold off, you know, what can you say? I do not think that that is a matter of this problem. You know, India had refused for many, many, many years to be involved in research of this sort because the population was concerned, or many of the populations were concerned, about being used as guinea pigs, and I think there are countries that are more or less sensitive to that.

The -- and as far as country leadership is concerned, I mean countries are faced with terrible diseases or terrible conditions. I do not know how many countries would hold off if there was a sense that help was really on the way as opposed to research being on the way.

PROF. CAPRON: May I just follow-up though? So much of the science in this field, my understanding is, is going to be cumulative and so what one group of researchers does is going to be a little bit better tomorrow than what another group does today because

they are going to learn from each other.

If we said that this kind of obligation that you are describing, which is to be formalized in an agreement between the researcher or sponsor on the one hand, and the Ministry of Health, on the other, of the country, is very specific to this research project.

I do think that the sense not of holding off because you do not want to be a guinea pig but you want to be a guinea pig at the right moment could really be a problem. If we said that, look, Thailand participated in this trial, the next trial is being conducted in Indonesia but a year later and they are just that much more advanced and much more likely to get the product, is there some way of saying to the Thai's that your research participation will gain you as favorable treatment as the Indonesians are going to get?

Otherwise -- I mean, this reluctance to be involved in the real cutting edge, which is a necessary thing and it may strike gold. I mean the first time it may work, but it may not be the first

time. It may be the second, third or fourth iteration that finally works.

The people who have gone before have as much moral claim to having made a sacrifice for the general good as the people who are in the fourth iteration and yet they are not in the sponsor, researcher, letter of agreement, promise, commitment situation with that sponsor for that research.

PROF. GLANTZ: So the -- just to understand the question, so the second piece of research is done by a different sponsor or a different person?

PROF. CAPRON: A different sponsor, yes, but they have learned some things. Some things are now in the published literature. It turned out that growing them in egg -- this vaccine does not grow well in eggs so they are going to use this or that. So, I mean, you know, things are found out and leads are pursued and other ones that do not work are dropped. And you come along and you are in the group number three of four where it finally clicks.

PROF. GLANTZ: Right.

PROF. CAPRON: But in terms of moral status the people who came before you and got -- whose research involvement did not lead to the successful product are -- are they out in the cold? I mean, they have contributed as much to the final solution.

How do we get beyond these kinds -- in other words, I am very struck and it is very -- it is very good to say, well, we ought to press and see why can't there be formal agreements with real ironclad commitments up front. I think your suggestion that we basically go to Thailand and to VAXGEN and say spell out for us how close you were, what were the impediments, what questions kept the company from committing, what questions kept the other side from insisting that they get an ironclad commitment instead of intent.

It is all very good but that pursues a method that says this is all very specific to a particular country and a particular research sponsor and it does not look at this as a worldwide process in which contributions are made by others who come at a

different stage in the process.

I am worried about building an ethical argument that says that somehow the people who were there at the right moment are ethically and morally entitled. It is not just that their government might have to reach such an agreement. We ought to say that the research should not go forward without getting us as far towards that agreement as possible.

But what we are saying is something that could have this perverse effect on the whole research process. We could overcome that if there were some way of mounting -- of turning the moral obligation towards people in the earlier research into a real commitment of some sort. I just wonder if you see it as a problem and if you have any sense about how you would overcome that.

PROF. GLANTZ: I mean, I do not know that I see it as a problem because I am not sure how perverse the incentives are. I would certainly see it as a goal because I certainly agree with your outcome that everybody who -- with your premise that the

populations that were involved should reap the benefits of that from early involvement.

The difficulty that I have in trying to come up with something concrete to do, that is, that I am not sure who to impose the obligation on when you are dealing with different sponsors so that I -- so that as a moral obligation I could see it as sort of a free floating moral obligation in a sense that we all owe to the early volunteers but I am not sure whose obligation it is that one could actually point to at that point, so I see it as a practical problem.

Let me say by the way that, you know, the questions that you ask that I would not for a moment begin to think that this is a perfect solution to the inequalities of the world.

The point that I would make is that it may be a solution in appropriate circumstances and it may be a solution to some of the problems, and particularly a solution, I think, to the circumstance in which the argument is made that we are going into this country because we know what works and they cannot afford it.

I am saying that in that particular area that I think that this concept works particularly well and again it comes back to the issue of having an economic hypothesis because you are dealing with the resolution of an economic problem.

There may be other areas in which it does not work as well, and there might need to be alternative approaches so there might need to be a series of ways of dealing with the problem of economic inequality throughout the world.

DR. SHAPIRO: Tom?

DR. MURRAY: Thanks, Harold.

Len, I want to thank you for your presentation which was crisp. Your purpose was laudable, which I take it to be to find a way to assure that exploitation does not occur, and you had the courage to present, I thought, very clear and rigorous criteria. I think we will benefit in our deliberations from that, whether we accept them or not.

PROF. GLANTZ: Sure.

DR. MURRAY: And I am about to give you some reasons why I am not ready to accept them entirely at this time.

There is an image of research which is, you go in and you do the 076 variant trial, that that is the kind of research you are talking about, and that is a very important kind of research but it is by no means the only kind that is done, and Alex has just explained -- you know, just carried out the implications of the fact that there is a spectrum of research from more basic through a variety of applications, successful and not successful.

Furthermore, research trials often take place over several years so here I am going to list three problems.

One is we may be -- if we adopt your three criteria we may be asking scientists to do those things which they may not be at all well qualified to do, and that is to negotiate the sorts of economic agreements and to anticipate the kind of political developments that might occur that would affect the

future availability of whatever it is they are working on. That is number one.

So we are asking scientists to do something that maybe no one can do and they are particularly -- they have no particular qualifications to do. Some would argue they are particularly unqualified in many cases to do that, but we will just say they are not well qualified.

Second is this -- these principles as I understand them hold the science hostage to economics and politics in very palpable ways.

What do we say to the scientist who goes in with what she thinks is a pretty good agreement that this drug, if it works, will be available and the country sinks into a depression during the three years of the study? Or there is a change in government during the three years of the study? Should we then ask the scientists to fold up the study because we can no longer guarantee? I mean, you will have all those kinds of questions that scientists will have to deal with.

Thirdly, the standard that we are proposing here or that you are proposing would impose -- I know you are conscious of this -- much more strict criteria than we would ever think of imposing in the United States in the sense that we do not require scientists to guarantee that what they are working on will, in fact, be available to the American people at some point. Scientists typically hope it will but then we do not require them before they do their research to provide guarantees that they will. Maybe you accept that implication and do not find it problematic but I would appreciate your response.

PROF. GLANTZ: Sure. Here are the responses to those questions: Very, I think, thoughtful questions and real issues.

One is I do not think scientists should do it. I do not think scientists should do it. I think scientists should do the science so I do not think the scientists at VAXGEN should be negotiating this. I do not think the scientists at the NIH or the scientists at the CDC should be negotiating it, that there are

very smart administrator types who can be doing the negotiating.

I think the scientists should do the science, so I agree with you. Scientists are not able to do this and not inclined to do it. I would not ask them to do it, but again I do not think a scientist is working, you know, out of, you know, out of their home, that they work for, you know, organizations and agencies that are very adept at negotiating all kinds of things. I mean, you could talk to my overhead administrator some time and you will see how well the scientists are able to get things negotiated for them.

Certainly the economics and politics, and circumstances might change but I think that that is unavoidable and I think it happens all the time in research, by the way.

So, you know, when one does continuing review on IRBs, one sees changing circumstances which leads either the scientist or the institution to say we are not going to do this research anymore. It might be that the scientists leave, it might be that population

at risk really was not there, things change.

I think that the fact that things change later does not mean that you do not try to set those standards ahead of time with the understanding that there are things that happen that might cause changes to occur so that, you know, if a country has an economic collapse, they had said we are going to make this vaccine, then it is a perfectly justifiable reason for not following through on the agreement, but it does not mean they did not make that agreement in good faith ahead of time, which is why my concern was with the word "agreement" when I was talking about the legalistic aspect of it before.

I am not saying, therefore, you go in and you sue the country for breach of contract, but I think what it means is to have a realistic plan and a real plan and a convincing plan assuming all goes as planned, because in the absence of a plan it will not happen. I mean, I think that is the reality.

The final thing -- I would say this idea of being more stringent than in the United States, when

076 was developed in the United States, an expensive antiviral regimen, the people who it was given to were poor people. The poor people were the primary recipients of the regimen.

I think that the realities are -- I mean, it is hard for me to think of something that was developed in the United States, which has not been distributed because of economic problems. There are certain inequities. Okay.

But what I would say to you is, if there were research done in the United States and the research subjects are drawn exclusively from the poorest populations, okay, and then that was -- none of that was made available to the poorest of the populations in the United States, only the wealthy could get it, that that would be a scandal of major proportions. It would be absolutely unacceptable.

And so I am saying that in reality -- I am saying that the economic realities of the developed world, like the United States, are so different that you do not need that kind of promise in the United

States. It just happens because of the wealth.

Now in Massachusetts, after Harvard Pilgrim has collapsed, it may not happen there anymore but the -- but I am just saying that I think one has -- the reason why one needs agreement is because in the United States we have seen the distribution of these goods all across social strata without such agreements and in the developing world we see that these goods have not been made available in the absence of such agreements.

DR. SHAPIRO: Rhetaugh, do you have a question?

DR. DUMAS: I am so -- I want to wait a while. I am really troubled by this discussion and I need to get a little bit clearer about why it is so. I have a number of questions. For example, if we know that something works and although a country group can or cannot afford it, is that the basic criteria for deciding whether or not it should be tried for them or made available to them?

There are also a number of assumptions that

are being made about the nature of sponsorship and about the obligations that that carries that is confusing for me. How does a single investigator negotiate and manage these issues?

I also have a concern about the question about the assumption that the standards that are applied here and the way that we manage the research enterprise cannot be transported to other countries. So I am going to hold off until I can get a little clearer about what my concerns are there.

DR. SHAPIRO: Fair enough.

Larry?

DR. MIIKE: These are agreements so I assume that there is another side that you agree with. I want to know -- I would like to see about how hard and fast the conclusions are, although I do not want to use the word "rules" but loosely use the word "rules" in this.

Suppose I am in a country where my part of the objective is to build a research capacity in my country and I am willing to take on research that may

not be of direct benefit to my people in the initial stages with the ultimate aim that I am going to have research capacity later on that I can have a greater say in these agreements that we are going to have with the host and with the sponsoring countries.

In those kinds of instances -- I guess my question is twofold. Suppose the host country disagrees with the morality we are imposing on them and you have heard these kinds of arguments before.

PROF. GLANTZ: Sure.

DR. MIIKE: And that is one. And second of all is that if my ultimate aim is to do exactly what -- that I agree with what your ultimate aim is but my way of getting there is different, how much flexibility are you willing to budge, to move in on from your side?

PROF. GLANTZ: What I tried to say at the beginning, answering your second question first, is that I think that in order to demonstrate ahead of time -- in order to improve research, that there are a series of criteria that have to be met, I think one is

that subjects are equitably selected, and I think that the second is that the benefits outweigh the risks. Okay.

And what I was saying is that I think that in the kind of research I was talking about where it is done because countries are too poor to use what is already available -- to get what is already known to be effective, that there has to be a showing that if the research is successful that the products will be made available.

If there is an alternative way of showing that, I am delighted to hear it and of course that is the ultimate goal. But before the fact I would want some showing, some demonstration that if new products are developed out of that research that will be made available in that developing country. That is why I say there may not just be a showing of money. It could be a showing of, you know, free license agreements and manufacture without royalty in the countries.

What you need to know at the outset is that

assuming that that happens it is still how much will it cost. If it still costs $1,000 to make --

DR. MIIKE: But that is not what I am asking you. What I am asking you is that suppose as the host country representative I say to you, I am willing to -- we are willing to do -- allow you to do research among our population and our people that may not be of widely available benefit just given the economic situation of the country.

We would like to get there but the way I feel about it all is you folks come in and you conduct research and we sort of have to agree or not and you have imposed these conditions and the conditions you have imposed are, hey, we are not going to come in to do research unless the research we do is available to your people.

I would say, "Why is that your business to tell me to do that?" I would like to do that eventually but can we not do some studies in the beginning that help us to build a capacity among our researchers to be able to have a more equal position

with you when you come in and say we want to do a particular kind of research or work.

PROF. GLANTZ: Okay.

DR. MIIKE: Because right now we are sort of like, you are the great benefactor and we can say yes or no and you have imposed all these conditions on us.

PROF. GLANTZ: Right. I thought that was your first question and so I mean -- so let me try to respond to that one, which is I think we can impose conditions.

Now whether or not this particular condition in that circumstance is an appropriate one in all circumstances, again I want to say that I think this -- my proposal works particularly well in circumstances where the justification for the research is that there are these economic inequalities and that what one is trying to do is deal with the economic problem.

But I think -- I mean, from my own perspective, I think it is another discussion, is that sure, I think, that we can impose conditions. When we provide money, we provide resources, we could say we

are doing it on the following conditions because we think that there are certain essential elements of human rights that have to be regarded.

So if, you know, the country -- if you had a country which said, you know, all the risky -- we were talking about this at lunch, all risky research will be done on women. Okay. We -- you know, bring your goods, you bring the money, but that is going to be our rule that all at risk research will be done on women and not on men. I think it is perfectly legitimate for us to say, well, we are not doing it.

DR. MIIKE: Just one response then. Then you would not be satisfied if the risk/benefit equation is applied only to the test population? You want the risk/benefit equation applied to the whole country? If I come in and --

PROF. GLANTZ: That is correct because I do not think research is designed to address the problems of the research subjects. Research is designed to have more generalizable impact and that the -- and that one has to show that the benefit -- I do not

think that the benefit part of the equation is satisfied by showing potential benefit just at the subjects but I think you have to show potential benefit to the population from which the subjects are drawn.

PROF. CHARO: Excuse me. Could I get on the list, please?

DR. SHAPIRO: Okay. Alta, I will put you next.

PROF. CHARO: Thank you.

DR. SHAPIRO: This is Alta Charo, who is on the telephone.

PROF. GLANTZ: I thought I was having a hallucination.

(Laughter.)

DR. SHAPIRO: No, you are having a dream.

(Laughter.)

PROF. CHARO: And obviously, Harold, I do not mean to keep cutting off any other people who are on the list, I just do not know whose hands have been up.

DR. SHAPIRO: All right. Your hand is up and

why don't you go ahead, Alta.

PROF. CHARO: Okay. It actually follows a little bit on Larry's question. I wonder if you might give your reaction to the following scenario that actually did occur which raises some of these problems:

The commission has previously had distributed copies of a paper that described a breast cancer study that took place in Vietnam. And it was designed to test the use of oophorectomy in order to prevent breast cancer reoccurrence in a population where chemotherapy was unrealistic because it was both logistically and economically out of reach for the majority of people in the population.

One of the concerns medically with the particular protocol had to do with the use of oophorectomy in the population of Asian women because this is a particular treatment that is associated with osteoporosis for which Asian women are at higher risk than non-Asian women. So it is a study that could have been done, for example, in Sub-Saharan Africa

without that extra problem of osteoporosis.

The reason why the study was being done in Vietnam was not because there had been some global examination of potential populations and the selection of Vietnam is the best of all populations, but rather because there happened to be -- and this is not uncommon in the academic world -- a relationship between the academic researcher and some people in the research community in Vietnam.

As I recall, I could be mistaken, but as I recall there were underlying documents that explained that the Vietnamese government wanted this research specifically to improve the capacity of the research community in Vietnam to help train more physician researchers in that country.

So that the IRB in the United States that is looking at this potential collaboration has to consider whether this kind of cost benefit analysis on the part of the Vietnamese government is sufficient given that the therapy, if it works, might well turn out to be useful for this population despite the fact

that ideally if we were free of all these other kinds of considerations we might choose to start this kind of research in a different country where the risk benefit analysis to the research subject would be even better.

I wonder if you could comment on how you might approach this kind of problem.

PROF. GLANTZ: I do not know. I mean, I need more time to think about it, I think, to be quite honest. It is a difficult question. I am not sure. You know, just sort of thinking out loud a little bit, I am not sure that I am convinced that one has to go to the country where it is most suited to do the research.

The question, I think, is whether or not it is appropriate to do the research in this particular country even if it might be more appropriate to do it in another country and the factors that would go into effect have to do, I think, with the health status of the women generally, what the impact of the operation would be on their health status.

So even if there were no other country, is it that -- where one might be better off doing this? Is it still appropriate to do here and so I do not know that one has to start with the ideal place as long as there are legitimate reasons for doing it in Vietnam.

PROF. CHARO: Okay. Thank you.

DR. SHAPIRO: Let me ask a question which is, I think, trying to clarify for my own mind some of the exchange that took place between yourself and Larry. That is, I certainly understand we want the potential benefits greater than the risks both for the people who are participating directly in the trial and for the country as a whole. So let's just accept that.

And as I understood Larry's question, and I apologize if I got it wrong, it was who is it that adds up the potential benefits and who is it that decides what is on that list?

Now I understood the little interchange as you are saying that what has to be on the list is the products of the research itself. What I took Larry to be asking was, yes, that is possible but maybe

something else ought to be on that list.

And the question to you is do you care what is on the list or do you have some restrictions as to what is allowable to go on that list?

PROF. GLANTZ: Well, the question of who has to determine the risks and benefits, I think that both the country in which the research is done certainly has to do that but I think that assuming that the researchers come from the United States, and I think that is what we are talking about, we have to do that, too. Somebody here has to do that also.

And the fact that it is satisfactory that the particular country is willing -- has a certain risk and benefit equation does not mean that it is enough for us. What I am saying is that -- what I am proposing is that we need to add this into our risk benefit equations particularly in research which is done because of the economic differentials between this country and the other country.

DR. SHAPIRO: I certainly see where you are -- I mean, I agree with everything you have said up to

a point. However, I do not understand why -- even though we have to be satisfied with the level of benefits that flow, and I think that is fine, but why those benefits have to flow in a certain form is not clear to me.

Now it may fit the particular case of economic hypothesis that you brought up before but it is certainly not clear to me why the benefits have to be of a particular form that we like.

PROF. GLANTZ: Well, I am talking about -- I mean, to use the AZT trials in Sub-Sahara in Africa as an example, one that comes up all the time are vaccine trials, that it would take the form that I am proposing because that is the benefits, that is the ultimate benefit that is being promised, that we are doing this research so that poor people will have access to therapies that are now not available to them.

DR. SHAPIRO: I can certainly understand that.

PROF. GLANTZ: And the question is, well, how

do we know that will be the case? If that is the benefit, how can we determine that that is the benefit? If we look at benefit in other ways, it would require statistical analysis to show that we have, you know, adequate sample size, to show that we have scientific benefit. But now there is an argument for economic benefit and I think that that should be subject to demonstration too.

DR. SHAPIRO: Thank you.

Tom?

DR. MURRAY: I am trying to see, Len, how your principles would work in a case like this where the technology is not new, it is old. It is isoniazid, where it is not expensive, it is relatively cheap, although given the average per capita expenditure in a particular nation it might actually be a hefty portion of that and where the purpose of a study was to find out whether isoniazid actually prevented death and active TB infection among people who are already HIV positive. This is a real study and not a hypothetical study.

Would you feel that the researchers were morally prohibited from conducting that study unless they could receive some reasonable –- iron clad assurance from the local government that, in fact, isoniazid would be made available if it were shown to be effective in people at different stages of HIV infection?

As it turns out, they have different -- different results depending on the stage of the infection.

Or would you say that they can do that in the reasonable hope and expectation that that government would eventually adopt that?

PROF. GLANTZ: No, I do not think they could do it in the reasonable hope and that is exactly the problem that I have. I think that things that have been done with the reasonable hope have not worked out and I do not see the reason for relying on reasonable hope when I think that there are mechanisms and I think that one could explore what those mechanisms might be to not have to rely on hope.

Why -- what makes the hope reasonable in that circumstance?

DR. MURRAY: Well, the government -- the governments -- I go to the government and I say, "Look, we want to do this study. It would cost you $2 per person per year to provide it if we can show it is effective." And the government health minister says, "Well, that is an intriguing proposition. Show us the evidence. I cannot commit today but we would -- if you can show us that, in fact, it works, if it saves lives, it prevents transmission of TB from now --"

PROF. GLANTZ: Yes, if you can show us it works, yes.

DR. MURRAY: Yes. "-- then we would consider it."

PROF. GLANTZ: At $2 then we would consider it?

DR. MURRAY: "But I can make you no promises.

PROF. GLANTZ: But why would they consider it then and not now? What would change between then and now that would make their consideration different?

DR. MURRAY: That they would have evidence that it actually works.

PROF. GLANTZ: No, but I am saying assume -- why don't we say assume that it works, would you pay for it? When he says, "It is intriguing," what does that mean?

DR. MURRAY: He says, "I do not" -- and he says, "I do not know. We have got this public health budget and I have not --"

PROF. CAPRON: What was the process?

DR. MURRAY: I want to see how effective it is. Your results might be that it is, you know -- prevents infection in 30 percent or it might be it prevents it in 95 percent. You have got -- I do not know. Show me the results. I mean, I think if I was -- if I were a health -- if I were the health minister of that country I would probably give you an equivocal answer and I would be right to give you an equivocal answer.

PROF. GLANTZ: Why?

PROF. CAPRON: No, I would give you a firm

answer but I could only actually deliver an equivocal result.

PROF. GLANTZ: I mean, the thing that surprised -- I mean, one of the things that really surprised me was the fact that nevaripine was not widely adopted at $4 a dose. I mean, that -- you know, when South Africa, which is among the wealthier countries, said, "Nevaripine at $4 a shot, even though it might reduce or it looks like it reduces HIV transmission by 50 percent, we are not going to buy it at $4 a shot." That is surprising.

Of course, one would think realistically if you could do this -- I mean, there are economic analyses that shows once the prevalence is over 12 percent that at $4 a dose it becomes very cost effective and so forth and so on. They said, "We are not doing it."

It would be useful to ask them that and not assume that $4 looks like a pretty good deal and, therefore, they are likely to do it. Why put the subjects at risk at that point?

DR. SHAPIRO: Excuse me. I will have only a couple of short questions. Alex, Eric and Larry, Diane. They have got to be short otherwise just say pass.

Alex?

PROF. CAPRON: We were reminded this morning by Bob Levine that some rules that are established look to the people who are affected as being very paternalistic and we have certainly heard that, for example, in this country from the prison populations on whom a great deal of research cannot be done.

My question to you is when we look at research being done in a country I assume that we are thinking of the people in the country as being in a different relationship to the people who are the decision makers than the prisoners are to the wardens. We would not think it was appropriate to say, "Well, we will do the research here if we can get the warden to agree."

Why -- what criteria would you use for deciding in which circumstances the politicians who

are speaking "for the population" are truly doing that? Is that a relevant thing for a U.S. IRB to start getting into or does that smack in the end simply of too much paternalism?

PROF. GLANTZ: I mean, I do not think it smacks of too much paternalism. That is not a problem that I would have. Whether or not it should be IRB's that do it --

PROF. CAPRON: Or whoever.

PROF. GLANTZ: -- raises another question but I do not think it smacks of paternalism. I think that human research regulation involves protecting the rights and welfare and the welfare part, I guess, one could always see as paternalistic but I would say to this to use your analogy that if a Department of Corrections said, 'Yes, you can come in here and test this drug and see if it works but I could tell you this: We are not going to use it in our prison population, you know, it is just not going to work. We just do not have the money for it but sure, go ahead, give it a shot.' I do not think we should do

that and I think that we could determine ahead of time whether or not they are -- looking at the budget of the Department of Corrections and looking at the nature of the health care that people get whether or not that is likely to happen.

DR. SHAPIRO: Eric?

DR. CASSELL: I guess my problem with it is that -- my problem with your answers is they all have to do with this moment and they all have to do only with your concern. You come in and you made -- you say, "Listen, if we can show this to be a good and effective drug at $4 a shot will you use it," and I say to you, "We will have to see." Why? Because your's is not the only problem on the line.

I am a good person and true and it suddenly turns out we are beginning to have a tuberculosis epidemic in the north and my budget has got to go to that tuberculosis and maybe two years from now we are going to get back to your drug and I am glad it is only $4 and we are going to hold you to the $4 two years from now.

So my problem with you is it is wonderful if you are doing crossword puzzles but if you are working with the budgets of health departments in the world I find it not sufficiently complex.

DR. SHAPIRO: Larry?

DR. MIIKE: Yes. Just a quick answer from you. I seem to have -- you seem to have a very definite idea of what benefits were and I asked about capacity building. Yet when Alta asked you the question you did not dismiss that out of hand. So did you agree that -- did you agree with her that it was okay to conduct that experiment in Vietnam when the benefit explicitly was really capacity building and not availability of that procedure?

PROF. GLANTZ: So that -- I did not understand that from her question. So that when this was done that oophorectomy would not be available to the women in Vietnam?

PROF. CHARO: No. Well, to clarify, Larry, it was not clear at the time the research was starting whether it would ever become available. It depended

on the outcome of the research, how effective it turned out to be for preventing breast cancer reoccurrence, and how severe the side effects were, including things like osteoporosis.

My point simply was that this was an example of a protocol that was being proposed and justified on the basis that it was on balance potentially beneficial for this particular population in Vietnam but where the real motivation that was driving the research collaboration was about capacity building and if it were entirely about the science of looking at oophorectomy as an alternative you would not necessarily start with that population. You would start with one where the risk benefit analysis would be more favorable from the beginning.

I mean, as with most things, it was not really clear at the outset how it would all turn out both scientifically as well as economically.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: It seems that some of the issues that we have brought up might be addressed by

looking at what has happened when U.S. researchers go to developing countries to do their work and for us to have a careful analysis of what has happened, in fact, instead of speculating so much about what might happen or speculating about whether people feel a sense of paternalism.

I feel just a strong need for some empirical evidence of what happens and could you speak to what typically happens when researchers do this kind of work?

PROF. GLANTZ: You know, I do not know if I could say what typically happens and I think that given the epidemics of AIDS, in particular, that in terms of research that is done in particularly in the developing countries, so if you look at things like polio vaccine and stuff like that, you know, that research was not done in the developing countries. About 15 or 20 years after it was distributed in the United States it got distributed to developing countries.

But I do not know if I could tell you

typically. What I can think off hand -- I do not know, maybe Bob could help on this -- is research that is done to resolve those economic types of problems where we need less expensive things for those countries that get developed and then are widely paid for or distributed.

DR. SCOTT-JONES: Okay. Well, polio is an example. Polio vaccine -- how widely distributed is that in say Sub-Sahara in Africa? Isn't polio still a problem there?

PROF. GLANTZ: I cannot talk about Sub-Sahara. I do not know. I do not know what the answer is.

DR. MURRAY: We are very near worldwide eradication on polio.

PROF. GLANTZ: That is my understanding.

DR. SCOTT-JONES: We are?

PROF. GLANTZ: Yes.

DR. MURRAY: Yes.

DR. SCOTT-JONES: Okay.

PROF. GLANTZ: Close to it.

DR. SHAPIRO: Well, thank you very much. Once again, thank you for coming here. You are welcome to remain. You are not obligated but you are welcome to remain with us this afternoon.

PROF. GLANTZ: Well, I appreciate the opportunity to speak with you. Thank you.

DR. SHAPIRO: Thank you.

Let's turn now back to Professor Levine who talked to us this morning.

Now this afternoon, as I mentioned earlier today, we are really asking Bob to take on a subject which is more directly relevant to the subject that we will be talking about tomorrow morning, which is the overall -- our so-called comprehensive report.

As you know, federal regulations in this area very often start off by having you decide what research is so if you talk about looking over a system from the top down a concept of what we mean by research in this context is extremely important to put it mildly and Bob has thought about this a good deal over time and so we hope to benefit from your

observations.

Thank you again for being here yet again today. Thank you.

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS

PANEL I: THE DEFINITION OF RESEARCH: PROBLEMS AND ISSUES

ROBERT J. LEVINE, M.D.,

YALE UNIVERSITY SCHOOL OF MEDICINE

DR. LEVINE: Being here for two different topics caused your executive director to tell me this morning that I was entitled to two muffins for breakfast.

(Laughter.)

DR. SHAPIRO: Only two, right?

DR. LEVINE: I only took one.

DR. SHAPIRO: In that case we owe you a few.

PROF. GLANTZ: But I took a letter of intent.

PROF. CAPRON: People speaking on only one topic got three muffins, Bob.

(Laughter.)

DR. LEVINE: Good point.

The discussion you were having with Lenny Glantz, I would really personally prefer to continue that discussion but then you might take one of my muffins away.

(Laughter.)

I do want to make one comment, though, and that is when you bring up the experience of the United States in thinking about research involving prisoners, that would be a marvelous case study for you where a national commission confused the agendas of prison reform and research involving prisoners, and set up a bunch of criteria for justification for research in prisons that even the prisoners launched a class action suit saying that the regulations that derived from this deprived them of their constitutional rights to participate in research without due process.

This suit was never litigated because on the evening before it would have been litigated the Food and Drug Administration withdrew its regulations but it is important to keep clearly in mind what the

agenda is in developing guidelines for multinational research. So much for that.

Now that I have given advice on guidelines for research I will turn to what Marjorie thought I should talk about and that is just what is research.

I am going to have a much less formal presentation this afternoon than I had this morning and I hope the reason for that will become clear soon.

I think really that there are so many particular problems in the consideration of definitions and in consideration of what is at stake in the definitions that I would like to allow maximum time for conversation about this.

First, I will begin by telling you something you already know.

(Slide.)

Here are the definitions of research and of practice that were developed by the National Commission and somewhat modified for incorporation in the federal regulations.

It is important to notice that as the National Commission developed its definition it partly created the definition by showing a contrast between research and practice. It said, "This is practice not only in the field of medicine but also in various fields of behavioral therapy."

Why would it do this? Well, the main reason for this is that the National Commission was given the mandate by Congress to consider the boundaries between research and something that it called the routine and accepted practice of medicine or routine and accepted practice.

So it was responding to a congressional charge. An awful lot of the legislative history of why the Congress decided to create a National Commission has to do with people persuading Congress that it was very, very difficult to tell the difference between research and practice.

As you look in the legislative history the majority of cases that the Congress identified as evil research, there was no research at all going on. What

was really going on was malpractice like one of the cases was sterilization of two sisters with mental retardation. This was not research. No one was attempting to contribute to generalizable knowledge. They were attempting to solve a public health problem and that is the passage of what they considered defective genes on to the next generation.

This is something -- this is why we have this -- these definitions that are developed as a contrast between research and practice. This, I think, explains why although this definition might apply quite well to the mainstream of biomedical research that it is a poor fit for social sciences. It is a poor fit for public health work and it is a poor fit for research in the area of health policy just to name a few.

Now looking more deeply into the definition of research, there is in the first line the word "designed." This is an artifact of what personalities were involved in developing the definition.

It was my assignment to write the definition

and I relied on what the class of activities was intended to accomplish. As it turned out, one of the commissioners was a radical behaviorist named Joe Brady and behavioral psychologists do not recognize anything called "intent."

There was a long debate lasting around 14 months with some breaks and we finally negotiated a compromise with the word "design" but many of us walked out believing that this really was what the researchers intended to do. The behaviorist position is you cannot see or measure intent.

My position was if all you do is look at the behaviors then you have no possibility of prior review. You have to wait until they behave and then you evaluate it. So that is the meaning of the word "designed."

As a footnote to that I want to say that my job for the National Commission was in their words to write its background theoretical essays so each sentence in Part II.B of the congressional mandate to the Commission became the title of a paper I wrote for

the Commission.

The very first paper I wrote was a paper called "A Consideration of the Boundaries Between Research and the Routine and Accepted Practice of Medicine." It is the worst paper I ever wrote and that is the one that was selected for inclusion in your briefing book.

About six months later I wrote a better paper in which I took all of that back. Basically when I wrote that first paper I, too, like everyone else, had bought into the distinction between therapeutic and nontherapeutic research and when I recognized the error in that and the National Commission endorsed my recognition I then wrote something else.

And what I did is after your briefing book was put together I Fed Ex'd a copy of part of chapter one of a book I wrote called <u>Ethics and Regulation of Clinical Research</u>, which contains what the Commission finally decided with regard to definitions.

Also in contrast to the papers I wrote for the Commission it is very much briefer. I think it is

only four or five pages long and it has all you need to know about this.

(Slide.)

Now the National Commission did recognize that there was another class of activities which many people called research and which many of them called therapeutic research.

It gave the name "innovative or nonvalidated practice" to this class of activities and I have snipped part of their definition of this. "Significant innovations in therapy" should be incorporated into a research project. That is the therapy itself is not research. Rather you want to do research to see whether or not this novel therapy is all you hope it is. So the research would be designed to establish their safety and efficacy while retaining the therapeutic objective.

(Slide.)

Now I think there is almost no analogy to innovative practices in social sciences, in laboratory psychology or social psychology, in epidemiology, and

there is little analogy to this in public health, and this also is symptomatic of the fact that the definitions really do not -- there is really not a good fit with the requirements in these fields.

I think what we all desire is a term that will define the scope of applicability of guidelines for the conduct of research. The term "research" properly understood does not solve that problem for you.

I want to also go on to say that it cannot solve that problem for you and it should not be distorted in an attempt to solve that problem. There is, in general, a problem with stipulated definitions in public policy documents and many of our public policy documents have extensive stipulated definitions.

The big problem is that when you stipulate a definition for a word that is commonly in use that it does not convey meaning to people who did not participate in the stipulation unless you have a footnote repeating the stipulated definition each time

you use the word.

The term "research" as it was defined by the National Commission has the advantage of being roughly identical with what is in Webster's Dictionary. In fact, in the days when I was writing these background theoretical essays for the Commission usually the top few pages in the -- in what I submitted to the commission were photocopies of various pages out of Webster's Third International Dictionary just to make sure that we were all talking about the same thing.

One time in order to amuse myself I kept track of the proceedings of the Commission's debate on research involving the fetus and in the course of one afternoon four separate apparent agreements, consensus agreements dissolved when the Commissioners were informed that they had departed from their stipulated definition in reaching that agreement. I just cannot emphasize enough to avoid stipulating definitions.

Now I think current public policy recognizes the problem that we have. It is not unprecedented for

us to say, "Well, the definition of research does not help us define the entire universe of activities for which we want to have, let's say, IRB review, informed consent of the type that conforms to the standards usually associated with research."

And also the definition of research is too broad. There are some things that fall within the definition that really we do not want to waste all that time and energy with IRB review and so on.

One example of a document -- one of the first documents that deliberately extended the scope of application of the standards for research was in 1983 when a group of people working out of the Hastings Center put together some guidelines for the -- for maintenance of confidentiality in epidemiologic studies on what was soon to be called AIDS.

What they -- we had, in fact, quite a contingent from the CDC participating in the deliberations on this and we went into what seemed to be endless debates about whether research guidelines should be applied to activities called "surveillance"

or "public health practices."

And the way we solved the problem was not by stipulating a new definition of research but by stipulating that in the field of HIV infection that the requirement for IRB review and informed consent should be maintained equally to these variously named activities such as research, surveillance and the like. This seemed to solve that problem.

It was not that we were saying that all surveillance conducted by public health officials should be reviewed by an IRB but there were features of AIDS that it seemed to us would be -- the proper response to these features of AIDS could best be managed by requiring IRB review.

I am referring particularly to the fact that in the early 1980's the discrimination against the sorts of people who were in the so-called "at risk" groups for AIDS was formidable and we felt that it was necessary to have some systematic look at maintenance of confidentiality safeguards.

We also have in our public policy experience

various ways that we limit the application of research regulations to things that do conform to the definition of research.

(Slide.)

For example, in our Common Rule we have a variety of activities that are identified as exempt from coverage by the federal regulations. Now these exemptions were not recommended by the National Commission.

What the National Commission instead recommended is that for activities of this sort there should be, in general, expedited review. However, the nature of expedited review recommended by the National Commission is vastly different from what came out in the regulations that were published in 1981 shortly after the National Commission filed all of its reports.

What would be eligible for expedited review was largely related to the experience of the institution in which the expedited review would be carried out and what we got instead was a list of

procedures which the National Commission had published. What they did is they found a list of procedures that had been nominated for expedited review within the NIH Clinical Center and they published these as, for example, you might consider procedures like this but then the regulation writers got it and said, "It is not for example anymore. These are the procedures. No others." There has been quite a bit of inflexibility until recently in interpreting that definition.

Now why did we end up with a class of research activities exempted from coverage by the regulations? It largely has to do with the successful lobbying of a political scientist named Ithiel de Sola Poole (phonetic), who went directly to the Congress and said, "Social scientists like me, we are not like those NAZI physicians. We do not do anything but talk to people. And if you impose a prior constraint or prior restraint on our talking with people, this is unconstitutional."

What he did is he distorted the meaning of

prior restraint as the term is used in constitutional law. In any event, he got what he wanted and we ended up with a whole bunch of exemptions and they are really not all that bad especially if we keep in mind the exhortation I have put on this slide.

(Slide.)

This is by me. Not by the National Commission or the regulation writers. And simply put it means that exemption from coverage by the regulations is not the same as exemption from the ethical obligation to be responsive to relevant norms and principles. Just because it is not covered by regulation does not mean, for example, that you can do certain sorts of things to or with people without their informed consent.

What we think, though, is that the probability of injuring or exploiting people in the exempt categories is so small that it is sort of like a de minimus standard. We are not going to use the energies of the IRB to deal with these things.

Now I want to close with four

recommendations. Some of these are already implicit or even explicit in what I have said but this is also by way of summary.

First, I want to urge you to recognize that the term "research" does not define the scope of what you want covered by research regulations or by the Code of Federal Regulations. In particular, you cannot force this term to fit all of the areas in which you might want to have IRB or some other competent committee conducting review.

Secondly, you cannot stretch this definition or this term to cover all areas in which informed consent is necessary. Even the National Commission in defining research as something to be contrasted with medical practice acknowledged not only did you have to get informed consent in medical practice but every single requirement in the regulations for the protection of human research subjects was, in fact, derived from the Common Law developed in the course of litigation in medical practice, not in research. So there is a strong relationship between the areas at

least with regard to informed consent.

My second recommendation is please do not stipulate definitions of terms that are already in common use. It will inevitably lead to confusion.

My third recommendation is to define the categories for which you would like to see review by an IRB or some committee like that. It might be that you want to say public health surveillance in the field of HIV infection should be reviewed by something that looks like an IRB but I do not think you would want to extend that for public health surveillance in response to reports of food poisoning. You just do not have similar features that would call for this degree of review and prior approval.

And finally I would recommend blending exemptions with expedited review procedures. There are many areas where there are judgment calls. If something is in an area that you have exempted from coverage by the regulations many inexperienced people in the field who really want to follow -- who really do not aim to be cutting any corners, they really want

to be behaving ethically and in accord with regulations, may misread the set of exemptions and say, "I think I am dealing with research in exempt category."

What I would do is have expedited review of activities in the exempted fields. Now the expedited review would not be the full fledged selection of subjects, you know, informed consent, balance of risks and benefits. The expedited review I am calling for is simply to verify whether the proposed activity really meets the criteria established in the exemptions.

Thank you for your attention.

DR. SHAPIRO: Okay. Thank you very much again, Bob, for those thoughtful remarks.

Members -- any questions from members of the Commission? Comments, questions?

PROF. CHARO: Request to be put on the list.

DR. SHAPIRO: You are on the list and you are speaking.

PROF. CHARO: It happens every time.

DR. SHAPIRO: Alta.

PROF. CHARO: Bob, first, thanks very much.

I am trying to understand how one would implement your four recommendations. Okay. And I am thinking now specifically about your last one where you said define the categories of things for which you would want an IRB or IRB type review because I am trying to understand how one might develop such a list.

Am I right to understand that you are thinking things like any research that involves a physical invasion of the body would be on our list of things to be reviewed? Anything that involves questioning people about the sexual habits of their family members as opposed to themselves only, right?

I am not sure I really understand how you would implement the suggestion.

DR. LEVINE: What I am --

PROF. CHARO: I am sorry. I cannot hear you. Can you use the microphone?

DR. LEVINE: With that reminder, too.

DR. SHAPIRO: You have good eyesight, too.

(Laughter.)

DR. LEVINE: You could tell the red light wasn't on. All right.

Now what I am talking about are the things that are outside the biomedical mainstream.

PROF. CHARO: Okay.

DR. LEVINE: So physical intervention is something that is rarely done outside the context of biomedical research and when it is done outside that context as, for example, the NASA does research on osteoporosis, this comfortably fits within the medical model in its definitions.

What I am more concerned about is research in such fields as epidemiology, demography, social psychology, other psychology, and so on.

Your question about, well, would you say anything that entails asking sensitive questions -- for example, the example you gave about, for example, sexual behavior, should that be reviewed by an IRB? And my answer is you are going to have to think about

that and my tentative response is you are probably going to conclude no because then you are starting to regulate the activities of journalists and other such people who inquire into such matters fairly often these days.

I do not want to go any further with this but it is mainly you are going to find -- for example, one of the activities that I recommended for the National Commission to consider is a form of practice which is not research which I call practice for the benefit of others. This would be proposals.

For example, one hot topic in the 1970's was using the major tranquilizers as they were called in those days to quiet people in mental hospitals and one of the purposes of doing this was to create -- was to contribute to the comfort of those who had been annoyed by the noisy patient.

I thought even though that does not conform to the definition of research that is something that you might want to have reviewed by something like an IRB to see whether or not particular cases or policies

in general -- other areas that I would consider under this would be, for example, program evaluation. Do you want IRB review of all program evaluation?

You will probably decide for the most part no but the example that came out in the New England Journal about ten years ago of rewarding residents in a hospital for decreasing the numbers of laboratory tests they got as routine tests on admission, there is something in there that might want you to say maybe we would want to regulate something like that. That is the sort of thing I am aiming at, Alta.

PROF. CHARO: Well, if I can -- may I just clarify or ask for clarification?

DR. LEVINE: Sure.

PROF. CHARO: Bob, first of all, the reason I gave that second example about sexual habits is because of the e-mail that I think it was Kathi Hanna distributed yesterday for the commission members from the story about the Virginia Commonwealth University. One of the objections had been from a man who had discovered that his daughter had been surveyed with

questions about whether or not her father had various kinds of, you know, genital abnormalities.

So I guess I am beginning to wonder if at this point rather than lists of specific kinds of research that would be issued by somebody and you have used the phrase "you would want to" and I am not sure exactly who the "you" is, is what you are really getting at is situations in which there is an expectation of a certain kind of relationship between the professional and the nonprofessional that is not, in fact, present.

And the reason why I am comfortable with IRB review of research even when it is comparing two standard therapies, one against the other, even though our investigators here may bitterly complain about it, is precisely because to a very small extent but nonetheless to a real extent at this point the investigators are now putting the interest of science as their primary concern and the interest of their patient second.

They do not tweak things as best as they

could possibly guess just for the patient the way they would in a purely clinical encounter. They try to put people on standardized regimes and they are going to try to keep them there until there is a real good reason to take them off because they want to get something out of it.

And that actually transforms what is usually a situation in which the patient feels the doctor is looking out for her interests to the exclusion of all other interests into something slightly different.

So is it possible that what we are getting at here in your examples about benefit for others and the resonance, any situation in which one senses that there has been a slight change in the kind of fiduciary duty that is usually expected between this kind of professional and this kind of lay person?

DR. LEVINE: Thanks again, Alta.

First, the topics that I am discussing now that -- of activities that lie outside the mainstream of biomedical research are topics -- are areas in which we tend not to have a professional with

fiduciary responsibilities.

PROF. CHARO: Yes, exactly.

DR. LEVINE: So I think in most of the research area where you are dealing with folks that have fiduciary responsibilities you are dealing usually with practitioners of either medical or behavioral or related practices.

Now the VCU, the Virginia Commonwealth, experience was appalling. I do not think it had anything whatever to do with whether or not the guidelines were adequate to direct activities to -- or to class -- this was clearly a research activity. I think the thing that strikes you most -- the thing that strike me first is why were they having young females describe the sexual behaviors of their fathers? Where -- I think something must have been left out of the story that got to me. There must have been some basis for thinking that these young people would know about the sexual behavior of their fathers but the issue there was not whether or not something required review by an IRB. I think it was clear that

it did.

Now your discussion, Alta, of research in which you compare two standard therapies, I do not see the problem there. As far as I am concerned if you do a formal evaluation of two standard therapies you are introducing into the practice of -- let's say these are medical therapies -- into the practice of medicine interventions or procedures that are done for no purpose other than to develop generalizable knowledge.

Just the fact that you are randomizing people to one treatment or another. So I see this as a non-problem. I also cannot restrain myself from recalling the last conversation we had in December. This is why I hold that there is no such thing as therapeutic research. There is always components of the activity that are not designed to be beneficial to the individual subjects.

Thank you.

DR. SHAPIRO: Thank you.

Jim?

DR. CHILDRESS: I think in a way I am just asking another version, a looser version of Alta's question. I think what you have provided, Bob, has been exceedingly helpful both in terms of historical perspective but also in terms of some of the difficulties in trying to set conceptual boundaries and, in particular, trying to use research as a category that will help us really to determine what we want to cover under regulations.

But then that -- now to raise Alta's question in a more general way -- that does force us then to consider -- not -- since you have asked to define categories -- the kinds of criteria we will use to define categories that we think should be brought under some kind of protection, particularly some kind of committee review, IRB review or IRB-like review, and informed consent.

So I wonder now sort of loosening it up a bit, tell us about the criteria you think are important -- would be important for what we should include as we are trying to define those categories.

DR. LEVINE: The categories that I think are important -- I am just going to give a partial list of these categories. The first is a category in which you have in general terms somebody who is socially relatively powerful interacting with people who are perceived by themselves as socially somewhat less powerful in which the purpose of the interaction could be confused. I am thinking particularly of areas in which people might presume some sort of fiduciary relationship where none really exists.

DR. CHILDRESS: Thank you.

DR. LEVINE: I am also thinking about areas in which people are asked to do things that are for the benefit of the collective, small collectives or large collectives, and which put them to either some risk of physical or social or psychological or for that matter economic injury where it may not be clear what the purpose of the activity is or what the nature of the risks might be.

These are the sorts of things that I -- and as -- I would not say all things that have those

criteria ought to be made the object of regulation but within those categories you could identify -- earlier I tried to develop a distinction between surveillance for the incidence or prevalence of HIV infection or the incidence or prevalence of risk behaviors in that field and said you might want to -- Alta, when I say you might want to, I mean the NBAC might want to develop some sort of guidelines for review of activities in that field while at the same time activities that are in all superficial respects identical that are conducted in response to reports of outbreaks of food poisoning.

You might decide that there are -- this lacks the features, particularly in this case the grave consequences of breaches of confidentiality that would trigger a need for oversight.

Now I realize that what I am proposing is not likely to be found -- is not likely to make the garden variety bureaucrat enthusiastic. They, I think, in general, would require very broad definitions and everything that conforms to this definition must be

done one way and everything else need not but I think it would lead to a more sensitive approach to providing oversight for the various activities we are talking about.

I think, also, you have a big -- I mentioned health policy research. There you have got a big problem. There are certain sorts of activities where the unit of measurement is not the individual. The unit of measurement is na collection of people. I mentioned the project which was designed to evaluate the effects of rewarding residents for ordering fewer routine laboratory tests.

But there is many health policy research where the -- you have a controlled clinical trial where one arm of the trial is hospital A and the other arm of the trial is hospital B, and the trial is designed in such a way that if you happen to be in hospital A there is no way you can get treated the way they are treated in hospital B. That is one where you would have to have special oversight procedures which may not involve classical informed consent.

DR. SHAPIRO: Thank you.

Marjorie?

DR. SPEERS: Bob, first let me begin by just thanking you for doing double duty and staying here for this afternoon.

I have two questions and they really follow, I think, on what Alta and Jim have asked.

One is, is what you seem to have suggested is that there are a number of activities that should be covered that are now not currently covered and so I just wanted to push you a bit on how broad you would want to be and particularly thinking in terms of the nonbiomedical area.

Would you say that all data collection, data analysis activities, should fall under some type of human subjects protection? And then assuming again from there that you have exemptions or expedited review process or something so how broad do you want to go?

The second question is it was interesting to hear your history and to think about we are in the

situation we are in, in a sense, because of the mandate that the National Commission had and that was the charge to differentiate between medicine and practice, which led us then to divide the world into research and nonresearch, and then what fits under the regulations.

And it leads me to think about whether we should not define research. Research may not be the issue as you were suggesting perhaps with some of the categories that you named. But instead to define areas where there is potential risk and, therefore, some need for ethical review and informed consent.

DR. LEVINE: Thanks, Marjorie. I am going to try to deal with these two questions.

There -- you and I have discussed these questions before and I think you know that I do not have the answer. I have some suggestions of what might be some of the answers or subanswers.

Should we establish regulatory oversight or regulate all data collection? That for me is pretty easy. The answer is no. There are certain sorts of

data collected for certain sorts of purposes that I think you should take a closer look at.

I do not think there is a problem with collecting data, let's say motor vehicle people collect data that have to do with, you know, what they think is important about who drives cars in this state. I am not going to worry for the most part about that.

On the other hand I think one might want to be concerned about collection of data by insurance companies, particularly when these data are fed into widely shared data banks where everybody in the insurance business has access to the data and where if you happen to be working for a corporation that is self-insured that means your employer gets your medical history and other such things.

I think there is something in activities like that that you might want to wonder about whether you would want some sort of oversight for that.

I do not think I would turn a job like that over to an IRB. I mean, we heard earlier today about

how hard it is for an IRB to understand the ethics and social conditions in places like Vietnam and Burma. I do not think that our IRB is quite capable of understanding the safeguards for privacy that exist in Washington, D.C. We have all we can do to keep up with what is going on in our own city. So to ask IRB's to contemplate such things as nationwide or even larger databanks would be problematic.

To get to your other question should we link it to potential risk and my answer there is risk should be a criterion but never the criterion. There are many, many activities that are far riskier than research that we do not regulate. Medical practice, for example. I do not think research -- if you believe the Institute of Medicine, I do not think research accomplishes or research leads to the death of 98,000 people every year.

If you want to find ethical violations you are much more likely to find them in the clinic and also we have data from the Secretary -- the HEW Secretary's Commission for the Study of Compensation

for Research Induced Injury.

They compared what the outcomes were for people who have the same diseases in the same institutions and they enumerated the instances of permanent or temporary disability and found right across the board you were much safer if you were in a research program than if you were not.

So it is not risk. Risk is not the only thing. But risk is something. If something is utterly risk-free and I would include among the risks the risks of dignitary harms then I do not think you -- it may be that you might accomplish something by regulating it but I do not think that your accomplishment would measure up in a cost benefit analysis.

DR. SHAPIRO: Alex?

PROF. CAPRON: One of the things that you had on your list of recommendations for us was avoiding the use of stipulated definitions and yet every time you speak on any of these subjects I always expect to see you riding in on a horse with a lance aiming at

windmills on your favorite topic of therapeutic and nontherapeutic research because certainly those are terms which have wide currency and are used all the time, which you would have us abjure.

I wanted just to make sure that I understood what the reasons for that were because you have stated over time a number of different reasons. Some of them have to do with the peculiarities of the -- or infelicitous of the Declaration of Helsinki.

Some of them have to do with the way in which the terminology reinforces the therapeutic misconception that people can get in research projects, particularly those that are denominated therapeutic research although not exclusively. And so it is a way of saying do not use the term sloppily. It is an oxymoron to speak of therapeutic research, research is research, and it may be done in the context of researching on a disease with the intention of trying to develop a better treatment for the subjects but it is still research as to them.

This Commission itself used the division of

those things which are related to and intended to benefit people and those that are not in our report on research with -- on conditions that may affect decision making capacity. I wonder if -- since I know you are familiar with that report -- if using that as a jumping off point or other work that you think we would be familiar with, you would say for us when you think such a distinction is usable and has ethical validity, some such distinction. Draw the lines as you think is appropriate.

And then how we ought to express that most felicitously and in a way which does not fall into the problem that I started off with which is the stipulation. In other words, coming up with terminology which we know what it means but which is not going to sit well with people if they are not constantly reading the definition.

DR. LEVINE: Well, first let me give you some side effects of this semantic mess. At least one person in this room who is a member of the Commission has argued vociferously with me that the NBAC did not

use this distinction in the report on mental incapacity.

PROF. CHARO: And I would continue to take that position, Bob.

DR. LEVINE: Alta, you are not in this room. I am not talking about you.

PROF. CHARO: Oh, that makes two of us then.

(Laughter.)

DR. LEVINE: But there are two members of the Commission who have argued vociferously --

(Laughter.)

DR. SHAPIRO: Anyone else like to raise their hand?

DR. LEVINE: Secondly, I have in the aftermath of the publication of the NBAC report on mental -- you know, the mental incapacity report, I have asked several Commissioners what if you had a placebo controlled trial of an antipsychotic drug in patients with schizophrenia, would this be therapeutic or nontherapeutic research? The responses I have received from members of this Commission are equally

divided. Half have told me it is therapeutic and half have told me it is nontherapeutic.

The immediate spin off of that is whether or not your recommendations, I think they are number 11 and 12 or maybe -- the number has changed a little from the draft to the finished product, whether or not you would evaluate one according to one recommendation or the other. You would have quite a difference of opinion among the people who created the policy recommendations.

My main objection -- first, therapeutic research is itself a stipulated definition but my main objection to the use of the term is that it leads to what I have called the fallacy of the package deal, that what has happened is that in general those who are guided by the concept of therapeutic research will look at a protocol if it contains one component that is intended to be therapeutic.

Like, for example, in a placebo controlled trial of an antipsychotic drug the antipsychotic drug is intended to be therapeutic and, therefore, the

entire protocol is evaluated according to the standards developed for therapeutic research.

The standards in the ethical codes that use the distinction tend to be much more relaxed for therapeutic research and so when I wrote my paper for the New England Journal I just mentioned a few of the procedures that had been justified according to standards developed for therapeutic research.

These included the performance of multiple endoscopies on patients who if they were treated in clinical practice would have received no endoscopies. This was a requirement that was during the placebo control trials of the H2 receptor antagonists in the treatment of peptic ulcer.

We also see the insertion of a catheter into the coronary artery for purposes of administering a placebo injection. We see liver biopsies performed on patients for no reason other than to maintain the double blind in a placebo controlled trial of cholostriamine (phonetic). I can go on and on and on with this. I do not think we should continue to make

it possible to have these packaged deals.

Now what I have recommended instead is exactly what you will find in the current federal regulations on research involving children. They say you do not look at the package. You look at in the language of the regulations. You look at interventions and procedures that hold out the prospect of direct benefit or that do not hold out the prospect of direct benefit.

Then you have got separate passages in the regulations that say here is how you justify the former category if they hold out the prospect of direct benefit and here is a different way -- a vastly different way of justifying not research protocols but interventions or procedures that do not hold out that prospect.

Now if you are working with an intervention that holds out the prospect of direct benefit you could have a mortality rate of five percent. If what you think you have is something that is going to reduce the death rate from a disease that is at 15

percent without treatment, if you are going to reduce it down to a level that makes it worth taking a risk of a five percent mortality.

On the other hand if you are dealing with an intervention or a procedure that does not hold out the prospect of direct benefit you are limited to a ceiling of a minor increase above minimal risk in the children's regulations. It is a vastly different way of looking at things.

One final statement: I do not want to imply that the endoscopies, the coronary catheterizations, the liver biopsies and so on that I mentioned a little while ago, I do not want to imply that these are inherently unethical. What I want to say, though, is that they should have been justified according to standards that were not -- that were not used to evaluate them.

DR. SHAPIRO: Thank you very much.

I am afraid we are going to have to end this particular session because we do have still quite a number of things to get done this afternoon.

Let me propose that we try to take about a ten minute break and then reassemble and begin our discussions on some of the material that Ruth referred to this morning. Dr. Berkley will be here shortly and then we will go to his discussion and return to our own discussions.

Thank you very much.

(Whereupon, a break was taken from 3:07 p.m. until 3:20 p.m.)

ETHICAL ISSUES IN INTERNATIONAL RESEARCH (continued)

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: All right. Let's begin our discussion this afternoon and turn to aspects of some of the written material you have distributed with a call to this meeting.

I think I am going to turn it over to Ruth in a moment but I think it is 2B. That is right. Is it 2B or is it 2D? I guess it is 2D.

PROF. CAPRON: 2-David.

DR. SHAPIRO: 2-David, right. Choosing

research design -- study design, I think.

Ruth?

DR. MACKLIN: Okay. Thank you.

We have here a 19 page document. We are not going to go through a 19 page document. I think the most efficient thing we can do in the relatively short time is go directly to the findings and recommendations. They are bolded and we will walk you through it and I hope we can get through those. If we do not get through it before Dr. Berkley's presentation is scheduled for or before he actually comes and is ready to give it, perhaps we will have time in the remaining session in the afternoon to discuss some of this as well as to go to the -- what the main theme was of the day.

So the first finding -- and these are -- remember what -- the first finding appears on page 11 at line 5 and please recall what this is all about. These findings -- all of the information that proceeds leads up to the findings and provides evidence for them and also attempts to provide some kind of

justification for the recommendations that follow the findings. The findings -- the recommendations are based on the findings and the text that precedes both elucidates and tries to justify. Okay.

So the first finding -- and I guess we will just stop after each one and then go on to the next.

The first finding, 1A, page 11, although the potential benefits of participation in research may be an inducement for people in resource poor countries who lack access to medical care, it does not diminish their voluntariness to the point of being an undue inducement.

DR. SHAPIRO: Tom?

DR. MURRAY: First, my compliments to the author or authors of the document, which I found very, very well done. I worry a little bit about finding 1A in that it seems -- the argument seems to rely heavily on the particular definition of what counts as undue inducement. Now a definition is cited on page 10, lines 26 and 27. It is a definition that was quite appropriate in the context of studies done in the

United States where the reason one might get somebody in a study would be to make an excessive, unwarranted, inappropriate or improper reward.

I guess I am not comfortable relying exclusively on that definition and I could readily imagine making in the vernacular an offer you could not refuse to a subject that would not constitute excessive, unwarranted, inappropriate or improper reward but would be a function of access to something, to good health care or something in a very resource deprived country.

So I guess I am saying the class of morally problematic offers one cannot refuse is larger than those stipulated in the definition and that we should be attentive to the larger class.

DR. MACKLIN: Can I just ask --

DR. SHAPIRO: Yes.

DR. MACKLIN: Would you -- since I think we know, if it could be documented, and I think people can document it, that there are people ho -- many people who enter research in the United States in

order to get better care than they can otherwise get. Those were uninsured, those were under insured, those who perhaps have -- go to public hospitals where they do get care but they would get better care on a research context.

Would you say there is a close enough analogy between those potential research subjects in the United States and those in another country such that it may have arisen in other ways in the United States but the fact of entering research in order to get medical benefits is true in this country, too, for some people?

DR. MURRAY: I think that is correct on the facts, Ruth. It is true in the U.S. for some people. Whether it is true to the same extent and with the same kind of moral weightiness, I am not certain but I think it is -- you draw a very good analogy and it would be worth pursuing that a bit.

DR. SHAPIRO: Alex?

PROF. CAPRON: I have three comments and I will try to be very brief in making them that I hope

you take into account in the redrafting. I will not attempt to redraft it now.

The first one is that the pronoun "it" in the second clause is ambiguous. Is the "it" the potential benefits of participation in researching or the disparity between those benefits and the person's existing condition? I think that is important then for the second point.

If one is talking about this, the way it is written here, in talking about voluntariness it sounds as though what our concern is something that is going to lead to the validity of their consent. If that is the case the point ought to be rewritten to take out this language about undue inducement which has all the problems that Tom just pointed to, and say it does not so diminish their voluntariness as to make their consent invalid or something.

And the third point is conversely if what we are concerned about is what we are usually concerned about, which is the -- when we talk about something being an undue inducement, it is that the researcher

is engaging in something -- a practice, the making of the offer of something, which is being made in a way to overcome someone's good judgment and to get them in. In which case we can drop the voluntariness from the discussion here and focus on the undue inducement by saying it does not amount to a condition or something which ought not to be offered.

Do you see what I am trying to say? It is sort of -- I think the present recommendation -- finding combines two disparate ideas. One is the effect on the individual and the other is the action being taken, the offering of medical care as part of research to people who do not otherwise have access to it.

I think it would be clearer if we could decide one way or the other of expressing it. So those are the three thoughts.

DR. SHAPIRO: Thank you very much.

Ruth?

DR. MACKLIN: Could I make this as a general plea? Maybe it is not. When the comment goes to the

wording, when it seems to accept the spirit but it goes to the wording and how to make it clearer or better, could I ask the commentators if they will provide that wording?

PROF. CAPRON: Well, excuse me, generally I would agree to do that. Here I would be happy for us to have a discussion as to what point we want to make because what I am sort of -- maybe instead of making three points I really made one point which is this does not convey to me whether what we want to express in this finding is that the offering of a good level of medical care to people in resource poor countries who do not otherwise have it is an acceptable act because the amount of effect that it would have on people is within an acceptable range and, therefore, it is all right to do it.

Or what we are doing is making a finding about people when faced with this that they continue -- they can continue to exercise the kind of judgment that we want people to exercise, that it does not render them involuntary. It is a great inducement but

it -- because it is not done as you point out on page 10, it is not done in a way which is unwarranted or improper. It sounds like a very good thing to do for people. It is, therefore, not going to overwhelm their voluntariness.

I mean, another way to see it -- it is a different -- the other way of doing it says, yes, it may overwhelm their voluntariness but because of what you are doing to them is basically a good thing it is okay to do it. I mean, you do things for children which they are not voluntarily choosing but we are perfectly happy to have you do it because it is a good thing to do for them, whatever the X, Y, Z that we are talking about here.

And so I think we need a substantive discussion because this is a finding and it sounds as though it is almost an empirical finding. If it is an empirical finding I would be very much more inclined to put the word "necessarily" between does and not because it seems to me that there would be certain situations in which a person's need would be so great

and the medical care being offered would be -- sound so wonderful that there -- if we are talking about voluntariness, you would say actually that has diminished their voluntariness to the point where they just cannot choose otherwise.

I mean, no rational person would forego this opportunity because the risks to the research, although existence, are not very great and the opportunities are just so great but we should stop talking about voluntariness. We need another mechanism.

So I cannot rewrite this until we have a discussion that says what we really want to say is it is okay to go ahead, you want to have a review mechanism to make sure it is okay, but we are not going to be relying on voluntariness as our justification here any longer. We are going to be relying on that review mechanism.

Or are we making an empirical finding or are we making a moral finding that although it is very likely to weigh heavily on their voluntariness it does

not deserve the pejorative name undue inducement. If that is all you are saying here, if undue inducement means something which is morally bad it is an improper or inappropriate reward, then the finding has kind of Bob Levine's problem with it. By having stipulated what undue inducement means so much you have disguised your real meaning here and it is a very minor point. It does not deserve a slap against the investigator but it really has still affected the voluntariness.

I do not know if that is clear but I know that this is not clear to me what is intended here and I cannot rewrite it without knowing what is intended and having a group discussion of that.

DR. SHAPIRO: Any other comments on this particular issue?

DR. DUMAS: My interpretation is that the possibility of undue inducement does not overwhelm the voluntariness of the subjects. Now if that is intended to say anything else I do not -- I did not get it.

I think the whole idea of what constitutes

undue inducement is not discreetly defined and we are making this decision a priori so we are talking about the possibility and we are saying that that possibility does not outweigh the possibility of wise choice on the part of the subject.

PROF. CAPRON: It is an empirical judgment.

DR. DUMAS: Yes.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I had similar concerns. I think they can be handled by adding to line 7 "does not in all cases or does not necessarily diminish their voluntariness." I agree with what Tom said earlier that there could be cases when the benefits of participation would constitute an undue inducement but that is not always the case. Finding 1-A reads as if it is always the case that it diminishes voluntariness. So I think it could be handled by adding just a few words to the sentence.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, I think I am addressing the same thing in a somewhat different way. I am

somewhat concerned by the absolutist quality of the statement and I am trying to look at what is the purpose of these statements. One of the purposes is this expresses the opinion of -- after all nobody really knows this for us -- is in a statement at this time, at this era what we believe, and I think that this is also going to be true of later ones.

The question of undue inducement, what country, when, what is the situation, but the issue of undue inducement remains an important issue all the time so that one of the things about the finding is that people should always know that that issue is always up there.

I actually put in just that we believe that it does not diminish their voluntariness because to get it away from that absolutist quality, and I have to leave for 15 minutes so I am going to miss the fight but I think that that is an issue that comes along --

DR. SHAPIRO: We are not going to fight.

DR. CASSELL: -- that comes along in all of

these things because we have to see what are we doing. Well, I think we are trying to, among other things, get everybody to know what we think are the issues that are on the board.

DR. SHAPIRO: Larry?

DR. MIIKE: Well, I read the statement completely different from this discussion. I agree that the comments that are made about this particular way of phrasing it brings the problems -- particularly what Diane said about it is not an absolute statement.

I read this to simply mean that just the mere fact that there are potential benefits in a research protocol does not mean that it is -- you cannot do the research in these under developed countries. To me that was the gist of this first finding, which is just because there may be potential benefits, does not mean that you cannot do the research ever.

DR. MACKLIN: Can I just say --

DR. SHAPIRO: Ruth, yes?

DR. MACKLIN: When someone has said what was intended we ought to acknowledge it. Okay. That is

exactly what this was meant to do. It certainly could not be an empirical claim and we could not put it forward as an empirical claim because we do not have any evidence for it. We do not have any criterion for what would be or would not be an inducement and surely if it were an empirical claim then we would have to take away the absolutist nature and say in some cases it is and in some cases it is not. Here are the criteria for determining whether it is or it was not.

It was meant as an in principle statement and I think Larry captured it as an in principle statement the mere fact or the very fact of providing benefits to people in developing countries is not in and of itself -- I do not like that language -- in and of itself an undue inducement such that it would make provision of benefits unethical and it should not. That is what is intended.

We need to fix the language. We will certainly do it because it is quite clear that intelligent, thoughtful people interpreted it differently.

DR. SHAPIRO: Bernie?

DR. LO: Well, along those same lines are there limits? I mean, are there situations that we can conceive of where both the benefit being offered compared to what otherwise the patients will receive and the nature of the risk or study they are being asked to undergo does, in fact, in and of itself constitute an ethical barrier so that, in general, you could -- I think we are saying you ought to be able to design a study where you can benefit all the participants and it is still ethical but I think there is also that flag that beyond a certain point there are real ethical problems. And to the extent that we can help sort that out I think that would be useful.

DR. MACKLIN: Well, if we could do that by way of example, it is going to be easier to do it by example than by providing criteria. So if we could ever do that by way of example that we would all agree that in this case of providing benefits, indeed, would rise to the level of an undue inducement and we could

use it as an example to make the case.

DR. SHAPIRO: Alex?

PROF. CAPRON: Well, one way to test the idea would be would people who are not offered this particular benefit agree to be in the trial? That is to say if you were doing it in a country or with a population that already has access to the care that goes along with the research would people agree to it because if the answer to that is no then it seems to me as a prima facia matter you ought to say this begins to look worrisome because to me there is no difference between offering a person who has access to health care tens of thousands of dollars for doing something which is very risky when what the person lacks is money. They need the money to feed their children but they have health care. And offering a person who does not have health care where their life is at risk just in the ordinary course where ordinary health care would be very beneficial to them that care.

I mean, what is the difference between the

dollars to the person who does not have the dollars and the health care to the person in the resource-poor country who does not have health care?

Now in this country most of our focus has been on the notion of financial rewards but I would not draw a distinction and I would be very suspicious and very worried and maybe I would be inclined, as I just said, to treat it as a prima facie matter where you could present a strong enough argument for going ahead anyway.

But where the answer would be no, people who have enough money for whom the inducement of the money is not going to be enough or who have enough health care for whom the inducement of the health care is not going to be enough to make a difference would never agree to be in that research. The risk of the research is simply too substantial.

And so I would be more inclined to get rid of this discussion of voluntary -- just using the conclusory word "voluntariness" here and to say, as Larry suggested, that the mere fact that there is

benefit to people because of the health care they get as a research subject is not enough to rule out doing research in resource poor countries among people who lack access to medical care but I would think we need another statement to address this question of proportionality between what people are being asked to do and the risk involved.

PROF. CHARO: Putting a hand up.

DR. SHAPIRO: Alta, and then Larry.

PROF. CHARO: I actually find this section less problematic than some of my colleagues on the Commission but it may be because I am separating two issues that maybe are coming together a little bit. One is the notion of undue inducement/voluntariness and the second being the notion of exploitation which I am trying to hold separate in my mind.

I mean, as somebody -- I have mentioned this before -- as somebody who used to be a research subject in any number of experiments, I can tell you, Alex, I would not have done them without the money and it had nothing to do with risk. They were not risky

at all. They were just paying. I did not want to have to walk over to William James Hall to do them but if they paid me enough I would.

I think that the discussions in public about the concerns over transnational research have often focused on the -- among other things, on the idea that somehow there really is a problem with an offer that is too good to refuse and I would urge that we actually do continue to address it explicitly and that we take advantage of the opportunity to say that offers that are extremely good are offers that can be accepted by somebody who is truly making a very voluntary decision in the sense that they are rationally calculating their own self-interest.

That does not necessarily mean that we think those kinds of protocols should be approved. There may be separate reasons why we think that they are exploitative or unduly risky or any number of other reasons why we do not think they should be approved but the reason for not approving them is not premised on the lack of the ability of an individual to decide

yes or no to go in.

And if I understood the section correctly, the only purpose here was to emphasize that the mere provision of medical services that are otherwise unavailable is not fundamentally different than the provision of any other kind of benefit that might seem terribly attractive.

PROF. CAPRON: Actually, Alta, I think you and I are in agreement because I assume that the research you went over to do as an undergraduate was research which at least some people would have been willing to do without being paid.

PROF. CHARO: I do not know of anybody who would. That is why they were paying us.

PROF. CAPRON: Well, that is because --

(Laughter.)

PROF. CHARO: I mean, if people want to --

PROF. CAPRON: That is because you were all very well taken care of Harvard students but if you -- that, in principle, if the only -- if the -- if the research involves burdens which a person would not

otherwise accept if they were not given a particular reward no one would -- no one would. I just want to say as a prima facie matter that issue deserves examination.

PROF. CHARO: Well, Alex -- I mean, Alex, seriously, I mean I participated in research for an entire year where I had to sit in a little room without windows from 7:00 a.m. to 9:00 a.m. five days a week. Now I challenge you to find anybody on that campus who would have done that out of altruism. Only poor people like me.

DR. MURRAY: We are doing it for eight hours a day right here.

(Laughter.)

DR. SHAPIRO: Okay. I want to get on to the -- I think I do gather the sense of this. I think Ruth does as well and I want to get on to at least a brief discussion before turning to Dr. Berkley.

Diane and then Larry.

DR. SCOTT-JONES: I have another concern and that is this is written about the potential benefits

of participation in research and it does not address the issue of what the participants think about research, that is whether participants believe that they are going to be cured of AIDS if they participate in the research or whether they believe that they are going to get individualized medical care.

There is another issue and that is what the participants actually think that I think is a somewhat separate issue from the one of the potential benefits of participation as the researcher defines it and I do not know if that has been addressed.

DR. SHAPIRO: Larry?

DR. MIIKE: Just a comment on this discussion. If you look at the bold face we have not discussed 1B and the recommendation and obviously this is leading towards that specific recommendation.

DR. SHAPIRO: Right.

DR. MIIKE: So I think it is just a matter of refashioning these things and saying just because there are potential benefits does not negate the study. Providing effective treatment is not an undue

influence and that is where it leads to and so one could just rethink the way this is written.

DR. SHAPIRO: Let's focus our attention for the next few minutes on finding 1b and recommendation 1 and then I would like to go to our guest we have already kept waiting longer than we should have.

Bernie?

DR. LO: Yes. In both 1B and the recommendation we use the term that I guess Steve Lagakos at our last meeting proposed of established effective treatment and I know that at the beginning of this discussion you sort of said there are problems with a lot of the other terms used but I actually have problems knowing what we mean -- what Steve meant by that and what we think we mean by that and why this is a better term than all the other vague ambiguous terms that are being thrown out because I think it really begs the question do you -- at what point do you know that it is effective anywhere in the world? I mean, do you assume that it has been shown to work in one country it automatically works in other countries? Is

that an open question that -- where there might be some equipoise?

I think there are issues that we tried to dodge by sort of changing the terms but I think they are actually pretty serious ethical and scientific issues.

DR. MACKLIN: I just have to respond to that one.

DR. SHAPIRO: Yes, Ruth.

DR. MACKLIN: The question of the choice of terms -- I mean, we have to get to the bottom of why. Okay. Your suggestion, and we would agree that there are a lot -- there is built in vagueness to these terms and I think there is going to be built in vagueness or uncertainty to any terms that are chosen.

This term was chosen not because it is not vague or because it is going to be absolutely clear to anyone who looks at it or clear and able to be applied unambiguously. Instead it was used to avoid the other -- the best proven treatment with all the arguments.

We can use Bob Levine's arguments that he has had in print, some of the things he said today and some of the others to show the flaws in that reasoning and that is what he presented to us today and he has got that in his written articles as well.

So it avoids the pitfalls, not just the vagueness but the pitfalls of that term, and it also avoids falling down to the lowest common denominator, which is no care that is captured by the term "standard of care."

Now if we need to put in a lot more caveats that this language does not solve these other problems and how do we ever know when it is established or that it would be effective elsewhere, that is fair enough and I think we --

PROF. CAPRON: Just drop the adjectives, Ruth.

DR. MACKLIN: What do you mean drop the adjectives?

PROF. CAPRON: In 1B, the adjectives "established effective." What if you just said the

offer to provide members of a control group with treatment that is unavailable outside the trial? Doesn't that make your point?

DR. MACKLIN: No. No.

PROF. CAPRON: Why not?

DR. MACKLIN: It certainly does not.

PROF. CAPRON: Because you are not -- the question here is not what your obligation to them is to provide. It is just -- here you are saying if you provide them with X, which they could not otherwise get, that does not constitute an undue inducement to participate in the trial, which in a way is a clearer statement of finding 1A.

DR. MACKLIN: Well, I guess the point here was that the argument that was given -- I do not know if it was an argument, a statement or an utterance that to give people AZT -- the 076 regimen, which it was not available, that was the best proven treatment but it was not established effective treatment, would be and would have been or would be an undue inducement. That was an additional argument used in

the context of the AZT.

So what this is meant --

PROF. CAPRON: But if you had offered to give them normal annual physicals, which they did not have access to, wouldn't that fit the statement just as well? The question would be is that an undue inducement?

DR. MACKLIN: No, because that is more like 1A. What we had really meant to do was ratchet it up here. 1A is giving them medical care. Okay. Now suppose in the context of the AZT we said we are going to give them vaginal washings. You cannot get that outside the research. I mean, is that what we are worried about, that a vaginal washing is going to be an undue inducement? If anything, they would look at it as a burden or an unacceptable thing and not want to do it.

But if you give them something that is available in another country that is known in another country to be a treatment, that is the question of the undue inducement. So this has to ratchet it up from

what medical care -- ordinary medical care would be otherwise we are not addressing the concerns that people have expressed.

PROF. CAPRON: But that is not the language that anybody recognizes for that. I mean, if that is what you are trying to ratchet to the top you better say the best available care because you are trying to go up to the ceiling. I mean, whether or not you like it, an annual exam fits that definition -- fits that sentence. That is an established effective treatment, that is to say the American College of Physicians recommends people over a certain age have an annual exam. We know it is -- it has some benefit.

DR. MACKLIN: It is not a treatment. It is a diagnosis.

DR. DUMAS: That is right. Tell him.

PROF. CAPRON: Well, it might -- it is not a diagnosis. It is intervention. All right. Well, then not that. Then aspirin for -- I mean, just anything that they cannot get. Penicillin for a bacterial infection which they cannot get and you

offer -- you say people in this trial, we are going to try to keep you otherwise as healthy as possible.

I mean, maybe that is a good research design and maybe it is not but that is what you are offering them. And people know that the rate of dying from bacterial infections is such that that is -- why wouldn't that fit this sentence?

DR. MIIKE: Ruth, I, for one, thought that the intent was clear and it is explained enough in the discussion about why you used established effective versus best available. And that was your answer to Bernie, which was that that was the purpose of using that and not to get into the issues about how we measure effectiveness and what is established, et cetera. I thought it was pretty clear in the discussion.

DR. SHAPIRO: Arturo, and then Jim.

DR. BRITO: I want to make two points. One addressing this issue directly and I think it is important to put established effective treatment or some other term like that in here and not just

deleting it because of the -- what is addressed earlier on page 7.

In fact, I have made some notes about this because this is something that you need justifications for repeating the placebo groups in other countries that was -- it was utilized to justify repeating 076 in other countries of the placebo groups is the fact that there were discussions about possible differences, physiological or biological differences in the HIV virus, et cetera, like that among other populations, subpopulations, et cetera.

But yet there was no good evidence before those trials that that actually existed or that there would be any difference in the reaction to AZT of these viruses or et cetera. Okay.

So when we talk about established effective treatments and to go back to the first line two on page seven, if there is good reason or evidence to believe the biological factors are sufficiently different, I think this is the key why it has to be included in here is because there has to be evidence

that something is different to say something is not effective. And if you just put something as treatment as a general term then the scientist or researcher or sponsoring organization can just go into another country or subpopulation and say, "Well, this is a treatment that is available that is different than what is established for the United States population." Does this make sense?

I guess the note I had made to myself is I want this emphasized here that the evidence has to exist and I thought that was important.

My second comment is that when we are discussing 1A and now on to 1B, when I had read this the notion I had gotten, and maybe -- and this addresses something Bob Levine mentioned before, is that one of the criticisms of bodies -- U.S. bodies and westernized bodies is that we are very paternalistic in our decision making.

When I read this about the voluntariness, irrespective of how we phrase it, I think one of the things this addresses is that it is up to the

individual or the community to make the decision for themselves and not let us, us meaning the western or the industrialized country, make the decision for them. So I think it is one of the things that somehow has to be emphasized here that what we are trying to do here is address this criticism of being too paternalistic.

DR. SHAPIRO: I just want to take one or two more questions and then I want to turn our guest.

Bernie, you had a question?

DR. LO: Yes. Again to raise my concerns about the ways this is set up on page one, I mean I appreciate your point, Ruth, of wanting to avoid the kind of acrimonious debates that centered on these catch phrases. My concerns is that our definitions at the beginning of established and effective are not very clear and are going to raise a host of questions which if we are going to use the term I think we need to parse it out of it and explain what we mean because I think what we have done by ducking some of the tougher issues is leave ourselves open to different

people interpreting this in different ways.

Is it effective because it meets, you know, the most rigorous standards of evidence based medicine or do people say that, well, I have got historical control, I think it works pretty well. I mean, those are exactly the types of disagreements that I think we need to have some sense of how -- what standards are we going to use to resolve it.

So I am not objecting to the new term. I just think we have to be a little more specific about what we are trying to say here.

DR. SHAPIRO: Jim?

DR. CHILDRESS: Following up on that, I actually found the language in the new language to be quite acceptable and illuminating.

I guess, Bernie, what is said on 1, you would like to see page 1, line 27, for example, "established," you would like to have that parenthetical comment elaborated?

DR. LO: Well --

DR. CHILDRESS: I think one of the -- the way

it is set up here that one of the problems is that this important discussion of established effective occurs early and then we have several other pages by the time we get to the discussion where it really comes into play. We have sort of forgotten what was there but I found it quite useful and that I really like the flow of the argument in this discussion but tell us more.

DR. LO: Right. So what do we mean by medical profession? Is it -- are we assuming that there is a single standard around the world? Does it have to be accepted by the host country? Suppose it is accepted in the country that is funding it but not the host country. Those sorts of issues. An effective successful -- well, how do we judge whether something is successful? I mean, some people say that, you know, I want a randomized clinical trial, control trial.

We should say, well, you know, historical controls for this condition are good enough for me. Some people say, "Well, you know, that group that you

studied in the randomized control trial differs from my population in this way and this. You know, we breast feed, they do not." I do not know if the results apply. Other people say that is close enough to me.

So those are the kinds of debates that are substantive sort of scientific ethical debates that create the problems and we need to at least acknowledge that apparently clear terms like acceptance and successful are going to lead to pretty serious disagreements.

DR. SHAPIRO: Tom, if it is very, very short bacchus we do --

DR. MURRAY: Yes. There is -- I know of no expression that is going to alleviate those ambiguities. However, it seems to me the morally problematic cases are those where there is a treatment which is quite clearly established and quite clearly effective and where there really is not a lot of dispute about how it would work and that it would work in the country at issue. So, I mean, I think the

phrase works well enough. We should acknowledge all the complexities and uncertainties but to capture the morally -- what is morally important, I think the phrase is adequate.

DR. LO: Let me just say that here we are saying it is okay if you do it. If there is then a discussion of do you have to do it as an obligation then it becomes, it seems to me, much more critical to say if you are going to have to do it what is it that we are saying you have to do.

DR. SHAPIRO: Thank you.

Ruth?

DR. MACKLIN: One last point, though, of having to do it. If you take a look at what the recommendation here actually says, later on we get to what you have to do but this was only, as Larry correctly points out, leading up to this rather modest recommendation, which is that researchers and sponsors may offer to provide members of a control group. That is this is simply saying it is not an undue inducement to do this.

Now later on we get into the more worrisome thing about the obligation but right here it is kind of a weak thing.

DR. LO: In this situation we have got to be clear about what we are talking about.

DR. SHAPIRO: Thank you very much.

I think I really do want to now terminate this part of our discussion and we will come back to it a little later, other parts of this recommendation under 2D but I want to now turn to Dr. Berkley.

Let me apologize once again for keeping you waiting. I know that we are running late today and I apologize. I know you are very busy and we very much appreciate you taking the time to come here and spend a little time with us.

I think you all know that Dr. Berkley is president of the International AIDS Vaccine Initiative. I think it is known sometimes as IAVI. I do not know where that came from. I guess from the initials. IAVI, I think, is what people commonly use to referring to it, which is, as I think you all know,

a very interesting and provocative initiative to address obviously an extremely important health problem.

So we very much welcome you here today and look forward to your remarks especially because IAVI has really produced some, I think, rather original approaches to the formation of agreements and cooperative agreements of various kinds, including at the other end of the work possible provision of effective product -- excuse me, effective medicines and so on, vaccines in this case, that would be developed.

So thank you very much for coming here. I am very glad to have you.

SETH BERKLEY, M.D., INTERNATIONAL AIDS VACCINE INITIATIVE, NEW YORK

DR. BERKLEY: Thank you very much. I assume if I take ten minutes and say a few things about what we are trying to do and why and then open it up for questions --

DR. SHAPIRO: That will be fine.

DR. BERKLEY: Okay.

I obviously do not have to, to this august body, talk about the magnitude of the problem that we are trying to deal with but what perhaps I want to emphasize is the effect it is having in the developing world. There has now been, as you know, 50 million cumulative infections. Currently there is about 34 million people living with HIV around the world. About 15,000 infections a day.

And perhaps the most profound numbers to me are what is happening now to life expectancy in the developing world and we see nine African countries have a life expectancy that has gone down more than 20 years and the most striking of these, I think, is Zimbabwe where life expectancy has gone from 68 years into the 30's, 42 percent as a result of this single disease. So obviously an enormous problem to those countries as well as globally.

The problem with this is that one would argue that a vaccine is the only way that we can successfully stop this epidemic. After all a vaccine

is the only traditional way to control viral infections. It is an international public good in that if we create a vaccine not only will it work for the people who are at risk but those people will not infect other people and, therefore, we will change the dynamics in the population. So it has effects above and beyond the people who take it.

And IAVI came out of a history that around 1994 the vaccine effort was almost completely dead. People said why, that is unusual. I certainly did not believe it when I heard. Well, a couple of reasons. On the public sector side initially the world said, "My, God, in '84 this is a virus. We need a vaccine. That is the only way we know how to do it."

But what happened was the advocates who stepped forward said rightfully so, "My, God, we are infected with a fatal disease. We need treatment. Treatment is what we need." Science said, "We do not know how to treat virus and viral infections." But they persisted and they deserve the Nobel Prize because, in fact, we now have a whole set of antiviral

drugs.

But interestingly what happened was the priority in the public sector shifted from initially vaccines towards therapeutics and at the time we got involved it was 10 out of 10 priorities at the NIH. The percentage globally of money going into vaccines was less than seven percent of the overall research expenditures and less than one percent of what was going into AIDS.

In addition, there is a difficulty with working with industry and I am going to come back to that because that is important in what we have tried to do.

On the private sector side it also had shifted. One is the science was tough. We know that. Vaccine development is long. It takes -- it is very expensive. But also the market began to shift to the developing world and with 90 percent of the infections in the developing world, God forbid you succeed and make a vaccine for Zambia, say. What are you going to do with it? How are you going to get it out there?

Who is going to pay for it? How is it going to be distributed?

You end up in the worse case scenario where the world is pounding on your door saying you must make this life saving technology available. There is no mechanism to get it out. There is no money for it.

And lest you think that this is theoretical, hepatitis B vaccine found in about 1981, we are now almost 20 years into the development of it, it is still used by less than 50 percent of the population that needs it in the world and it has now gone from $150 down to about a $1 or $1.50 for the full course of treatment for it and hepatitis B kills a million people a year.

So it is not -- I mean, it is not an exact analogy but the point is that industry, I think, has the right to say, "Well, we are not sure that it will really happen."

Lastly, there was a big decision in '94. Industry had invested about $50 million in two candidates and in '94 a decision was made not to move

those forward using public sector finance. The reason was a sense of fear of failure, the theories had changed, and so that vaccine was not moved forward.

It is now in clinical trials being privately financed but one clear point to make to the group is that 20 years into the AIDS epidemic no vaccine has been tested to see if it works. Okay. There is one in testing now but no vaccine has gone through Phase III testing to see if it works.

Okay. I wanted to lay that as the background of where we are.

So IAVI was started with the idea of trying to do something about this and our focus -- our mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. We say "ensure" because we do not have to do it.

"Throughout the world" because that is where the epidemic is and we mean global. We need it in the United States because of resistance patterns, because of the continued spread, but we need it mostly in the

developing world where there is no access to treatments or even the basic prevention strategies.

Three major strategies. The first was to get it back on the agenda with an aggressive advocacy campaign and we have worked hard on that. Important to this group deliberation was this is not only about getting it on the agenda in the north. It is critical that the south has it on their agenda and up to that time developing countries had not been arguing articulately for vaccines.

Why? If you go and ask people they say, "Well, we thought that somebody else was going to do or it is too tough. It is too difficult. We do not know how to do it." But it was to get people involved and engaged in this and this leads to what this gentleman -- and I am sorry, I do not know your name -- but there is a sense that up until that point both it would get taken care but also some of the decisions were quite paternalistic and there was some worry that decisions were being made not by the people involved and that is a tenet that I will come back to but it is

something that IAVI thinks is very important.

The second component was to create an aggressive science program and the way we did that is we asked what needed to happen and what we found was that a lot of money was going into basic research, and that is fantastic. That is the basis everything is built upon. But applied vaccine development was limited and that for the developing world was virtually nonexistent.

Now why is that important? Well, it turns out there are different strains in developing countries. That may or may not matter but also there are characteristics of vaccine delivery that are critical.

If we have a vaccine that requires ten doses, requires refrigeration and requires extensive follow-up it might as well, you know, not be a vaccine at all because it will not be applicable at least to the very poor in rural areas.

So there are characteristics as well as strains.

We met with the head of industry. The heads of industry said the way you can move vaccines forward is to pick one of these candidates that exist. It does not have to be the perfect one but just show the world that you can move it forward, that you can get it through the different stages of testing, and show whether it works or it does not work. That was what they suggested.

We chose two vaccines. One for South Africa, which is CLADE-C, the most common circulating CLADE, and one for Kenya, a CLADE-A. We created what we call vaccine development partnerships. That means bringing the developing country researchers together with the people developing the vaccines at the beginning so they are co-developers of the vaccine. They have ownership in it. They believe in it.

We began the process of working with the companies to not only move them forward and go through the clinical test process, et cetera, with the ultimate goal initially to test them first in the north and then secondly in the south but with

discussions down the line that we might make vaccines specific and only for developing countries.

Now as part of those debates we asked the question what do we do about making those vaccines available because isn't that the ultimate goal and isn't it our duty if we are going to bring the countries into this? So what we decided to do was to try to create intellectual property agreements that helped us with this access question.

Now if we were to walk into a small biotechnology company with a large amount of capital and make a very large investment we would get equity from that company and we would, therefore, control the company and sit on the board and whatever.

Instead of that we said you get to keep all of the intellectual property because that is obviously the life blood of these companies. What we want instead is access for the poor at a reasonable price. If you do not do that then we have the right to take that technology and license it somebody else. So that is the agreement that we have tried to broker.

We also had a small royalty that would go back into funds to work on better vaccines but the critical issue here is trying to get access for the public sector of the developing world.

Now that implies a couple of things. One is that the pricing -- that tiered pricing will be permitted by the world and that is, as you know, a controversial thing. And that the vaccines -- you know, that we can manufacture them in sufficient quantities.

So another thing that we have done as part of our science program is begin to create national vaccine programs in the large countries. Why? Those countries have the problems. They have the market that is large enough and they potentially have the capability to make vaccines.

So we have worked on creating national programs. Not IAVI programs. National programs in China, India and South Africa. Countries that conceivably could take a vaccine if it was the right technology and produce it in that setting and

presumably have it be cheaper, although that is not certain depending upon the technology.

The third component of the strategy of IAVI is to create a better environment for industrial investment. Industry does not have the incentives as I have already laid out to enter this very expensive and long-time consuming area.

What we want to do is try to do what we can. So we are doing two things. One is to jump start the research, to go ahead and get biotechnology companies to make vaccines, to get them tested as soon as possible so that when a company chooses a vaccine they already have the initial science work done. They have got some clinical data. They know it has gone through a regulatory agency. They know something about how to manufacture it. So it reduces their risk.

At the same time we have this problem of the developing world and how to get it out there so we are trying to create vaccine purchase funds, mechanisms that can create a market in the developing world to purchase these vaccines and to distribute them.

The idea would be that we -- before the vaccine is ever made -- would have a mechanism in place to have the vaccines purchased. Say -- I am using a number -- throw in about a billion dollars worth of vaccines for Africa and a distribution mechanism to go with that.

And the World Bank has created a bank-wide task force to look into this. It has now gone through a serious investigation on it and that is now going to the bank's board as a second incentive that we can do with industry.

There also is a range of potential bills working their way through the U.S. Congress, through the European Union and other places looking at incentives such as tax credits for research on vaccines for the poor, et cetera.

I think that covers kind of the broad sets of issues. What I want to make just in closing and open it up for questions is the real ethical challenge here is if you look at the world as a whole, the world spends about $20 billion a year on AIDS.

There is no question that a vaccine is needed but if you go to any one group, any one department, the development agencies say, "We do not do research." The national research agencies often say, "Well, we do not do research for developing countries." The groups that do pharmaceutical companies say, "Well, we do not focus on the developing world." So there is not a mechanism to specifically focus on products that are necessary for the developing world.

We have tried to create that. The challenge is now to get industry, to get politicians, to get the world to accept the fact that one of the goals of putting large amounts of public finance into something like this is to assure that the people who need it have access to it.

And since there is not a mechanism to do that, we have got to create these types of artificial mechanisms and, frankly, it is quite difficult to do that when there is not a precedent for it and when other money often goes in without any types of linkages like this.

We have come across companies that have said, "Well, we really do not want to do that because we can get other money that has no restrictions." But I fundamentally believe that it is the right thing to do for both the companies and for the world because they are going to have to deal with providing vaccines for these places anyway and this is a way that we can have a win-win situation if we get the political support to do something like this.

Let me just say one last thing and then I will stop. You might want to ask what our strategy is in terms of dealing with ethical questions in countries of testing. I am happy to discuss that.

We have not set up our own separate mechanism. We felt that that was not just adding another layer on to it. What we try to do is work with the country to assure that they have adequate mechanisms and to use U.N. AIDS, which has a global mandate to work with countries to assure that it meets international standards.

A combination of those two things are the

mechanisms we use to assure that it has gone through the proper review process.

DR. SHAPIRO: Thank you very much. Let's go to questions of members of the commission. Bernie and then Alex.

DR. LO: I want to thank you and I think all of us thank you for coming and laying out your program so clearly to us.

One of the things we as a commission have to do is think about policies that will apply across the board to a lot of conditions and I am going to ask you to try and generalize from your AIDS vaccine experience or vaccine experience more broadly, in listening to you it sounded like you have a chance to work with boutique companies sort of starting to try and develop the intervention.

I am wondering if you change some of those parameters for other illnesses so that if you had to work with established pharmaceutical companies who own a patent to a drug that is used elsewhere and you are trying to develop a short-course cheaper regimen, or

if you are dealing with a condition where there is not the sense of, you know, global urgency that, you know, came through sort of dramatically in your earlier comments. So, you know, malaria, river blindness. I mean, big diseases elsewhere but sort of are not on the map in, you know, the northern countries.

How would a -- I mean, it sounds like what your organization has been able to do is to say as a guiding principle we are going to require these kinds of understandings, agreements, whatever language, before we enter into these partnerships because, you know, that is the appropriate way to do it.

Is that kind of requirement going to work in other context for other diseases for different partners that you would deal with?

DR. BERKLEY: It is an excellent question and I suppose the question, of course, is it going to work even in our setting and until we are fully successful I do not know if I can answer that but I think there is two ways to look at it.

First of all, you need a model and the way I

see HIV vaccines is, one, an unbelievably urgent need but beyond that I see something with some political support at all levels. A problem that is both in the north and in the south and a problem that right now everybody thinks is under control but it is not and is going to once again get quite severe in the north because of spreading viral resistance.

So when I see this as a chance to begin to develop the mechanisms that make sense, that can be used across the whole range of different products. When we sit down and compare the issues on malaria to HIV, they are not that different.

What is different, however, is, of course, there might be a much larger market in the north for an AIDS vaccine than there is for a malaria vaccine but maybe not. Maybe travelers, maybe the army, maybe, you know, others would buy it.

When we go to something like onchocerciasis clearly there is no current market we know of in the north and so it is a different thing but it is all in relative degree. What the onchocerciasis example

would bring is there would not be any market incentive to take it forward. Whereas, for HIV if you reduce the barriers enough and you increase the push enough you are likely to tip it over into being a positive set of business decisions.

So our sense was create the mechanisms, drive them forward, and then use that. But the second point is it relates to the political will issue and that is until recently there has been an attitude in this country that the developing world does not matter. I mean, I am over generalizing obviously. Many citizens care but there has been an issue, for example, for business that we can supply this market. People will pay anything. Health care is going up. You know, there is no problem.

What we have begun to see is first of all we are beginning to cap health care. Secondly, there is an issue on size of market. It matters for vaccines. It matters enormously. If you can produce 100 million doses of something your cost per dose is much lower than if you produce two million doses. And so you can

sell it even in your primary market and make more money.

So what has begun to be see is as we globalize it is going to be more important and what is critical is we have to develop a situation where people understand tiered pricing as a critical component of this. If we do not have that, if the attitude is, you know, why should India get it at the same price as we pay in New York, we are going to have a problem with being able to do that and get things out.

If we accept that there is some type of natural tiering, how and what and in what structure, then I think we can move closer towards having the political reality of working out these deals.

DR. SHAPIRO: Alex?

PROF. CAPRON: The first couple of thigns I wonder about are just factual questions. In your description of the agreements that you are reaching with the industries that are developing the vaccines, when you talk about making the product available at an

affordable price, are you drawing any distinction between making it available in the countries which have participated in the research process and other countries where the disease is rampant?

DR. BERKLEY: It is a tough issue because there is a free loader problem if you want to look at that. Obviously what we would like to do is work in countries, get those countries to have national programs, get them engaged, work with the bank, work with other institutions.

They are more likely to have mechanisms in place to, one, have the vaccine available when it is done because, first of all, it is the strain that is appropriate from there. It has been tested there. It is going to go through their regulatory. There is a whole set of reasons why it is likely to appear there quicker.

On the other hand what we do not want to do is have a situation where it is not available to the countries that are next door that may not have that set up. So the pricing mechanisms we have set up at

the moment talk about the -- they are defined as the public sector of developing countries as defined by international bodies without regard to where it is and our expectation would be that the mechanisms would be put preferentially in place in the places that were involved in moving this forward.

All of that obviously has not been worked out because part of it will also depend upon where vaccines are actually going to be produced so if it was produced in India even if the research was in South Africa it might first appear in India and then in South Africa.

PROF. CAPRON: Just to make sure I understand, when you say "preferential" you mean sequentially, in effect? The first places you would go to would be --

DR. BERKLEY: Yes.

PROF. CAPRON: -- and that is largely defined on the kinds of practical considerations you describe.

DR. BERKLEY: Yes.

PROF. CAPRON: It is not a moral judgment

that they are more deserving of it.

DR. BERKLEY: Right.

PROF. CAPRON: The second question is at one point, as I understood the vaccine development in this field, the phrase "vaccine" was being used for treatments which might be given to people who are infected to reduce their viral load down to a very low or unmeasurable level but was not the same concept of vaccine that we commonly think of with small pox or polio or whatever where you are actually preventing the infection process.

DR. BERKLEY: Usually disease but not infection.

PROF. CAPRON: The disease, yes. Disease but not the infection, yes. I mean, is -- where are you -- could you say a little bit about that to clarify?

DR. BERKLEY: It is quite interesting because the industry, of course, is much more interested in a therapeutic vaccine than a preventive vaccine bacchus you can charge much, much higher rates for a therapeutic vaccine because people who are sick will

pay more and do not discount it, et cetera.

The problem is there is no precedent for therapeutic vaccination. That being said I fundamentally believe that ultimately what will happen is we will catch an infection early. We will treat it aggressively with drugs. We will stop viral replication. We will boost the immune system and then we will pull drugs away and the immune system will hold it in check. That is theoretical.

IAVI is focusing only at the moment on preventive vaccines because we think that is where the need is greatest. We think that is where the largest market failure is and we think that ultimately the knowledge gained from that will be the thing that will work on therapeutics but I must say one other point that is interesting is that industry in the past has taken an approach that may have been promising, has tested as a therapeutic vaccine. Very easy to do by the way because it is very easy to get an IND for a therapeutic rather than a preventive because it is healthy people.

And you can treat 10 people or 15 people and if it shows some promise then scale up. Whereas in a vaccine trial you have to have huge numbers.

Well, what they would do is they would test it on a small number. They would say, "It does not work." And all of a sudden that whole vaccine approach gets thrown out. Not just for therapeutic but for prevention as well and I think that has been a real mistake.

PROF. CAPRON: I will hold my other questions.

DR. SHAPIRO: Okay.

Rachel?

RACHEL LEVINSON: I think you have partially answered my question with your response to Bernie but I am not sure and I just want to go back to it. With the purchase fund you are talking about vaccines that are not yet developed and that the cmopanies seem to be willing to enter into an agreement without yet knowing the full cost of development but is it that the purchase -- I would assume that there is a total

amount set aside with an expectation that there would be sufficient dose to give to the population that you have targeted.

Are the companies -- I do not know if you have negotiated that or not but are the companies thinking of that as a loss leader to help them get through the development phase with the hope that they will have through the tiered pricing be able to charge developed countries a greater amount for that vaccine so that -- assuming that the strain is suitable and everything else? Is that the -- is that the plan? Is that what the companies seem to be willing to entertain?

DR. BERKLEY: Let me say that we have negotiated deals on moving vaccines forward. A vaccine purchase fund is an idea that is on the table that has not been fully worked out yet so that is work in progress.

Let me just say what the theory is behind it. The theory would be is that companies should not lose ever on any of the vaccines they make but there will

be differential expectations of what you will make in the different segments of the market.

The current return on investment for pharmaceuticals is rather high. You know, I do not know exactly what that number is but it is probably in the range of 30-40 percent. Clearly one would not expect that in the lowest tiered markets you would make that type of return on investment.

However, a lot of that return on investment goes towards marketing costs, goes towards, you know, executive salaries, other things that are not necessarily going to be added on if you now increase to serve the developing country market. This is often called the ROW. It is not -- that is rest of the world. It is not considered part of your profit making market and so you have a very small marginal cost to add -- I mean, if you had one dose the marginal cost is, you know, just raw materials because you have got your plant, et cetera.

On the other hand, to get plants that are sufficient in size, there may be much larger costs and

we have to deal with them. So the concept behind the IP agreements would also -- a purchase fund is to negotiate a reasonable profit margin in that segment.

Now that happens now. The U.S. is not tendering but UNICEF puts out a tender for vaccines and the European -- a number of companies in Europe buy those vaccines in a tendering process. They do not lose money on it. What they get is they make very, very little money. Very, you know -- half of one percent profit margin but they get the economy of scale as well as entree into those markets, which is really important.

And so I think that is going to be the critical issue which will not work for this gentleman over here and his onchocerciasis vaccine because there is no primary market, at which point we would have to come up with some separate scheme to do that.

DR. SHAPIRO: Thank you.

Diane?

DR. SCOTT-JONES: I have three questions. First, I would like you to say a little bit more about

the nature of the collaboration between researchers from the developed world and those in South Africa in Kenya. Would you say that those are relatively equal collaborations of the scientists?

And then the second one is the companies that are producing the vaccines in China, India and South Africa, are those companies from those particular countries, are they companies -- international companies that are doing the work? And then finally I would like you to speculate about whether it is possible that the development of all this wonderful work that you are doing ultimately will move up to the wealthier countries instead of in the opposite direction to the -- say African countries that are poorer than Kenya and South Africa.

DR. BERKLEY: On the first question, if the scientist -- if the full range of scientists existed in the south we would work with them only because we would let them develop the vaccines if they had the capability in their area. We are in China and India actually financing national, you know, vaccine

programs that are working on certain concepts that they have the capabilities to do.

The ones -- the particular ones I talked about, the two we launched, were really state-of-the-art technologies. Very complex technologies and those are new technologies that both were identified, one by a company in the U.S., one by an academic institution in the U.K.

What we have done is we have brought the scientists at the Ph.D. level to work side by side, to work in every aspect of it, and for them to go home and become the champions, and become the leaders of the effort, and to say that they were truly involved with all aspects.

So there is a technology transfer part of it as well as they are feeling part of the effort, as well as them receiving finance to do the work.

The specific example in South Africa, different aspects are being done by different groups so the vaccine design work is being done in North Carolina at the company but the isolation of strains

from newly infected people, the cloning of those, working through those were done in South Africa by South African scientists. So it is truly a partnership where we can, you know, best make that.

Your second question was about companies in the developing world, what type of companies, they are different in each place. In India we are working with a private sector company in India. In South Africa we are working with a national company that makes vaccines. It is part of the government. It is kind of a parastalsis (sic). And in China we do not have any formal agreements yet but the discussions we have had have been both with new joint venture types of companies as well as production facilities that the government maintains.

In each case, in those cases we are not yet doing it because we will not be able to transfer vaccine technologies until we have a better idea of what is working, and that will define which of these facilities makes sense.

It is not, by the way, an -- everybody makes

the assumption that vaccine production is always cheaper in the south. It may not be true. It may be more expensive. It depends on the technology. It depends on how automated it is, you know, et cetera, et cetera. But for many of the technologies we are looking at and we are specifically looking at simplistic technologies that can be used in the developing world.

So our next two vaccines we are about to launch, one is oral and one is a single dose. Those types of technologies happen to also be ones that could be produced in developing countries. It is part of what we are looking for in terms of the approaches.

Your third question, would it trickle up instead of trickle down? I hope it will trickle up. The world needs a vaccine, not just the developing world. I am less worried that if we get a vaccine that succeeds in Uganda that it is going to make its way to New York. I am worried vice versa. The history has been 15 years or longer time lag between vaccines produced in the north and the south and I

want to make sure it goes the other way.

Again the political will issue is if we succeed in South Africa, we get it in South Africa, we produce it in South Africa, somebody is going to have to make sure that the rest of the countries in the African continent who do not have the same per capita income as South Africa can have access to that, get it out there, and that is why these mechanisms are critical.

The vision should be -- my vision, I believe the vision should be that we have introduction of a vaccine in the north and south simultaneously. It never happened before but there is absolutely no reason why we cannot do it. That should be the vision.

DR. SHAPIRO: Thank you.

Arturo, do you have a question?

DR. BRITO: Second time today we heard mention the problem with hepatitis B vaccine and yet you went on to how it is not equally distributed particularly in the countries that need it most but

yet you wanted to mention that the cost has come down considerably.

Is it still an economic problem then that that is why it is not distributed or is it more political and is that -- do you think that is -- a problem like that would have been resolved had there been kind of like what you are doing now, these agreements made ahead of time? Is it the --

DR. BERKLEY: You know, I think again nobody knows. People say, "Well, it is AIDS and everybody will get an AIDS vaccine." I do not know that. People may be -- they may be so scared by the name AIDS. We know that in Illinois that the population has pulled hepatitis B out from childhood immunizations because they do not want their children to be promiscuous or drug users or whatever. I mean, there is all kinds of crazy ways. So I do not know whether HIV is going to be as different. It may be the opposite way than the way we are talking about.

But the problem is really a different one. It is a very interesting one. Vaccines are

unbelievably under valued. It is the most cost effective technology and we are to blame for that. The reason is when there was a big campaign to start vaccination globally what we said is, "My God, if these countries are too poor to pay for the vaccine we will buy it for them."

So there began to be an assumption that, one, vaccines should cost -- the current six immunizations cost less than a dollar. So, one, it should cost pennies.

Two, if we cannot pay for it, you know, it should be bought for us. Now if a government is doing its proper job its Ministry of Finance says to its Minister of Health, "My God, we have only a little bit of money. The first thing we should do is the most cost effective thing in the country. We should immunize. And then if we have left over money we should build hospitals or we should provide tertiary care or whatever."

Now, of course, that in reality never happens because the political demand is for care. There is no

demand for prevention and we give away vaccines. So the system is backwards.

Why this is important and why the political will and why the changes that are occurring now is important is if we can get the World Bank as an institution, which talks to finance ministries to get in the heads of finance ministries that it is an economic issue, vaccination is cost-effective, can make a difference for the health care as well as the development of a country, then you end up in a situation where people understand that vaccines -- you should use resources for them. You should get them out. In fact, you know, people should -- it is okay for a vaccine to cost a dollar, two dollars, five dollars, ten dollars. It could still be cost-effective. Even in places that have low public sector expenditures it still can be cost-effective.

It is getting that message out there that is absolutely critical and we are trying to do that.

DR. BRITO: Now, one follow-up question to that. Regarding the vaccine -- HIV vaccine trials

going on right now in South Africa and in Kenya, I was curious about the populations or the individuals that are volunteering for these studies, what the risks are to them and what kind of compensations are going to be made available to them should there be large risks, which I assume there will be.

And is the reason that these trials are being done in South Africa and Kenya more of an issue of numbers or what is the logistical reasons why they are being done there and not here in the United States?

DR. BERKLEY: First of all, the trials are not underway. We are making the vaccines now and trials will start. That is number one. Number two is most of the vaccines have been done in the United States. Overwhelmingly, almost every single candidate has been tested in the United States and Europe.

In fact, there has only been one AIDS vaccine trial in Africa. It was with a U.S. strain. It was done last year by the NIH and a French company, Pasteur Connaught now [Arenthis Pasteur] (phonetic). Phase I, healthy people, healthy, absolutely not-at-

risk people, and the purpose of that was purely to see did the people in Africa have a similar immune response to a vaccine that was not made of a strain that existed locally.

A lot of controversy about that. Shouldn't we have made the strain locally? The company said, "Well, why should we do that?" You know, there was no incentive for them to do that.

The government went ahead and tested this and, rightfully so, since this vaccine targeted not the antibody part of the immune system there was some theoretical reason to think that, in fact, it is not going to matter whether it is a local strain or not for that particular vaccine and so that was the question that was being on the table.

Why did we choose South Africa and Kenya? First of all, because those are the places that need vaccines and so we are focusing on places that are at absolute highest risk now because again if it turns out that CLADES are important, if it turns out the type of vaccine is important, we want to design those

for those places.

Secondly, that is where the good scientists were. And in Kenya -- the reason it was done in Kenya was quite interesting. It was the place where we found a group of commercial sex workers who had been exposed year after year after year after year and never became infected.

And the reason Oxford University was involved, they did a study and looked at these women and found out that, in fact, they had a certain type of immunity to HIV and they asked the question could we now replicate that immunity with a vaccination strategy. That is how the research came.

They have put together a vaccine that, in fact, they think replicates this immunity and it is made to cover all of the different genetic groups in Kenya, which is a complicated issue. It has 44 of what are called epitopes, pieces of immune recognition, to cover the entire population of Kenya. There is a lot of different ethnic groups that exist there.

If you were to make the same vaccine starting off in the United States you would make it for a different set of ethnic groups. Maybe it would work the same but maybe it would not. You would probably have to go back and do a second set of studies in these countries.

So the idea is to try to move it forward and just as a parenthetical it is important to note that that vaccine will first be tested in the U.K. so that it is mismatched going the other way. In other words, it is a vaccine that is made from African strains that is likely to work in African populations but not necessarily in the British populations but it is being tested in Britain with full disclosure that, in fact, this is a vaccine that is designed for African populations, et cetera.

DR. SHAPIRO: Thank you. Let me -- I am sorry.

PROF. CAPRON: Do you know why?

(Laughter.)

PROF. CAPRON: Because? It is being tested

in Britain because?

DR. BERKLEY: Because there has been a sense that has come up that, in fact, we should not test vaccines -- and it was part of the old -- I do not know if it still exists -- CIOMS guideline that you should not take a vaccine and test it in the south unless it has been tested in the north.

Now one of the challenges for us in the future is going to be -- and Japan has already had this challenge. What if you have a technology that is really good and nobody is interested in testing it? Does it sit on the shelf?

Now if IAVI does not exist the only way to get that technology moved forward theoretically, let's say the NIH was to do it, was to go through U.S. FDA, which is not an insignificant hurdle, and to pay for a testing done in the U.S., which is not necessarily a cheap process, before you transfer that technology somewhere else. A company is not going to do it any other way.

So the challenge in that circumstance is

those things sit on the shelf and do not get used. So do I think it has to be tested necessarily in the U.K. before? No. Do I think that IAVI should as a new institution follow the precepts that have been put out? Absolutely.

But I can tell you that my colleagues in South Africa are pounding on the table and saying, "Why are you slowing things down by testing it in the north at all? We want the vaccines now. We have the ability to make an informed decision about whether these are appropriate or not and should be able to move them forward without having any testing in the north?"

DR. SHAPIRO: Tom?

DR. MURRAY: Dr. Berkley, thanks so much. The materials you gave us in advance and your presentation today make IAVI sound just terrific. I do not mean --

DR. BERKLEY: I am waiting for the "but."

DR. MURRAY: No, there is no -- well, it is not a but. It is a question.

DR. BERKLEY: Yes.

DR. MURRAY: Any time the north is involved in this sort of relationship -- in a relationship with medical research in the south, there is a certain presumption of suspicion that shrouds, I think, even the most idealistically motivated endeavors.

So, I guess, my question is really a fact question. Have you had criticisms directed against IAVI either for its strategy that somehow you are a tool of industry or for the specific kinds of -- the ethics surrounding the specific trials that you are sponsoring?

If your answer is you have not had any such criticisms that is just fine.

DR. BERKLEY: No, I --

DR. MURRAY: But tell me if you have.

DR. BERKLEY: There has been. There was an article that appeared early on in Kenya entitled "Kenyans to be guinea pigs for AIDS vaccines." Now that was -- what happened was it leaked out that Kenya was one of the sites chosen. There had not been any

work.

And one of the things we do -- I really ran through our program quickly because we are talking about ethical issues here but we have a very aggressive campaign to get NGO's educated on this topic and so in Kenya there is a communications program that works with journalists, with the community, to try to get them to understand all the aspects, all the ethical issues, what it means, vaccine development, what phase -- different phases of trials mean, the fact that the vaccine -- really we do not know whether it works or not so it is not -- you know, you cannot assume it is going to be -- et cetera, et cetera. And that education campaign is underway.

I must say now that things are very quiet there in terms of any opposition. People -- in fact, the researchers got a standing ovation in their parliament when they went to present the fact that they were working on a vaccine.

I do not doubt, though, that there will be

issues down the line and I think the important point -- and that is why I think it is critical to have true partnership and involvement -- the first time a lightning strike hits a person who has been, you know, in an AIDS vaccine trial, I am sure that the world will say, "Well, that person, you know, died from an AIDS vaccine," and there is going to be a lot of controversy. The persons who answer that should be people who are really doing it from the country and can understand it.

And, by the way, I -- you know, we are northern. Our scientific advisory committee is from nine countries. Our board represents, I think, seven or eight countries, and so we have people from the different communities involved, scientists, researchers, ministers of health, et cetera, who articulate these issues in these different settings.

DR. SHAPIRO: Diane, is it short?

DR. SCOTT-JONES: Yes.

DR. SHAPIRO: Okay. And then I am going to turn to Ruth for the final comment, and then we are

going to have to move on.

DR. SCOTT-JONES: You mentioned that you have been careful to say that you do not know if the vaccine works or not. Does that idea go over well? Do people have a sense -- is it your sense that people know that this is research or will be research?

DR. BERKLEY: I think there is no question given where we are in the process that people know it is research. I think the idea does it work or not is a tough concept.

And we have worked very hard and that is one of the issues of trying to play out and have local strategies and local training. I mean, we do not make brochures in New York and then take them somewhere and translate them.

What we do is we hold workshops. We train people. They then create teaching materials, work through it and try to have people understand. It is very, very tough to have people understand that and particularly the media is a problem because the media does not necessarily understand the nuances, want to

understand the nuances, and that has been a real process of trying to educate them to be honest and open and to explain it well.

And, you know, it is -- again it is a work in progress but I believe that has benefit not just for HIV vaccines. It has benefits for all of the type of science work that we are all trying to do.

DR. SHAPIRO: Thank you.

Ruth?

DR. MACKLIN: Seth, you are, of course, to be commended for following the CIOMS guidelines and what they say just as they may be about to be revised in the opposite direction. As far as this commission's work is concerned people veer -- not people, but the commission is veering back and forth between worries about protectionism and paternalism on the one hand and worries about exploitation and the use of vulnerable countries or populations.

Just two small points. If those CIOMS guidelines were different or to just mention another document that has fallen into the black hole on Peter

Piot's (phonetic), the vaccine guidance document that --

DR. BERKLEY: I did not say we are following CIOMS. I said that is what they recommended.

DR. MACKLIN: Yes, that is what they recommend but, I mean, if there is enough evidence that the paradigm is shifting from the need for protection to an antipaternalistic mode and, of course, with better training among the scientists and the ability to represent that the science is good, the scientists are well-trained, there is capacity for ethical review, et cetera, et cetera, in those countries, would you then quickly shift and begin to test the vaccines, the early stages, I mean a Phase I or at least Phase II but let's Phase I in a country like South Africa?

DR. BERKLEY: I would like to go back to your question because, first of all, I do not personally believe that the CIOMS guidelines are appropriate anymore. I think the real issue is what is adequate preparation and knowledge base and that is something

that needs to be worked out.

And one area that I might make a recommendation, if I may, where you might want to consider -- I know Ruth has heard me say this. One of the tragedies has been we get very wise developing country scientists who sit across the table from a group of distinguished ethicists and the distinguished ethicists say, "Well, you do not have the credentials. You know, you do not know Judaic-Christian ethic, you know, principles; you do not have the Ph.D. in ethics, whatever the degree is," you know, and there is a sense of inequality in that.

I would love to see a fellowship program that trained professional ethicists from different parts of the world in Judao-Christian ethics that still they represent their values, still they can go back and talk from their communities as the scientists currently do but at an equal footing.

And that has been a real problem in the past in terms of where we get our ethical advice because we say, "Well, there is no expertise in China or there is

no expertise in Uganda." There is a lot of wise people who have been involved in a lot of research over the years. They just do not have the credentials so that is a recommendation.

But personally I believe, in fact, that we must do that, must, because again there is a whole range of issues. It is possible right now we do not -- and I will open a can of worms since we are running out of time to continue today, it is maybe possible that at some point we will recommend mandatory treatment for anybody who seroconverts for HIV, triple drug therapy, quadruple drug, you know, five drug therapy. If we do that how we will test vaccines in the United States? I mean, that is a real question.

Now you can say, okay, develop -- if we are going to say our standards are the same everywhere in the world then, therefore, if a U.S. investigator or a U.S. company wants to do research in South Africa, it must require quadruple drug or five drug therapy immediately if somebody seroconverts. You cannot test

the vaccine there so you end up in a quandary. You cannot test the vaccine period then.

Now luckily under that circumstance I presume what would happen is that those countries would say we need to test a vaccine and would try to negotiate. One of the tough issues in that set of circumstances is do they -- are they empowered to negotiate and can those countries ask the question 20 years into the AIDS epidemic why we have not tested a single vaccine to completion.

And the answer is they are not empowered to do that right now and so what we need to do, I think, is rethink those sets of power relationships such that they can truly engage in this and themselves ask the question, well, if for whatever reason it cannot be tested in a place that, you know, has different rules, we have the ability to take that forward.

And so I hope that when this commission deliberates on this issue that they really take on that particular issue because that is a reality that I think we are going to run head long into very soon.

DR. SHAPIRO: Thank you very much. We really appreciate your coming and patience and waiting since we were running late, and it has been really quite fascinating to learn a little bit more about this. Thank you very, very much for coming.

DR. BERKLEY: My pleasure.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: I would like to make a recommendation regarding our deliberations for the next short while. I am not sure how long everyone can sit here since we have been here since 8:30 this morning off and on.

I think a sufficient number of issues have been raised regarding the -- especially the effective -- established effective treatment and that comes up again and again. All the recommendations that flow through the study design.

So if Ruth does not mind I think we will come back to that as we can as you get to think about the comments that are made. Since we have just a short time this afternoon I would like to go back to what is

under -- I would like to go to, rather than go back to, what is under 2c, which is potential recommendations for chapter 4.

Now obviously -- I do not know how Ruth would characterize this. Obviously there is no supporting text and so on and so forth with any of these recommendations but I think -- I will let Ruth speak for herself -- that she would like to get at least initial reaction to these kinds of recommendations that might help inform her as they go to start drafting for and coming up with a set of either these recommendations or it will look quite different than these depending on what is developed.

But, Ruth, I will let you speak for yourself on this.

DR. MACKLIN: Okay. Well, this is actually following the pattern that we started at the very last meeting, which was setting out some bold propositions, hearing what the commissioners have to say, and then going and softening them or making them more nuanced and providing the supporting text.

But what we were hoping and, indeed, we heard it today, was that the entire discussion that preceded this -- I mean, including the last presentation by Seth Berkley, and everything on the preceding panels that we heard actually was supporting material. Not all on the same wavelength but certainly supporting and discussing these issues.

So it is not as if this is coming out of the blue. We are actually quite fortunate that the panels and the people we invited did address precisely the issues that these recommendations addressed.

So you can imagine that maybe there was some text and the text gave you on the one hand and then on the other hand, and then we can go to these and from the basis of this discussion we will then draft something probably roughly about the same length and the same kind of material that we did for the chapter 3, the preceding one that we discussed all too briefly today.

So this -- we are just asking you to agree or disagree and they are in this order but in some

previous discussion already with Harold and Eric we know that we could make a different order but I think since this is what was before you we should start in this order.

DR. SHAPIRO: Okay. Thank you.

Let's just take a look and perhaps share our reactions with Ruth to recommendation -- stated here as recommendation 1, lines 8 and 9.

Eric?

DR. CASSELL: I agree with all of them. My problem was with only that one, whatever responsive to the health needs of the host country means. It is so vague that it is a little difficult but that is the only one which I had any trouble at all and only because it was, you know, that vague.

PROF. CAPRON: What is meant is the research should involve problems which are common in that country or relevant to the country.

DR. MACKLIN: Well, it means that and it means a little more. For example, you do not -- it is not appropriate to study a disease that only exists in

a northern country and for whatever reason does not occur in a southern country if that is the example. So the disease or the condition you are studying has to be one that is prevalent in that country. That is number one.

Number two, it is being responsive to the health needs also may take into other -- take into account other situations -- other factors in the country so that one would not do research and develop a product.

What Seth was just saying, here is an example, if it needs refrigeration and you have a country in which in the rural areas a very large number or part of the country there is no refrigeration, you would not develop the kind of product that you would for a -- in the developing country where it needs refrigeration and you could study it in the developing country but it could not be applied there because they do not have refrigeration.

So it goes a little broader than the condition in the country.

PROF. CAPRON: So that is the word "responsive" to?

DR. MACKLIN: This is an exact quotation from -- this exact wording is in the CIOMS guidelines but, of course, we will elaborate. I mean, what you are pointing out is absolutely true and this is just a statement. We will then have to say what it means to be responsive to the health needs.

PROF. CHARO: Hand up.

DR. SHAPIRO: Okay, Alta. You can start speaking.

PROF. CHARO: First, I agree with the recommendation. I would like to offer a possibility of strengthening it a little bit and going a little further. I am thinking again about the example that Alex mentioned earlier of the birth control pill trials in Puerto Rico back in the '50s and '60s.

That is an example of a trial for a drug that is going to be responsive to the health needs of the host country but where the primary market really is not in that host country and where the trial could

just as well have been done in an industrialized country, which was, in fact, the intended market.

And so without wanting to cut off the possibility of research like the AIDS vaccine trials that we were just hearing about in the south by requiring that it always has to be tested first in the north, I would still love to find some way to express the notion that research should be done in these countries because there is a particular need to do them in these countries as opposed to doing it in other countries where the research is less problematic.

I mean, I appreciate the fact that to some extent you handle a little bit of this in the subsequent potential recommendations that talk about distribution afterwards but imagine a situation where you protect equally easily in the U.S. or in Uganda for something which is going to diffuse Uganda just as rapidly regardless of whether it is tested first in the U.S. or in Uganda.

Would you want to support the testing in

Uganda simply because it happens to be responsive or would you want to say it should not be done in that more problematic circumstance unless there is a particular need and reason to do it there?

DR. MACKLIN: Well, this takes us back to the tension between the protectionism and the -- or the paternalism or let's say the protectionism and the need to make things available as soon as possible.

Now what we just heard from Seth Berkley and we have heard it elsewhere in other contexts is if there would be a delay in the introduction of a product that could be tested simultaneously in both countries but if there would be a delay if it is tested first in the United States and then has to go through the whole process of testing and drug approval here and only then to be tested again there on the assumption that it is not just going to be introduced then you are actually delaying it and failing to provide the benefit to the people in the developing country.

PROF. CHARO: I understand that, Ruth, but I

did actually temper my comment by saying assuming that it would diffuse Uganda at the same time regardless of whether it were tested in Uganda or in a developed country. In other words, assuming that there would be no delay.

DR. MACKLIN: Okay. I mean, that is a condition and we probably have to build that condition in. Whether we could know that in advance is another question. What we heard at an earlier meeting from someone who spoke here was that -- and also this is known from other sources is that there are sometimes for political reasons, sometimes for scientific reasons, there is resistance on the part of ministries of health or leaders of other countries to introduce something that has been tested -- that has not been tested in their own country. So, I mean, we would have to deal with that caveat and condition.

PROF. CHARO: Okay.

DR. SHAPIRO: Alex, and then Larry.

PROF. CAPRON: My comment about the first recommendation is that I do not quite understand why

it is in this chapter. As Alta began the process of saying, well, don't we want to add in further qualifications such as there is a special reason to do it here and not some place else, the question I thought this chapter was addressed to is what is owed to research participants during a clinical trial and after successful completion of the research.

And this question as framed -- and this recommendation number one seems closer to the questions of study design and the choice of the method by which a study will be done and I just want to suggest that perhaps these additional qualifications indicate you have a bigger topic here but it really belongs over in the other chapter.

Is that possible?

DR. MACKLIN: I will tell you what the -- actually it belongs in both.

PROF. CAPRON: Okay.

DR. MACKLIN: It belongs in the other chapter and I think it is already there. I mean, in those conditions.

PROF. CAPRON: Right.

DR. MACKLIN: The reason it belongs here is -- as well because there is an overlap in these chapters, the reason it belongs here as well is that it is a necessary condition that must be fulfilled if we are going to go down the list and look at the later recommendations.

In other words, if one does not -- I mean, the later ones here. If it turns out that products are not made reasonably available, whether it is for economic reasons or any of these other reasons, then the research itself fails to be responsive to the health needs of the country.

If you have reason to believe in advance, if there have not been any prior agreements, any discussion, any commitment, all the things Len Glantz was talking about, then it turns out you have done research in that country and it turns out after the fact not to have been responsive to the health needs of the country.

PROF. CAPRON: Yes. I have --

DR. MACKLIN: So it is a precondition in a way.

PROF. CAPRON: Well, I have no problem. I mean, my assumption is that the design stuff is really chapter three and coming out of it you would simply introduce it by saying one of the considerations we looked at there was the notion of being responsive.

Part of that assumes that the research product, if successful, would have application but what kinds of arrangements have to be made in advance? What is owed to the subjects? What is owed to the country? What is owed to the world?

May I comment on another one of the recommendations?

Number five says, "As a general rule any product developed from the research should be made reasonably available at the completion of successful testing." There is no object to that availability. It does not say made reasonably available to. In a certain way number six begins to get into that complication so really five and six are all part of

one idea.

I asked Seth Berkley the question about their assumptions about what they meant by available and at an affordable price precisely because of this issue I have been pushing all day of if we are making a moral argument that somehow participation in research entitles you then is that specific to the particular research project? That is one question.

And a second question, is it specific to the research subjects because we have been going on some assumption that it somehow generalized to other people who might have been research subjects.

I want us to -- I am -- I can understand that there is some moral weight to that argument. Part of the weight is much stronger as to therapeutic modalities if they have worked and a person is getting them and their fatal disease is being held at bay, there is something psychologically as well as morally disturbing about pulling the plug on them at that point and saying, "Well, thank you very much. Now you have proven something works but you are not going to

get any more of it because you cannot afford it." I mean that somehow seems wrong.

But for the person next door is it equally wrong because had they been drawn in the lottery or had they been farther up in the queue from which the first 100 people were taken, would they have also gotten it? Is there some sense that the entire country is involved and then what about the neighboring country?

I do not have answers to all of those but it seems to me that some of the argument has to do with necessitous, that is to say it is a resource poor country and if there is a treatment somehow the world, not just this individual company, but the world ought to address the health needs. And if they can be addressed at a price that is affordable for the world but not affordable for this country, whether it is through the World Bank and telling people to invest their money or making loans or intervening in some fashion, the argument is very strong.

And then the other one, as I say, is much

more specific to I have been a research subject, I have given you something, I have risked my life, now you owe me, and that says nothing about the other people who did not happen by whatever chance the wrong town, the wrong, you know, whatever, to be in the research project. And as to them the argument of living in a country seems to me largely irrelevant.

So I -- when you start to go on to this I think we need available to, we have to address the "to."

DR. SHAPIRO: I think -- go ahead.

DR. MACKLIN: I just want to point out that one category you mentioned actually is taken care of in chapter three. In other words, what is the obligation to the specific research subjects after the trial is over and one of the things we did not get to this afternoon is a discussion of the people with a disease and do you pull out the drug that has been --

PROF. CAPRON: Right.

DR. MACKLIN: So that part is in. It is kind of a segue from that into here and these are the

harder ones. These are much harder.

DR. SHAPIRO: I think with respect to five and six, and I agree they should be -- they are part of the same idea, however we want to structure the N, I agree it is the same idea.

An issue that came up today and you have just mentioned again, Alex, is what I call -- there is the direct versus indirect. That is people in the successful trial, they get something, and it came up earlier today, what about all the people in the unsuccessful trial?

Well, I do not know how to even think that out, frankly, because there are many, many unsuccessful trials. We really draw this back. It goes back till, you know, the first person who invented the idea of a test tube made all this possible and so on. So I think it is an interesting issue but I just do not know what resolution one can give it.

PROF. CAPRON: Actually I think it is the idea of the first person who invented a guinea pig.

DR. SHAPIRO: A guinea pig. All right. So I think my own just sense of it is, and maybe people have a better idea than I have, is that the primary focus should be on the people in the trial. You know, there is lotteries all over life and this is just another lottery and -- but we do have a clear obligation here it seems to me.

DR. CASSELL: I think that is right and I think, Alex, if you take your's further then we get back to the -- you know, why not the neighboring country and then why not all countries, and then we are into why don't we -- you know, take care of everybody and then we have -- (a) it is impossible and (b) it totally obscures the question of what to do about research subjects because they get right down to generality and yet they are the ones who did the volunteering and they are the ones that we are immediately responsible to

PROF. CAPRON: I do not disagree but a lot of the discussion and some of the discussion has aimed towards other people in the country and certainly the

notion that a particular sponsor would negotiate with the country to make available within the country to the entire population the drug or whatever at an affordable price for that country in advance struck people as morally going in the right direction but that then gets to the same lottery question that Harold just said, "Well, why was it that country rather than another?"

As I tried to explore with Leonard Glantz, we have to see that there can be some unintended consequences of having certain kinds of rules built in not to a marketplace negotiation solely but as though an IRB were going to say, "Well, we have read this report and we will not approve our researchers being involved in research in which that process has not yielded what we regard as a satisfactory conclusion."

And Leonard was sort of saying to us, "Why was it just a letter of intent" with, I think, the clear implication being it would be morally much better for it to be a contract. But then I worry about the health minister in another circumstance

saying I am going to hold back a little because I do not want to be the loser in that lottery and, yes, who knows what the sequence is and, yes, subjects 100 years ago who were in the first cow pox vaccination contribute today to an AIDS vaccine but we cannot pay them back.

But I do not want my country to be in the unsuccessful trial and then have the neighboring country once they have found out what does not work, to find out what does work next door and they get the good deal and I do not so I will just hold my country back, thank you very much, until you are closer to having something that looks like it is going to work.

DR. CASSELL: Well, there is another --

PROF. CAPRON: And that is an unintended bad effect of having a rule which has a good purpose in and of itself.

DR. CASSELL: There is another way -- a previous step. One of the reasons we had in this here is that there are, in fact, trials in which people are being treated. The treatment is successful and to

remove the treatment at the end would do them great harm.

And so an initial step is to prevent that harm without going on and getting into this endless lottery business so that it might be well that we specify that no harm should come to a subject by the withdrawal of the drug that could be made available.

PROF. CAPRON: That is chapter three.

DR. CASSELL: Well, but it is -- it ought to be -- I mean, if we are going to discuss this in two places then it is here, too, or you could say see chapter three for the real details.

DR. MACKLIN: Well, unfortunately, we are not going in order but if we had had unlimited time we would have gotten to recommendation number three on page 17, line 3, which says, "Researchers and sponsors have an obligation to subjects with a chronic condition to continue to provide beneficial treatment following the conclusion of the research." So that is where that is.

Now, I mean wherever -- however we do it, it

-- we are going to make an artificial distinction somewhere because we are talking about the research design but the research design not only from a methodological point of view, from an ethical point of view. In other words, you are talking about the research design. It is what ought to be given to the control group.

So somewhere or other in this seamless web we have to put some recommendations in one chapter or another. If the commissioners want that one in the chapter four you can have it there. I mean -- but all we have to do is -- what we have to do is -- unfortunately, we are going -- we are going back and forth.

DR. SHAPIRO: Let me ask a question with respect to what is on page number one here, recommendation 2 and 3, for example, and see what -- if any of you have any reactions or issues you would like to raise with respect to those.

DR. CASSELL: Which ones?

DR. SHAPIRO: Two and three, which are on

this page.

PROF. CAPRON: Back to the --

DR. SHAPIRO: Back to the ones we were doing. This is under 2c. Excuse me. I apologize.

DR. CASSELL: Oh, I see.

DR. SHAPIRO: I want to keep you ill at ease here, Eric.

DR. CASSELL: Yes, why do it in a way we can follow?

DR. SHAPIRO: That is right. You might get a good idea that way.

Arturo, did you have --

DR. BRITO: I think -- you never want to say never but I think these two, three and four, it -- I would be hard pressed to find -- I do not think there is anyone that is going to disagree in theory with what these are saying and I think this is the key here is to start with these and to say that the clear understanding has to be there at the very beginning to both the community leaders or the political leaders in those countries and in number four also, the research

participants themselves, and then go from there, and then -- and then based on everything else, I think at minimum that the research subjects should have the compensation. In terms of the community or the country I do not know where to go beyond that but I think a main thing here is to have a clear understanding from the very beginning of some contractual agreement or what have you. That would be key.

DR. SHAPIRO: Any other --

DR. CASSELL: Could you tell us where we are?

DR. BRITO: 2c.

DR. SHAPIRO: It is this page that you agreed with completely, Eric.

DR. CASSELL: I did. I did. And then you said, "Now let's go on to so and so."

DR. SHAPIRO: I did not say that.

DR. CASSELL: And faked me out.

DR. SHAPIRO: I did not say that.

PROF. CAPRON: Ruth said that.

DR. SHAPIRO: Ruth said that to illustrate a

point.

DR. MACKLIN: I said, "Let's go back."

PROF. CAPRON: I hope that the discussion will bring out what I thought was Eric's good comment to Leonard about the realities and the complexities of people committing that certain things are going to happen, particularly when the commitment is coming from a government minister, whatever, who may or may not have the ability to deliver on it having nothing to do with bad faith but just change circumstances and he may or may not be or she may not be in office or the political coalitions may have shifted. Who knows?

It is one thing to say what the commitment is. It is another to say that that is the make or break point when the commitment may be written in invisible or disappearing ink, in effect.

It is a question obviously -- maybe this is the reason you chose the word "can" rather than will. What can be provided. If something is totally unrealistic there is really no way that the country is

going to be prepared to provide that either for logistical reasons or financial reasons then that counts against approving it.

But -- I mean, maybe the word "will" was considered too strong because who can predict the future fully. Otherwise the "can" sounds odd there. You know, what -- if you agree what will be you are in a better position to say, "Well, this is what I will do." But can be, I mean, the world may change. It may not even -- you cannot do it. It turns out there has been a flood and all the power stations have been knocked out. There goes refrigeration, I mean, and all that.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: When I first read through 2, 3, 4 and 5 I just went through marking "agree" because upon rereading them I could see that the statements are relatively soft statements. They are not filled with content about what would be provided. It is what can or cannot be. What, if anything, will be made available.

The real questions that we would have difficulty with are there in six. How should reasonably available be defined? It seems to me that two, three, four and five are very easy to agree with because they are not making strong statements about the hard issues.

DR. MACKLIN: Good. This is a good thing, not a bad thing that they are easy to agree with.

(Simultaneous discussion.)

PROF. CAPRON: No, but it would not amount to much. It is like the present requirement that subjects have to be done that they will not be compensated if they are injured. It is better than not knowing that but it does not do you a lot of good if you are injured.

DR. SHAPIRO: Bernie?

DR. LO: It is nice to have things we all agree on but one through five are pretty easy to agree with. I mean, it is hard to imagine someone disagreeing. I think Diane is absolutely right. Six is where the rubber hits the road.

And it seems to me that we had some very different models presented to us today by our three speakers. You know, one of them was sort of saying that you have got to have the financing in hand to be able to actually buy the drug and other people are saying, well, let's try and find out a way of making the drug available at a lower cost through technology transfer, licensing agreements and such. And those, it seems to me, are very different kinds of agreements. I think we need to sort of think -- and it gets to the question of who is responsible for what. It seems to me it is much easier to think of creating an agreement to have a technology transfer or a licensing agreement but not a commitment to actually commit to the dollars it would take to buy a certain amount of drug for a certain number of people.

I think we need to be careful about -- first of all, it is not clear any of these strategies will work or if they do, which are are more effective, so I hate to sort of commit us to something that is a theoretical concept that has never really been carried

out and even if it has been carried out once or twice may not apply across the board.

So I think six is what we have to pay attention to and maybe just to lay out clearly what some of these options are would be a good starting point.

PROF. CAPRON: I have a factual question.

DR. SHAPIRO: Yes.

PROF. CAPRON: Perhaps someone who has been involved in vaccine considerations like Ruth would know. In the eradication of smallpox to what extent was the program paid for by WHO or other international organizations and to what extent was it paid for by the governments of the countries in which vaccine programs were carried out?

Because -- I mean, I guess, I do not have to say any more. It is obvious what the consideration there is. If you have a ministry that says, "Great. We want to get it. A dollar a piece we can afford." And then you say, "Okay. Here it is a dollar a piece," and they are not buying.

Does that mean that it has been a failure or does that mean that other people should step in and put up the dollar a piece and what has been our experience because this is not the first vaccine which would be used on a wide basis around the world.

DR. SHAPIRO: That is an interesting question. I do not know the answer. Perhaps someone else.

DR. CASSELL: Well, there is some history about it. First of all, there was a long argument. Eradicationists were radical people. Nobody believed that you could eradicate any disease and along came the possibility with smallpox and this was a WHO policy, you know, which everyone finally agreed that it was worth a trial.

It had more to do than just smallpox so the stakes for doing it were very high and were determined, you know, centrally so that when -- so that is why governments followed through on it. I do not know who paid for it but the fact is that the idea of doing it was not something imposed from the outside

by WHO. And, also, it was very cheap.

PROF. CAPRON: I agree but we were talking -- I mean, if Seth Berkley has any scientific sense of what he is talking about -- of the potential if you are making 10 million doses of an AIDS vaccine that the price for it on a unit basis would be very low. It is something where the demand in the stricken areas of the world is high. It is something which has a U.N.-WHO type basis. The U.N. AIDS effort and so forth.

So, I mean, in some ways it resembles it. Was there a barrier in the smallpox story when some countries simply said, "Well, it sounds wonderful but our treasuries are empty." Did the world through WHO or something step in and say, "All right. In your country we are coming in with a scientist and a vaccine and we are going to do it for you because if we do not do it here we will not have eradicated it and we do not want weak links and it is important. You are poor and we will do it for you."

DR. SHAPIRO: Bernie?

DR. LO: I am very much in sympathy with Alex's hope that we can get some empirical and historical economic data. It seems to me that ought to make a nice side bar case study for our report. I think the more we can sort of take our general recommendations and sort of see how they work out in actual cases, the stronger our report will be.

DR. SHAPIRO: Thank you.

Bette, please.

DR. KRAMER: Actually Alex and Bernie have taken care, I think, of what I wanted to say. I was going to make Bernie's usual suggestion that we come up with some case studies but I think a lot of -- a lot of what we have heard today lends itself to or might lend itself to actual ideas.

I mean, ideas that have actually been tried or suggested ideas that might be tried and maybe just getting them down in boxes and taking a look at them trying to -- gleaning from them -- even if the go into the report only as suggested ways of talking about -- thinking about these issues and I thought we heard a

lot of good things today.

DR. SHAPIRO: Larry?

DR. MIIKE: Yes, just three comments on my note taking about what has been going on. My guess would be that it is public funds that -- on the smallpox issue because there has not been a case in years and I cannot imagine a poor country turning to pour money into an area where they really do not see any smallpox.

A long time ago I wanted to make a comment on what Alta had mentioned about one and then putting in some additional caveats about if it is effective, if it is a problem in a developed versus an undeveloped country, and putting it in here. But I think one of the premises we are going -- we are going in into this study already and I think we all agree if you can do it in a developed country you are not going to do it in an undeveloped country.

So it seems that we do not need to reiterate that point again in recommendation one. That is just sort of a lynch pin of the kinds of conclusions that

we are reaching in terms of research in developing countries.

The third point is that when we talk about two, three and four and hardening these issues, I hope we do not harden it to the point where it is either all or none just like the best available sort of -- you have to replace it with established effective rather than best available because if you literally stick to the best available then you do not do anything and I do not want us to sort of get dragged along into such hardened positions that in the application itself we actually shut off research rather than facilitating research that is for the better of these countries.

PROF. CHARO: Hand up.

DR. SHAPIRO: Hands up. You are talking. Hands up.

PROF. CHARO: This is great. I am going to do this every time instead of ever coming to the meeting.

(Laughter.)

PROF. CHARO: I have been sitting here staring at number six after comments about how that is where the rubber hits the road and I would like to throw out something just as something to think about. I do not know -- I do not think it works yet but in terms of operationally defining to whom and for how long, et cetera, would it make sense to start at least thinking about this from the point of view of the actual subject of the research and saying, "Okay. What can we say about the likelihood that if a product does get developed from this research you are participating in, what can we say is the chance that you in your own lifetime would have access to that product?"

That does not answer the question of what is reasonable and unreasonable but it is a point of view question as opposed to using a kind of more economic point of view in which you ask, "Well, you know, what percent of the population has to have economic access, for how many years," but instead shifting the focus to this much smaller group of people and using them as a

proxy both because they are subjects and because -- so that there is some sense of obligation of that personally and because it also then dovetails nicely with the notion of the kind of information they ought to be given before they volunteer.

DR. SHAPIRO: Thank you. My own initial -- thank you, Alta. My own initial reaction to that particular part of item six was as a kind of first approximation to start off with making it free if it is useful to the participants in the trial, both control and otherwise, and everything else is a matter of negotiation in item two or whatever the item is where the negotiation takes place as a way to think about that.

Incidently, I can actually think -- I think I can think of a case, Larry, where you could do a trial in either developed or under developed -- or a developing country but you might proceed -- you might decide not to proceed if forced to do it in a developing country not because it -- it becomes just more expensive and you line up your priorities and it

falls off the list. It may, in fact, be a greater health benefit even though it will apply to both north and south. The real benefit might go to the south. I mean, I can imagine such a case.

So I think I agree with your general notion that we have to be careful about setting any absolutes here because, you know, we just have to leave room for judgment on these issues.

PROF. CAPRON: It seems to me that number six, which is just a set of questions after all, in a funny way it is odd to say the rubber meets the road there. Well, the tire is invented there but it does not -- has not met and produced any skid marks of any sort.

I thought we were talking here about something that was not specific to the individual subjects because I did think that was covered in recommendation three in chapter three. Now I am not talking about where it falls in the eventual report.

I thought the reasonable availability was this larger question which IAVI has tried to work out

by saying either you are going to sell it at an affordable price or you are going to let us license it to someone else who is going to try to make it at the affordable price where it is either -- it is too expensive to make in your factories or it does not have enough marginal return and you do not want to dilute your shareholder value in that way or you do not like that kind of differentiated market. You are going to get criticized for selling it cheap but you will not get criticized if some other company sells it cheap and whatever reasons.

But that is what this had to do with because the question of for how long following the completion, that sounds much more like the question of the chronic disease. Like are you buying in to giving AZT to someone for the rest of their life if they are in a research because they were in the research study and you got them to a point where they were not dying from this and it is pulling the plug issue.

But you are --

DR. MACKLIN: Well, it is not intended to be

that. In other words, if the claim is and if there were agreement that researchers and sponsors are under some obligation to make a product reasonably available, let's say just for the sake of this argument hypothetically, in the country where the research --

PROF. CAPRON: Yes.

DR. MACKLIN: -- was done, okay, is the company -- does the company have that responsibility in perpetuity? In other words, the research was done there initially but things have moved on. I mean, a company might, for example, be prepared to make a limited time agreement but isn't going to sell its future investors down the road indefinitely. So it really does -- I mean, it is a practical matter but it really is meant to raise a question about how long after research is done in a particular place does an obligation, if there is such an obligation, continue to the country from which the research subjects --

PROF. CAPRON: I think it is a reasonable question. If I could -- well, I had another thought,

which is -- I think I will hold off.

DR. SHAPIRO: Rhetaugh -- because we are going to conclude in just a few moments. I think we have gone on for long enough.

DR. DUMAS: I wanted to share the assumptions that I talked about earlier that seemed to be coming through in this discussion and in the presentations that we heard earlier that the focus is on public health problems, that the concern also is on public sector finance, and that the emphasis is on treatment over prevention.

Is that an accurate appraisal of what we are talking about? And the design is clinical trials.

DR. MACKLIN: Well, there is not enough detail in here but I think -- I mean, you are asking what would be the assumptions underlying this.

DR. DUMAS: Well, it seems to me that --

DR. MACKLIN: Let me say first why it is not clinical trials.

DR. DUMAS: Okay.

DR. MACKLIN: Let me go to the last one.

There may be research interventions and if they are not clinical trials then they will probably pose less risks to -- fewer risks to the subjects but interventions of the sort that David Griffin was talking about.

For example, there may be a risk reduction program for reducing the likelihood of transmission of HIV/AIDS or other sexually transmitted diseases, for example. Marjorie Spears mentioned a very different kind of intervention that CDC has done which was getting people to use bed nets as protection against malaria. The product was not the bed net, okay, but the research was an intervention getting people to use these safer things.

So any of those things would count and some might require that something be made available following the research. It is not just teaching a few people to do it. There may be something else that would be required. I mean, maybe required to actually give the bed nets in the future. So that is one assumption.

The second is certainly not treatment versus prevention as I just now gave the example of the bed nets and the intervention --

DR. DUMAS: Right.

DR. MACKLIN: -- the safer sex but the vaccine is a perfect example. That is a prevention, not a treatment.

DR. DUMAS: But it is not -- well, it is not going.

DR. SHAPIRO: Not yet.

DR. DUMAS: Not yet.

DR. MACKLIN: Well, I mean, but other vaccines are -- have been tested. I mean, I do not -- I am not sure what you had in mind by prevention but I think the assumption is not exactly correct because of these examples. I am sorry, your first -- was it the public sector or public --

DR. DUMAS: Public health problems. The focus is on public health problems. Broader population problems rather than smaller group individuals.

DR. MACKLIN: What would be an example of smaller group?

DR. DUMAS: The definition of the problem.

DR. MACKLIN: Give me --

DR. DUMAS: Broad public health problems that have implications for countries not necessarily for smaller groups or communities.

DR. MACKLIN: That is probably right.

DR. DUMAS: And that -- okay. You said that the assumption that the preferred or the priority as far as design is concerned is not necessarily clinical trials but there is a great emphasis on public sector finance because of the a priori commitments that people are talking about.

DR. MACKLIN: Well, I guess the question is public finance from whom. I mean, these are --

DR. DUMAS: Well, it does not matter. It has to be beyond an individual investigator if you are going to propose that people are going to get treated after the studies are over and maybe for the rest of their lives. This is something that is -- assumes

that there is going to be some finance coming from somewhere other than the individual investigator.

DR. MACKLIN: Yes.

DR. DUMAS: And then when we talk about drug trials and that kind of thing. We are really talking mostly about public sector finance, aren't we? You are talking about --

PROF. CAPRON: Predominantly applied research today. I think the figures we gave -- we had before has a larger amount -- dollar amount from the private sector today than the public sector once you get to the stage of clinical trials.

DR. DUMAS: Oh, okay. All right.

PROF. CAPRON: Yes.

DR. SHAPIRO: All right.

DR. DUMAS: I got that mixed up. I should have said private sector finance.

PROF. CAPRON: Right, exactly.

DR. DUMAS: Private I mean.

DR. SHAPIRO: I think we are going to call today's session.

PROF. CAPRON: Can I put one thing on the table?

DR. SHAPIRO: Yes.

PROF. CAPRON: I just --

DR. SHAPIRO: One thing.

PROF. CAPRON: -- it is a question of sort of a heuristic. If it would be helpful in writing this to ask ourselves what is the implication of conclusions that we reach if we were talking about domestic research and always having --

DR. MURRAY: Done here.

PROF. CAPRON: Yes. The research done in the United States by domestic, I mean -- yes, within our nation. And we have asked that from time to time. We say, well, that seems as though it would be the same or sometimes we say it would be different and I just hope that we will do that and the best people to do that, frankly, are the people who are writing the report because in our meetings we focus in on different -- but if you can ask that and just point it out to us.

DR. MACKLIN: Yes. In fact, that is already going to be very clear. Harold has been urging that from day one and brings it up whenever he gets a chance.

PROF. CAPRON: He actually passed me a note and asked me to say that.

(Laughter.)

DR. MACKLIN: And, in fact, one thing -- you will recall that we jumped into the middle of this project as we did not -- I mean, when we started providing materials we never gave you an introductory chapter that set up the problem and the introductory chapter, which probably should be written soon actually because we are learning a lot at these meetings. I mean, I always write the last chapter or the first chapter last but we are learning a lot.

One of the things that is going to be brought up is that the report is about international collaborative research. Much of the focus is on the obligations of industrialized countries to resource poor countries and that is something that does arise

when that is the nature of the collaboration.

But as you will see next month in the materials that start coming out for next month there is at least as much, if not more, in the topic that is for next time, which is the research collaborations and how those work when any two countries are collaborating, that is following their rules or whatever. That is going to be as much if not more of a problem because more research has been sponsored by industrialized countries.

So what we will do in the initial -- the introductory chapter is set up the problem and say in some cases we are going to be dealing with ethical problems and obligations that arise between industrialized and resource poor countries. In other cases the conclusions or the recommendations will apply to both, whoever is involved in the collaboration.

I suppose it will be relatively rare that we will only be talking about what arises in -- with one industrialized country and another but we may have

something to say about that, too. So we are going to flag this distinction whenever it comes up.

DR. SHAPIRO: Thank you.

Before closing I want to thank Alta for joining us today. I judge by the periodic cough that you are still not completely well so I wish you well and I hope you will be able to join us tomorrow. I do not know if you can.

PROF. CHARO: I will be here.

DR. SHAPIRO: Thank you very much.

She will be here the way she was here today.

PROF. CHARO: Here as in sitting in my bathrobe here.

(Laughter.)

DR. SHAPIRO: What a vision. What a vision.

(Laughter.)

DR. SHAPIRO: Well, thank you all very much.

We are adjourned.

(Whereupon, at 5:30 p.m., the proceedings were adjourned.)

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