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NATIONAL BIOETHICS ADVISORY COMMISSION

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OPENING REMARKS

HAROLD T. SHAPIRO, Ph.D.

DR. SHAPIRO: Okay. I will call the meeting to order.

I want us to get underway as soon as possible since we have guests here this morning who have been kind enough to come at particular times and I do not want to keep them waiting.

In any case, we are all looking forward to their contribution to our thinking on the particular issues that are before us.

The agenda for the next day-and-a-half focuses on the first day, that is today, on ethical issues in international research that, indeed, will take up all of our time today.

Tomorrow we will be returning to the Oversight of Human Subjects Project, which is a large project that comes right after this one, at least in the time schedule of our reports.

The discussion this morning will be primarily focused around our guests -- we have visitors who will be here -- and our interaction with their presentations and our interaction with them, although we will begin with a few updates on where projects are.

Most of the discussion amongst ourselves will be coming on later on today some time after lunch.

So with that, let me turn to the mike over to Eric to give you any brief update he has before we turn to Ruth and Alice to see -- get a brief update from them on our International Project.

Eric?

EXECUTIVE DIRECTOR's REPORT

ERIC M. MESLIN, Ph.D.

DR. MESLIN: Just very briefly I wanted to welcome everyone and let both the commissioners and the public know that a new staff member has joined us, Ellen Gadbois, who is here, and I wanted to welcome her officially to the NBAC staff.

We are looking forward to her assistance and you will be hearing more from Ellen later on in our deliberations over the next couple of months because her expertise is in public policy and science policy. She has recently joined us from Senator Kennedy's staff.

DR. SHAPIRO: Thank you.

Let's go then directly to Ruth who will give us a brief update or overview of the work done to date.

Ruth?

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

OVERVIEW OF WORK TO DATE

RUTH MACKLIN, Ph.D.

ALBERT EINSTEIN COLLEGE OF MEDICINE

DR. MACKLIN: Okay. Thank you very much and I apologize to the commissioners for my absence last time.

I read the transcript in detail and was sorry that I could not have been here to put in my two cents.

DR. SHAPIRO: You get four cents today.

(Laughter.)

PROF. CAPRON: Too late, Ruth.

DR. MACKLIN: Okay. Well, we will come back to it. We will come back to it.

As you can see from the memorandum at Tab 2A in the briefing book, we are more or less following the outline, which has not yet been revised but may still be subject to revision. That is the tentative outline, chapter outline for the report.

So at the October meeting the informed consent discussion is intended to comprise one chapter and following the discussion Alice and I prepared a -- put together what was a background document along with the findings and recommendations that were discussed at the October meeting and those were merged or melded.

And, as you can see, they are not on the agenda for this discussion for today's meeting, this

month's meeting, but they are in the briefing books and we are seeking feedback because the next step is, of course, fleshing it out and writing a chapter, which will then be brought for the usual evaluation and editing of the chapter by the commissioners.

So we are, hopeful, that you will make comments. I guess the electronic way is the best way so everyone can see everyone else's comments and then we can get to the task of actually fleshing it out and writing that chapter.

The meeting this month is devoted to what is expected to be the next chapter of the report, Chapter 3, on risks and benefits and some methodological questions that raise ethical concerns and, of course, we are just beginning that process.

In the hopes of trying to resolve what are some controversial questions we have prepared some propositions, as Trish Backlar told us last night, in multiple choice form, it was not meant to be a test but it was meant at least to get our thinking going and see where there are agreements, disagreements or uncertainties about some of the central propositions regarding risks, benefits and obligations to subjects that will form the basis for that chapter.

We are in the process now of putting together

the agenda for -- and seeking panelists and testimony for the January meeting and that is pretty well in place, and that will follow the next chapter, which is entitled "Obligations to Subjects or Obligations of Researchers to Subjects and to Others." So we will hear more about that as we make the agenda final and then we have to move into February.

Our hope is that following these meetings with the feedback that we are urging you to provide we will begin to have drafts, if not of entire chapters, of portions of chapters based on the discussions at these meetings and at the testimonies that are provided by the experts.

So I think that brings us up to the present.

DR. SHAPIRO: Thank you very much.

We will have, of course, plenty of time later today subsequent to the input we will have from our panelists and material that Ruth has already provided us under Tab 2F, which is, I think, entitled "Assessing Risks and Potential Benefits: Ethical Aspects of Research Designs." We will have ample opportunity to get back to that.

I hope we will, also, have opportunity for a limited amount of time to look at the informed consent, revised informed consent, proposed findings and

recommendations.

We might be able to give some initial feedback to Ruth and her colleagues on that as well. That will be a second priority today but I hope we will find at least a limited amount of time for that.

Ruth, thank you very much and thank you for all the material we have been receiving in this area.

I would like to go now directly to the -- our first panel in which we have Dr. Whalen and Dr. Wolfe. If they could -- Dr. Whalen is here.

Thank you.

First of all, I want to express our thanks to both of you for being willing to come here today and address these issues.

Dr. Wolfe, welcome back. I know you have spoken to us before when we began thinking about this project. So thank you very much for coming again today.

I am going to go just in alphabetical order if that is -- though, you are probably both used to being last in line --

(Laughter.)

-- in this way. There is a nice thing about lexigraphical order. I mean, you usually can make way even within the W's.

But in any case, Dr. Whalen is professor of

epidemiology and biostatistics at Case Western and we have distributed his CV to you. He has had obviously very extensive experience in an area which we are very, very interested in.

So, Dr. Whalen, I will turn it over to you first. Thank you very much for being here today.

PANEL I: RISK -- BENEFIT ASSESSMENT IN INTERNATIONAL RESEARCH

CHRISTOPHER C. WHALEN, M.D.

CASE WESTERN RESERVE UNIVERSITY

DR. WHALEN: Thank you very much.

I would like to thank the commission for inviting me to testify regarding the risks and benefits of international medical research.

DR. CASSELL: Can you lean into that microphone a little bit more?

DR. WHALEN: Okay.

DR. SHAPIRO: Sometimes you have to sort of behave like a rock star at these meetings.

DR. WHALEN: I have never been a rock star before.

DR. SHAPIRO: Neither have any of us. We are learning.

(Laughter.)

DR. WHALEN: Okay. Fine. And then I will

need overheads in just a minute.

My comments will focus on the risks of placebo trials and the difficulties of applying uniform standards of care.

I will illustrate my points by drawing upon my experience from research studies on tuberculosis and HIV infection.

DR. MESLIN: Dr. Whalen, I still do not think your mike is on.

Can we make sure that his microphone is on, please?

Sorry to interrupt you.

DR. WHALEN: My apologies.

DR. SHAPIRO: It is our fault. Not your's.

DR. WHALEN: I think I hear it now. All right.

DR. MESLIN: Thank you.

DR. WHALEN: My comments will focus on the risks of placebo trials and the difficulties of applying uniform standards of care in an international setting.

I will illustrate my points by drawing upon my experience from research studies in tuberculosis and HIV infection performed in Kampala, Uganda.

I will first review the natural history of tuberculosis by way of background because of the

complexity of the issues and then turn to the detailed discussion of two studies and the ethical issues surrounding them.

So if I can have the first overhead.

(Slide.)

Tuberculosis is a disease caused by mycobacterium tuberculosis. It is estimated that one-third of the world's population is infected with the organism. Six to seven million cases of tuberculosis disease develops each year and 2.5 million deaths are attributed to the disease.

There are two states in the natural history of tuberculosis. Following exposure individuals become infected they are healthy and not contagious. The only way to detect that a person is infected is through the use of tuberculin or PPD skin testing. About ten percent of infected individuals go on to develop disease.

Half of these cases develop within two years of infection and the remainder develop later in life. Sometimes after decades of latent infection. It is active pulmonary tuberculosis, the pneumonia, that poses the greatest threat to individual and public health because it is the most common form of disease and by far the most contagious.

(Slide.)

Four strategies are used to control tuberculosis. Passive case finding and proper treatment. Preventive therapy or treatment of tuberculosis infection. BCG vaccination of children and environmental controls.

The key strategy is the first. The identification and treatment of infectious cases of tuberculosis. National tuberculosis control programs throughout the world, including the U.S., place this strategy as first priority. Preventive therapy or the treatment of tuberculosis infection is used in the United States but not in most countries where tuberculosis is endemic.

BCG vaccination prevents disseminated and life-threatening forms of disease in children. It is the most widely used vaccine in the world and is given at birth as part of the World Health Organization expanded program on immunization.

(Slide.)

The global tuberculosis situation is exacerbated by the HIV pandemic. HIV confers the greatest known risk for the development of tuberculosis. The annual incidence of tuberculosis. The annual incidence of tuberculosis in co-infected persons ranges

from three to twelve percent, a risk that is 100 times greater than that of HIV seronegative individuals.

Moreover, tuberculosis may accelerate the natural history of HIV infection. These to organisms interact at a community level. In many developing countries of Africa, for example, 50 to 75 percent of tuberculosis cases are infected with HIV -- this is shown on the right bar -- whereas, only 10 to 15 percent of the population is infected with HIV -- that is indicated on the left bar.

As a small proportion of the population -- thus a small proportion of the population is giving rise to over 50 percent of the tuberculosis problem in many developing countries, one potential strategy for tuberculosis control is to prevent the development of tuberculosis in HIV infected persons co-infected with M. tuberculosis. This was the rationale for the Preventive Therapy Study.

Thank you. That is all the slides.

The Preventive Therapy Study was designed to assess whether three different preventive therapy regimens were effective in reducing the risk of tuberculosis in HIV infected adults. The study was designed as a randomized placebo controlled clinical trial in HIV infected persons with either a reactive

tuberculin skin test or cutaneous anergy to tuberculin and candida antigens.

The trial was conducted in Kampala, Uganda under the auspices of the Uganda Case Western Reserve Research Collaboration and was funded by the Centers for Disease Control and Prevention through a cooperative agreement.

The study protocol was approved by the AIDS Scientific Subcommittee at Makerere University in Uganda and by the Institutional Review Board at Case Western Reserve University.

I have been involved in all stages of the tudy from its design to implementation, analysis and presentation.

The study design used a placebo for two reasons. First, the efficacy of the different forms of preventive therapy was not known in HIV infected persons at the time of the study. Second, the safety of isoniazid and other anti-tuberculosis medications was unknown in HIV infected persons.

I will go into some detail here because it illustrates the issues raised by the use of the placebo arm and the process we use to address them.

The rationale for preventive therapy is to eliminate the organisms that lie latent in the body,

thereby reducing the individual's risk for developing disease in the future.

When applied within a program of tuberculosis control this intervention will reduce the pool of infected persons at risk for the future development of disease. Although six to twelve months of isoniazid preventive therapy has been proven beneficial in HIV seronegative individuals and is the second most important strategy for tuberculosis control in the United States there are cogent reasons why preventive therapy may not be effective in all settings.

In particular, the level of tuberculosis transmission and the prevalence of HIV-1 infection in the community are important determinants of preventive therapy.

Preventive therapy provides protection only against past infection. It does not act like a vaccine protecting from future infections and disease. Thus in a setting where the transmission of M. tuberculosis is high preventive therapy may have limited effect because people can become reinfected after completing their course of therapy.

Isoniazid therapy is effective in the United States because the likelihood of becoming reinfected is small after finishing therapy.

The annual risk of tuberculosis infection is .03 percent in the United States.

By way of contrast, in Africa, the value of preventive therapy may be greatly diminished because of the high annual risk of infection with tuberculosis. About three percent a year or 100 times greater than that seen in the United States.

The benefit of preventive therapy has never been shown in Africa even in HIV seronegative persons. In the setting of a high risk of transmission and infection with M. tuberculosis the long term effectiveness of preventive therapy as a strategy for TB control has been questioned.

As mentioned, the risk for developing tuberculosis and HIV infection is high. One hundred times the risk of HIV seronegative individuals.

Even if preventive therapy were effective in reducing the risk for tuberculosis in HIV-1 infected persons, would it be -- would it reduce the risk enough to warrant its use as a public health measure? These concerns were best articulated by our Ugandan collaborators because they looked at the potential impact of the study on their tuberculosis control program and its policy. It was not possible to assess the efficacy of the intervention without the proper use

of a placebo arm.

We also asked whether there was sufficient information relating to the effectiveness of isoniazid preventive therapy at the start of the trial to preclude the use of the placebo.

There was only one observational cohort study at the time that provided any information on the effectiveness of isoniazid in HIV-1 infected persons but it was in patients with cutaneous anergy.

In this study zero of 27 patients receiving preventive therapy developed tuberculosis as compared with four of 25 patients not receiving therapy. This information was of limited value in assessing the protective effect of preventive therapy because it referred to patients with anergy and did not include patients with reactive tuberculin skin tests, the largest group at risk for tuberculosis.

The therapy was not randomly allocated so that results were subject to a treatment bias. The size of the study was small raising issues of uncertainty in the findings and the study was performed in intravenous drug users, a group with other risk factors for the development of tuberculosis besides HIV-1 infection.

One may question why the placebo was used when the Centers for Disease Control and Prevention, the

sponsor of the study, recommended in 1989 the use of isoniazid preventive therapy in HIV infected persons with a positive tuberculin skin test reaction. This recommendation was made in the absence of relevant data on the efficacy of preventive therapy in HIV as acknowledged by the report. The report stated, "It is not known whether isoniazid prevents TB in HIV infected persons." The report was intended to provide guidelines for clinicians, not rigid rules for therapy, while research was performed to substantiate the recommendations.

At the beginning of the trial in 1993, both U.S. and Ugandan investigators believed there was genuine equipoise regarding the efficacy of preventive therapy in HIV-1 infected persons and a placebo arm was merited.

Five months after starting the trial we faced a dilemma regarding the use of the placebo control. A study from Haiti showed that isoniazid preventive therapy given for 12 months reduced the risk of tuberculosis by 85 percent in HIV infected persons with a positive tuberculin skin test. On the surface these results would appear to be convincing but a closer look raised questions.

In a trial of only 118 participants, 15 cases

of tuberculosis -- clinical tuberculosis developed but only six of these cases were confirmed by mycobacterial culture, a standard method of making the diagnosis. Of the 15 cases only eight occurred in the PPD positive patients, six in the placebo and two in the treatment arm.

The report does not indicate whether any of the cases in the PPD positive subjects were confirmed by either mycobacterial culture or smear. Misclassification of even one case could render the results statistically insignificant.

Nevertheless, this was the first randomized and controlled assessment of preventive therapy in HIV-1 infected persons so we considered the use of the placebo -- we reconsidered the use of the placebo in our study.

As a group we decided that the Haiti study did not provide conclusive evidence for the effect of isoniazid in HIV infected persons.

In April 1994 this decision was reviewed by the WHO Therapy of Mycobacterial Disease Steering Committee with representation from Africa and the Centers for Disease Control. The ethical issue of continuing the placebo arm in the Uganda study as well as two other placebo controlled studies in Africa was specifically discussed. This committee of experts who

had available to them the final and interim results of all ongoing research in the field recommended that no changes be made to the protocol in Uganda.

In the face of the new information from Haiti, however, we moved forward our timetable for interim analysis of the trial. As indicated in the original manuscript published in the New England Journal of Medicine the study was stopped early because of significant differences in short-term protection between treatment and placebo.

One aspect of risk is whether the effective therapy is being withheld from study participants. Another overlooked aspect of risk is whether the intervention causes more harm than good.

The safety of anti-tuberculosis medications in HIV infected persons was of concern to us in the early 1990's as reports from Sub-Sahara in Africa indicated that patients with HIV associated TB were at increased risk for the development of Stevens-Johnson Syndrome, a severe condition in which layers of the skin desquamate.

This condition carries with it a high mortality especially in regions where complex skin injuries such as burns cannot be managed with modern techniques.

In 1990 in Kampala patients were known to say that TB treatment burns because of these side effects. Although the studies published at the time implicated thiacetazone as the agent most likely to be associated with the untoward effects, it could not be demonstrated conclusively because isoniazid or another medication, streptomycin, were almost always given concurrently.

In HIV infected patients with active tuberculosis, a disease that carries with it almost certain death without treatment, patients often accept the risk of side effects from the medication so that the disease may be treated.

In tuberculosis infection when individuals have no symptoms attributable to tuberculosis the risk of side effects may preempt the use of preventive therapy. At the time of the study there was no published information about the safety of isoniazid therapy in HIV-1 infected individuals. The use of the placebo was the only way to determine the risk of side effects in these patients.

In brief, the evaluation of risk to study participants began during the planning stages of the trial and continued throughout the study. Assessment of risk required that we considered the local transmission dynamics of tuberculosis and critically review the

existing information about preventive therapy. Assessment of risk also considered the potential side effects of therapy. Without a placebo arm in the study it would not have been possible to assess efficacy and safety in a way that was relevant to the Ugandans.

I would like to turn now to the discussion of what is called the prednisolone trial.

By way of background, since the early years of the HIV epidemic, the impact of HIV-1 on the natural history of tuberculosis has been apparent but the interaction between HIV and M. tuberculosis is not one way. It is bidirectional. That is tuberculosis appears to accelerate the natural history of HIV infection. This is seen in the form of more opportunistic infections and increased mortality that is not directly related to tuberculosis itself.

There is now a large body of evidence pointing to the immune and virologic basis of this bidirectional interaction. In short, the host immune response of TB is detrimental in HIV infected individuals. The body's immune defenses against tuberculosis stimulate the cells that are infected with HIV-1 to increase the rate of viral replication. The consequence of this immune stimulation is to reduce CD4 lymphocytes and to increase the risk for opportunistic infections and death.

The approach I have taken with my colleagues to lessen the impact of tuberculosis on HIV disease is to attenuate the host immune response against tuberculosis. By reducing the level of immune activation produced by TB we hope to reduce the stimulus for viral replication and prevent subsequent events.

We designed a randomized placebo controlled trial of prednisolone in HIV-1 infected patients with tuberculosis treated with standard anti-tuberculosis therapy. We chose a corticosteroid preparation for several reasons.

Prednisone is an inexpensive drug that is available throughout the world and is commonly prescribed for other indications in Uganda. It would, therefore, be available in Uganda after the study was completed. It has been used for years in immunoadjuvant therapy for severe tuberculosis in HIV-1 seronegatve patients.

Its effects on host cellular immunity have been well studied and its side effect profile is well known. It has also been used safely to treat a number of conditions in advanced HIV infection, including PCP and HIV associated nephropathy.

During the planning stages of this study we asked ourselves whether we should offer all of our study

participants antiretroviral therapy. This question arose becasue highly active antiretroviral therapy that included protease inhibitors was quickly becoming the standard approach to HIV infection in the United States and Europe. Moreover, the World Health Organization was beginning a feasibility assessment of the use of antiretroviral therapy in poor developing countries, including Uganda.

In considering this issue, the initial discussion focused on two concerns.

First, antiretroviral therapy is not widely available in Uganda. It cannot be afforded by most Ugandans. To put this into perspective, the monthly cost of antiretroviral therapy in Uganda was and is about $800 to $1,000 per month. Whereas the annual per capita income in Uganda is less than $500. On average, an HIV infected Ugandan would have to work about two years to afford one month of antiretroviral therapy.

I have been told that some HIV-1 infected Ugandans have spent their entire life savings to buy six to twelve months of therapy. In some cases this jeopardizes the livelihood of the family as resources were diverted to care for the AIDS patient and were not, therefore, available for other basic necessities such as

food and clothing.

According to a prominent Ugandan AIDS physician, only one to three percent of HIV infected persons can afford to buy therapy even for a short period of time despite the subsidies provided by the WHO program.

Our second concern in the planning stages: Antiretroviral therapy would not be sustainable after the completion of the study either for individual participants or in the community. Short-term therapy might put the study participants at risk for rebound viremia and drug resistant virus.

Before finalizing the study I traveled to Uganda -- study design, I travelized (sic) to -- I traveled to Uganda to meet the Ugandan principal investigator, Professor Rory Mugaro, members of the Ugandan medical community, and with members of the National AIDS Scientific Subcommittee, including the head of this committee, Dr. Edward Ambidi (?).

In these meetings the study design and use of antiretroviral therapy was presented and discussed in depth. Three issues surfaced in the discussion.

First, the Ugandans were concerned that the use of antiretroviral therapy would provide a powerful incentive for participation. They indicated that

patients might join -- may join the study only to gain access to the antiretroviral therapy and may not fully consider the experimental nature of the trial.

Second, they were concerned with what would happen when the study ended. Would the antiretroviral therapy be continued? If it were stopped, how would this be explained to the study subjects? Professor Mugaro was particularly concerned about this point and likened the withdrawal of therapy at the end of this study to patient abandonment.

Finally, this group wanted to know how the results would be applicable to Uganda if the antiretroviral therapy was included in the study design.

I would like to elaborate on the final issue raised by the Ugandans because it points out an inherent contradiction if current guidelines of human research are followed.

I would like to illustrate this through a thought experiment relating to the prednisone study. If we agree that the best proven therapeutic method for HIV infection involves the use of antiretroviral therapy and we decided to use it in the study then all participants would be placed on standard TB treatment, antiretroviral therapy, and finally randomized to receive the

prednisolone or placebo.

Suppose now at the end of the study we find that prednisone failed to improve the survival of subjects with HIV associated TB. We cannot determine whether prednisone alone would improve survival because all subjects received the antiretroviral therapy. Yet the very relevant -- yet the very result most relevant to Uganda today is whether prednisolone itself affected survival.

Suppose now a different result at the end of the study. We find that adjuvant therapy with prednisolone improves survival of patients with HIV associated tuberculosis. When would these results be applicable? Only in settings where antiretroviral therapy is used and can be provided to the tuberculosis patients. Perhaps a more relevant question would be where would these results be applicable?

At this time antiretroviral therapy is routinely available in industrialized nations such as the U.S., Europe and Australia.

But would these results be applicable in Uganda? No, not now or in the foreseeable future unless there are dramatic changes in the cost and distribution of antiretroviral therapy along with the expertise and facilities to provide it.

In this scenario the Ugandan participants would be used to provide results that would be relevant only in industrialized countries or to the privileged few in resource limited countries. To me, this is pure exploitation.

The only scenario that made sense is one in which antiretroviral therapy is widely available to Ugandans at a cost that they can afford. It is my sincere hope that antiretroviral therapy and the expertise to use it spreads through Africa tomorrow but realistically it will be years before this happens.

The economies of these countries need to grow and a tax base must develop. The infrastructure in many developing countries is in disrepair and in need of rebuilding. Medical technology would need to be transferred and a cadre of informed and qualified health professionals would need to be trained.

The problems of HIV infection and tuberculosis affect millions of lives today. To stand by and wait while resource poor countries catch up to the U.S. as regards to health are would be unconscionable to me. I favor studies that are locally relevant and scientifically general now so that as countries grow and develop the public may benefit from affordable and sustainable treatments.

In fact, there are nonantiretroviral interventions that are effective in reducing HIV-1 transmission and alter the course of HIV-1 disease. The mass treatment of sexually transmitted diseases, the use of vitamin supplementation in HIV infected children just to name two.

The aim of the prednisolone study is to identify inexpensive yet widely available treatment that can improve survival in HIV-1 associated tuberculosis.

In the end, my colleagues, Ugandan and American alike, and I agree that the use of antiretroviral therapy in the study altered the scientific and clinical questions in a way that would not be applicable to Uganda.

We decided to perform a study that was relevant to Uganda and did not include antiretroviral therapy. The study design has been reviewed by the Ugandan AIDS Research Subcommittee, the IRB at Case Western Reserve University, and by the Data Safety and Monitoring Board of the AIDS Clinical Trials Group in the Division of AIDS at the National Institutes of Health.

This example illustrates how the application of one ethical principle can lead to a conflict with another providing the best proven therapeutic method.

Where that method cannot be sustained after the study raises questions of exploitation, abandonment and relevance.

In these few minutes I hope I have illustrated for you how my colleagues and I identified and addressed challenging ethical issues around international research. The fundamental elements in this process were respect for individual health, a mutual respect among Ugandan and U.S. investigators, open dialogue about the issues in a public, scientific and international forum, and a common goal to improve the global situation as it relates to tuberculosis and HIV.

Thank you.

DR. SHAPIRO: Dr. Whalen, thank you very much for those very thoughtful remarks.

Perhaps we could take no more than ten minutes right now if there are any immediate questions we would like to address of Dr. Whalen and then we will turn to Dr. Wolfe.

Dr. Lo?

DR. LO: I want to thank you for your testimony. First a comment. In the copy some of us got skipped pages 8 through 10 so I do not know if it is an NBAC problem or if we could get the missing pages that would be wonderful.

DR. WHALEN: Okay.

DR. LO: But more substantively, I would like to ask you a little bit more about the process that you went through when you were considering the design of the prednisolone study and you said you traveled to Uganda to consult with people there and mentioned the colleagues you consulted with.

My question is first were you able to speak with patient advocates or community representatives or patient representatives about this prednisolone design and what were their comments?

Secondly, in the review process in Uganda where you went before several bodies, were there members of those bodies who were either community representatives or especially looking at the ethical issues as opposed to sort of the scientific issues?

Maybe that is not the best way to put it but were there people on those boards specifically charged and having expertise in the ethics as opposed to sort of the science of clinical trials?

My questions really are trying to get at how feasible or practical is it to do what is often done with AIDS clinical trials here? Go to community advocate -- patient advocates, community representatives, get their views on whether they think

the design is appropriate or not and often, as you know, they change the minds of many scientists planning studies?

And, also, are these Ugandan based boards able to sort of look at the ethical issues with the kind of scrutiny that say our IRB's are supposed to?

DR. WHALEN: At the time that this study began we did not have any patient advisory board or community advisory boards. When I was there I did discuss with people -- mostly individuals within the medical -- within the medical field the nature of the study but this included individuals from physicians and physician scientists to nurses and then individuals within the trial or within our group who had no formal training in biomedical science. These would be technicians, individuals who actually worked very closely with the patients, home visitors and so on, home health visitors.

So to get direct community feedback, we -- I did not do that.

With regard to the review process, Dr. Ambidi is the head of the board and he does not have -- he is a scientist but he also has, I think, a very strong background in biomedical ethics. So I think the board there -- the AIDS Scientific Subcommittee is led by

someone who has a good grasp of the issues relating to biomedical ethics of trials in developing countries.

In addition, there is -- as in the United States -- there are individuals who are not affiliated with the institution of the study that are included in the review board.

DR. SHAPIRO: Alex?

PROF. CAPRON: Well, I guess in some ways my question was similar and in a way it is a question that I want to put to you and then have in mind for our discussion.

You gave, for example, the illustration of the decision which you described being reached by yourself and others whom you named that would have a rather paternalistic ring in this country in a clinical setting although it would not be unknown as an issue in approving a research trial or designing the trial, and that was the sense that it -- the risk was too great to allow people to take it under circumstances where the existence of the antibiotic treatment would be -- I think we would call it undue inducement to their agreeing to cooperate in the trial.

And so I guess the generalized question I have is when it comes to the evaluation of what risks are appropriate, how do you conceive the relationship

between the potential population group, potential subjects and their family on the one hand, and national health ministry figures, scientists from the native research community, not only those directly involved in the research but others who seem to be the kinds of people who are making this decision with you.

A follow-up question, quite specifically, is this an issue which has come to be discussed in the general population in Uganda? Has this become an issue that the general press has taken up and there has been any popular discussion of the question?

So one is a generalized prospective question about how you conceive that relationship and the second is some factual information about how widely this has come to be discussed.

DR. WHALEN: Yes. I am going to start with the second question first.

The Ugandan press is very active in educating the community about HIV infection or at least that is my perception of it.

PROF. CAPRON: You are beginning to drift a little bit away from the microphone somehow.

I also wanted to ask you can sitting in a room with cold air being blown on you for a day give you tuberculosis?

(Laughter.)

PROF. CAPRON: Because, if so, I feel as though I am at risk right now.

(Laughter.)

DR. SHAPIRO: Legionnaire's disease.

PROF. CAPRON: It is not your problem. We are all sitting here.

DR. MESLIN: We are working on it.

DR. WHALEN: Not unless the organism is in the air.

DR. LO: We are all part of a covert study here half of us are getting a drug in our lunch today and half are not.

(Laughter.)

PROF. CAPRON: Go ahead.

DR. WHALEN: I think the Ugandan press is very active in trying to educate the community about the issues relating to HIV and international research. The focus -- I have to say that the focus in Uganda is more on HIV vaccines than it is on a study such as the prednisolone study which is dealing with a rather specialized issue in the treatment of tuberculosis.

So I think that Ugandans certainly know that HIV and TB go together and that so much so that they often feel stigmatized if they develop tuberculosis.

They feel as though they are being labeled as being HIV infected.

So I think at one level there is a general understanding in the community about HIV and TB and there is not a family in Uganda that has not been affected by one of those two diseases so they see it as a real threat.

Are they aware of -- I think many are aware of a vaccine and vaccine trials. In a vaccine study that -- HIV vaccine study that is currently ongoing in Uganda there were a year's worth of community meetings and discussion about the vaccine.

The discussion of antiretroviral therapy, I think, has been focusing around maternal-infant transmission as it relates to nevaripine and AZT. I do not think -- I would say at this time there is not a broad discussion about the use of highly antiretroviral therapy for the palliation of HIV disease. In Uganda, their interest is in preventing disease. They were interested in the prednisolone study because of its nonantiretroviral approach that may actually improve the clinical course of HIV infected individuals.

DR. SHAPIRO: Thank you. We wall take one more question now and then come back later.

Trish?

PROF. BACKLAR: I think it would be interesting for us to know a little bit about the demographics of the subjects that you use in such a study. For instance, what level of education and what economic class. I am interested to know who these people are who agree to be subjects in such a study.

DR. WHALEN: As in the United States, many of the people who develop tuberculosis come from lower middle socioeconomic groups. Fifty percent are men or slightly more than fifty percent are men and slightly less are women. The average age is around 30 years. Most of them are parents. They have children in the homes. And they are working people. Unlike the United States where we hospitalize TB patients, they steadfastly refuse to be hospitalized unless they absolutely have to and the reason is they have to go back to their jobs. So they see the threat of illness as the loss of income so most of them are working class individuals who when they are -- when they do develop disease they look for every day possible to continue working.

PROF. BACKLAR: And what level of education have they attained?

DR. WHALEN: The -- most of these individuals have attained what we would consider around sixth grade,

sixth to eighth grade education. Most do not speak English so I, unfortunately, cannot communicate with them myself. Some do and in those instances I will talk to patients when I am in Kampala. But they have -- I think a reasonable understanding. They certainly have the capability of understanding the nature of a research study and understand the issues of informed consent that we discuss with them.

PROF. BACKLAR: So people are literate and they can read and write?

DR. WHALEN: Many -- not all of them can read and write.

PROF. BACKLAR: Okay.

DR. WHALEN: But they are certainly bright people who can understand the nature of what we are doing with them.

PROF. BACKLAR: So the press in Uganda, in fact, there may be a number of people among these subjects who are not reading --

DR. WHALEN: Correct.

PROF. BACKLAR: -- newspapers and such.

DR. WHALEN: But they -- the use of the radio -- the radio is a translation of -- from the written word to the oral word there and even in the far bush of Uganda they have radios and they listen to programs and

many of them -- they invite -- doctors have, you know, programs in which they talk about HIV, sexually transmitted diseases. We do not have one on tuberculosis, though. That would be a nICH program to get going in Kampala. Most of our subjects come from Kampala, which is -- you know, and the surrounding suburbs so they have access to newspapers and radio as well as television in some cases.

PROF. BACKLAR: When you write up the study, which I -- do you describe the demographics of the subjects?

DR. WHALEN: Yes.

PROF. BACKLAR: Okay.

DR. SHAPIRO: Thank you very much and I hope, Dr. Whalen, you can stay for further discussion later on but I would like now to turn to Dr. Wolfe.

Dr. Wolfe, thank you very much once again for being here.

SIDNEY M. WOLFE, M.D.

PUBLIC CITIZEN'S HEALTH RESEARCH GROUP

WASHINGTON, D.C.

DR. WOLFE: Thank you. We have some slides. Dr. Lurie (?) is with me and we will have to move to our left as much as we hate to do something like that so that we can see these slides.

(Slide.)

Thank you very much for inviting us here. The suggestion was originally Dr. Childress' back two-and-a-half years ago that we approach your organization with the issues that we are and have been concerned with.

The issue of the benefits and risks to experimental subjects in developing countries must be viewed in the context of human rights and in the context of the researcher, also a physician, protecting the welfare of the research subject who is the patient.

We are excluding Phase I trials from the consideration here because in Phase I trials, which rarely, I think, can be done ethically because of coercion in developing countries. Those people are not necessarily patients. We are talking about patients or subjects.

Just as the physician must be committed to protecting the welfare of the patient he or she is treating, the researcher must be committed to protecting the welfare of the research subject. This slide here is a quotation from Dr. Kim writing to the <u>New England Journal</u> in response to the article that we published a couple of years ago.

Physicians, even those conducting research, must never abandon their principle duties as care takers

and advocates for the individual patient, human subjects in clinical trials are first and foremost patients and they thus deserve care that is both medically sound and compassionate.

There are forces both from governments and from the pharmaceutical industry which are increasing the globalization of human experimentation. Just as the last few days there has been discussions in Seattle about other kinds of globalization. Human experimentation in a way I would never have believed possible is being globalized.

The reasons for the globalization are sometimes obviously related to the unique diseases that exist in other countries and not here but as often as not and more often as not I would suspect they are related to issues such as economics, efficiency, speed and possibly easier recruitment and different ethical standards.

There has been a rapid and increasing amount of power and scope of what we call Human Experimentation Corporations or He's. Others refer to them as CRO's, Contract Research Organizations, but that does not really convey what they do particularly in the field of international research.

I would just like to refer to an example of an

ad directed at the pharmaceutical industry by the world's largest human experimentation corporation, Quintiles, with offICHs in more than 120 countries. On the front page of the ad it says, "Quintiles, whenever and wherever you want." And they are talking about doing studies around the clock because there are offICHs all over the world.

The appalling quotation from this ad -- remember this ad is directed at drug companies who Quintiles wants to sell their servICHs to -- "It is the middle of July and we are about to start a trial involving 500 flu patients. We recruited them in South America. Quintiles can even help you tap the vast drug naive patient populations of China, Korea and other emerging markets."

Another thing from their ad is "They are not going to make the deadline. They are going to beat it by a good two months or more thanks to Quintiles accelerated patient recruitment strategies. By appealing directly to patients we can often accelerate recruitment by as much as 70 percent. Why wait if you do not have to."

And, finally -- and this really has to do with the race to get as many people as quickly as possible so that drug company A can beat drug company B -- "The

stakes are enormous. The competition ferocious and the winner is the one who gets to market first with a new biological drug or device."

Anyway, this is something that is just -- I am concerned -- somewhat out of control and it has to do with the benefits and risks to patients particularly in developing countries.

In order to justify a number of these studies and grease the skids there have been serious efforts made to radically alter important elements of the Helsinki Declaration of the World Medical Association and CIOMS in ways which significantly alter the benefit/risk ratio for patients in an unfavorable direction.

I will just a mention a couple of these. You probably are familiar with them. The old version or current version of the declaration, "In any medical study every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method."

In the proposed rewrite, which has been considered, hopefully rejected but it gives you a glimpse into what people are trying to do, "In any biomedical research protocol every patient subject, including those of control group, if any, should be

assured that he or she will not be denied access to the best proven diagnostic, prophylactic or therapeutic method that would otherwise be available to him or her." In other words, the local standard of care argument couched in "ethical" terms.

Use of placebo: "This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists." That is the current. The proposed, "This principle does not exclude the use of placebo or no treatment control groups if such are justified by a scientifically and ethically sound research protocol undefined."

And then finally a new attempted introduction, "When the outcome measures are neither death nor disability, placebo or other nontreatment -- no treatment controls may be justified on the basis of their efficiency."

Discussing this in an article in the New England Journal of Medicine in August Dr. Troy Brennan pointed out that he is very concerned that efficiency and utilitarianism are beginning to trump ethical standards.

In the context of this globalization of research and the threats of lowered ethical standards or the existence of them in some instances, it is of

interest to reflect on the work of "Med Sans san Frontier" or "Doctors without Borders," which recently won the Nobel Prize this year for its work around the world focusing on human rights violations especially in developing countries.

The founding principle articulated by Dr. Bernard Kuchner (?), one of the founders in 1971, was the "Dua de ageranz," the "Right to Interfere" in human rights abuses or anywhere in the world.

It has been later expanded in a book in 1987 which Dr. Kuchner published. The title of the book is Le Devua de Ageranz, the Duty to Interfere, and I will come back to that in a minute. The duty to interfere if there are human rights abuses.

Some of the responses to our efforts a couple of years ago to bring attention to what we were concerned with were unethical studies were ones in which we and people who espoused our viewpoint were accused of ethical empirialism as in trying to impose "ethical" standards that we believed in on other countries.

It has been stated and we agree that this concept feeds into and is bed by an outdated and dangerous view of cultural relativism in which different standards of care justify different sets of ethics or different protections of subjects.

Human Rights Watch referring to repression in Central Africa said, "African solutions to African problems is no used as a thin cover for abusing citizens. This observation can be applicable to experimetnation on citizens as well."

The National Research Committees Council on Human Genome Diversity in the Context of International Research on Human Subjects has said, "Sensitivity to the specific practices and beliefs of a community cannot be used as a justification for violating universal human rights."

I want to bring up something that I would not have brought up except that it was raised at a previous meeting and I would like to respond to it.

Don Burke in discussing a benefit and risk brought in not just the benefit and risk to the patients, which is I think what we are talking about here, but a number of other benefits and risks and he prefaced his remarks or he mentioned that the reason was, "The first place was a question of distributive justice and the claims that if a treatment or vaccine were studied in a country then it should be made available to everyone in that country and that always troubled me." So he was troubled by the idea that if you did an experiment in a country that it should be

made available.

And went on when he appeared before you to talk about the research partners in the north, the academic community, the politicians and others, and then, "And lastly we will get to the individual research subjects, the funders as well." Lastly. I think that that is really the only thing that I would like to focus on today.

Before getting into some of the principles for delineating favorable benefit/risk ratio for patients in a study I just want to mention a couple other things.

One, it is the principle that is varying-ly referred to as the mother or the sister or sometimes the self principle. Which is as a physician and as a researcher would you if you were involved in a study administer this traetment, including a placebo if that is the case, to your sister or your mother or brother or father? It is a very important question because it glues in the notion of your responsibilities as a physician as well as a researcher to the patients who you are treating.

(Slide.)

These are now some of the considerations for selecting study design in trials, particularly ones that involve people in the developing world.

I would like to preface the remarks about this by first saying that the response -- one of the responses to what we have said for the last couple of years has been the notion that we are trying to impose American available technology everywhere like building a cardiac bypass center in a given country in order to do a study.

We have really never said anything like that and instead we believe that one should consider a series of principles, how strong they are, how present they are in every case where one is considering doing a study in a developing country.

I will just go through them generally and then use two case examples. One, the provision of counseling, HIV behavioral counseling and HIV vaccine trials, and secondly the perinatal HIV prevention trial design.

Availability of the intervention after the trial: Is there a realistically funded program for making it available after the trial assuming that the trial yields a positive result?

People cannot just talk about the availability and not deal with it in the concrete. Some of the details may need to be left afterwards as a function of the trial but there needs to be out front realistically

funded likelihood that the intervention will be made available elsewhere in the country.

This is one of two gateway issues which if not met you just do not do the study:

Feasibility of intervention in the trial. As I mentioned before, it has to be something that is practical in a developing country.

The strength of the prior evidence. Obviously it has to do with what one knows at the time that a study is begun.

Have there been other studies?

Is the strength so great that in some cases they have abandoned studies and are just giving the treatment out?

How severe is the disease? If it is mild pain where there is a strong placebo effect that is very different than a disease in which the outcome is fatal if not treated.

What is the magnitude of the likely benefit? If the person is getting a placebo the benefit is zero unless it is a study on mild pain.

What is the trial design related to the magnitude of the likely benefit? If the benefit is enormous, is very large, then one might easily be able to design an equivalency study to test it out. If it is

very small and so small that one is not even sure that there is a benefit it might make sense to do another placebo controlled trial.

Lack of evidence of differing biological factors in developing and industrialized countries. This has frequently been used in the past to justify doing studies but one has to have a compelling reason to believe that there really is some biological difference that is relevant to the trial itself before making an assumption that what we learned in country A is not applicable to country B. I think too often the assumption has been made in ways that are really irrelevant to what is going on in the trial.

Existence of satisfactory alternative design. That will be discussed later but this really has to do, amongst others, with the choice between doing another or a placebo controlled trial, which may be justified in the first instance versus a positive control or an equivalency study.

Availability of historic control data.

(Slide.)

Now this is the first example that we will try and apply these principles.

This is the issue of should behavioral counseling be provided as part of an HIV vaccine trial

design. What one can see is that the evidence is not that great. Post-trial availability of counseling plus to 2 plus, out of 3 that is, it is not likely to increase after a trial.

Feasibility of counseling in the trial -- obviously that is possible if one has the money to do the trial in the first place.

Strength of prior evidence. Two plus at best.

Severity of the disease, obviously very serious, three plus.

Magnitude of the likely benefit, because of the paucity of randomized control trials, the magnitude in terms of a well controlled study is really one plus at best.

Lack of evidence of differing factors in developing and industrialized country, two plus.

Existence of satisfactory alternative design, three plus.

Availability of historical control data, not applicable.

The point is here that despite the relative weakness of some of these factors and of most of these factors, there has really not been any dispute that this should be used as part of HIV vaccine trials.

(Slide.)

Contrast that with perinatal HIV prevention trial design.

Post-trial availability of drug, one plus to two plus. That obviously should have been considered before the study was done in a given country. It is more obviously in Thailand than in other countries.

Feasibility of intervention in the trial, three plus.

Strength of prior evidence, three plus.

Severity of disease, three plus.

Magnitude of likely benefit, lack of evidence of differing biological factors, existence of satisfactory alternatives, all three plus.

Availability of historical control data, two plus.

I will now just go through some slides that have to do with these studies. You have seen some of this before.

PROF. CAPRON: Sidney, before you go on --

DR. WOLFE: Yes.

PROF. CAPRON: What is it that you are comparing?

DR. WOLFE: Excuse me. What is the question here?

PROF. CAPRON: What is it that you are comparing here?

DR. WOLFE: Oh. Here we are raising the question about whether or not -- we are talking about in the HIV prevention trial design?

PROF. CAPRON: Yes. These are your pluses.

DR. WOLFE: These -- the pluses have to do with the strength of the evidence for post trial availability, feasibility of intervention, the strength of the evidence going into the trial before one started these trials but after the first -- the 076 trial had been done. In other words, after one had the results from 076 and before the variety of other studies were designed, what did one have available to consider in terms of the trial design. Okay.

DR. CASSELL: Does that mean that --

PROF. CAPRON: And if you had a low -- if you had a low number, if you had no pluses, it would mean do not do it?

DR. WOLFE: No. It would mean that those factors -- I mean, these are a list of factors that we want to consider in terms of the number of them that are present.

PROF. CAPRON: Well, but if you had no pluses or one plus on all these factors, just give me the

outcome of that as a decision matrix here.

DR. WOLFE: Well, in this particular case it would not be possible because you had already done another study. I mean, this happens to be --

PROF. CAPRON: Well, hypothetically. I am just saying as between one where you have a lot of pluses and one where you have --

DR. WOLFE: Well, let's go back then before 076 was designed. There was a legitimate question then as to whether the risk of AZT outweighed the benefits of possible reduction in perinatal mortality. The post-trial availability in the United States where the study was done was clearly three plus; feasibility of intervention was three plus; strength of prior evidence, there was not any prior evidence; severity of disease. Many of these factors were the same.

There may be some other situations other than this where one does not know anything and when one then has to design a trial some of the factors that you would consider would be is it going to be available afterwards. I mean, two of -- the first two questions, which really are the gateway issues, there has to be some kind of answer to because they are really independent somewhat of the specific trial. They have to do with the economics.

Peter, do you want to say anything?

DR. LURIE: Alex, the idea here is that in the two slides back, the one without any pluses, the notion is these are the kinds of things that one should consider in deciding how to design a clinical trial in a developing country so we identify first the criteria.

Then we take to case examples and we go through them in turn and we decide to what degree the evidence for each of those specific eight points is present. To the extent that the evidence is greater, which is more pluses rather than fewer, the ethical obligation of the researcher to provide the intervention is greater. To the extent that there are fewer pluses the intervention -- the obligation of the researcher is less.

The point is that in the behavioral -- when we go through -- going through the behavioral one, which we fully believe needs to be provided to subjects in HIV vaccine trials, and I think most people do agree -- in fact, if you go through these criteria, which we believe are reasonable, they are actually not that strong compared to the situation in the perinatal HIV prevention area where their evidence, if anything, on these criteria are stronger. That is the point.

DR. CASSELL: So that means just for a simple

mind -- that means that going into this trial you believe that there was a 30 to 60 percent chance that there would be availability of the drug to the general population after the trial? That is what you meant. You believe that there was a 30 to 60 percent chance that anybody in that population could get the drug after the trial. Is that correct?

DR. WOLFE: Well, I mean, our view and that of at least some others is that when you are in a developing country the chance should be -- it should be closer to 100 percent. Otherwise --

DR. CASSELL: Yes, we understand what it should be.

DR. WOLFE: Yes. Okay.

DR. CASSELL: But we are talking about the way life is.

DR. WOLFE: Right.

DR. CASSELL: So does that mean that you thought that in that particular country because after all I am trying to get it down to the cases, you know, where we are.

DR. WOLFE: Right.

DR. CASSELL: In that particular country there should have been up to 60 percent chance that anybody who needed the drug was going to be able to get it. Is

that what that means? That going into the trial we should have known that two-thirds of the people who needed the drug, up to two-thirds of the people who needed the drug should have been able to get it.

DR. WOLFE: Well, this is really -- these are qualitative things. These are not based on any numbers. They are based on --

DR. CASSELL: But wait a minute. One plus, two plus is not qualitative. It is quantitative.

DR. WOLFE: Well, it is the belief of people. I mean, given -- given that this has not been really pushed as hard as we think it should be.

DR. CASSELL: I understand all that. I am just trying to find out is that what you mean.

DR. WOLFE: We mean that the chances were not 100 percent. They were not zero. They are somewhere between that. Let's say that.

DR. CASSELL: As much as 50 percent?

DR. WOLFE: Maybe, right.

DR. CASSELL: Right.

DR. WOLFE: Somewhere in that range, right. Okay.

MR. HOLTZMAN: Could I ask for clarification -- a little further clarification? I understand that you are suggesting there are a series of criteria which one

ought to look at in determining whether or not to undertake a study. So, for example, that the drug is likely to be available post-trial is a good thing. Weighing three pluses would say that that is a good thing for doing the study.

But when I look at some of your other ones such as lack of evidence of a difference, I would have thought it would go the other way.

DR. WOLFE: What do you mean?

MR. HOLTZMAN: In other words, if there is no evidence of difference, right, then that argues against using that other population. So I would have expected the lower would weigh in favor of doing the trial.

DR. WOLFE: Well, again --

MR. HOLTZMAN: Because this is another -- existence of a satisfactory alternative design.

DR. WOLFE: Right.

MR. HOLTZMAN: If there is no alternative satisfactory design that would suggest that you should do the study.

DR. WOLFE: Well, as I mentioned before --

MR. HOLTZMAN: Because I am trying to understand --

DR. WOLFE: Okay.

MR. HOLTZMAN: No, forget the specifics.

DR. WOLFE: Okay.

MR. HOLTZMAN: I am trying to understand. You made the statement these are criteria.

DR. WOLFE: Right.

MR. HOLTZMAN: Higher says do it but I am not understanding how in those cases if I -- and I am really trying to understand --

DR. WOLFE: Well, let me just try and respond to that.

MR. HOLTZMAN: Does it make sense, the question?

DR. WOLFE: Yes, it does.

I made mention when I was discussing the magnitude of the likely benefit, let's assume that you have done a prior study and there is a huge two-thirds reduction in perinatal transmission, for example, so it appears a large magnitude of likely benefit. That obviously interacts with the question about existence of satisfactory alternative design because in that case we would argue you could do -- and one is being done right now -- an equivalency study.

On the other hand, let's assume that the first study that had been done there was very little evidence of any benefit at all such that you still were not sure whether the intervention worked. In that case you might

choose a different design as in the original one. You might go back to the original one and do a placebo controlled trial again in order to see whether there really was a benefit. There may have been something about the size of the trial or whatever that was not sufficiently powered to find that out.

So there is an interaction between the magnitude of the likely benefit and the existence of satisfactory alternative designs.

DR. LURIE: Let me -- okay. I will be very quick. When -- the slides -- to be perhaps more precise and I hope I said it this way, these slides are about the obligation of researchers to provide the particular intervention in question and to the extent -- and in this case providing AZT and in the previous case providing counseling. To the extent that there is lack of evidence of different biological factors in developing and industrialized countries, say at the three plus level, you need to provide it. To the extent that there is a satisfactory alternative design at three plus level that weighs in the direction of providing the intervention. It is not a do study/do not study. It is a provide intervention/do not provide intervention issue.

DR. MURRAY: When you say "provide

intervention," do you mean post-study?

DR. LURIE: No, this is -- we are talking about in the trial.

DR. MURRAY: In the trial.

DR. WOLFE: Within the trial.

DR. LURIE: Within the trial.

MR. HOLTZMAN: So intervention as opposed to placebo?

DR. WOLFE: Right.

MR. HOLTZMAN: The control arm?

DR. WOLFE: The traetment, right. Okay.

DR. MURRAY: Thank you.

DR. WOLFE: Okay. Thank you for your clarifying question.

I just want to go through now a few examples having to do with this.

(Slide.)

This was information available and, in fact, it was published in 1993, which really speaks to the issue of when perinatal transmission occurs. What you can see in the gray is that about two-thirds of it occurs during delivery. This is known again before these subsequent placebo controlled trials were designed. Two-thirds occurs during delivery. Another 33 percent in the last eight weeks and only two percent

occurs before eight weeks.

So from this alone before even doing O76 or getting the results of it one would know that most of the perinatal transmission will have occurred after eight weeks. Thereby, setting up the possibility, if not likelihood, if not certainty, that a short course of AZT will work.

(Slide.)

These are the published data in the New England Journal study in 1994 of the 076 trial and what you can see is that there is about a two-thirds fewer infections, 25.5 percent in the mother -- in the infants whose mothers got a placebo and 8.3 percent in the infants whose mothers got AZT. A very striking kind of result and one which resulted in almost immediate use of this drug in the developed countries, particuarly in the United States and France and others.

(Slide.)

This is the going into design of this trial. It was before they had actually done this trial and got the results. Women were stratified according to gestational age from 14 to 26 weeks or greater. Median duration of antepartum AZT was 11 weeks and ranged zero to 26. That is important because this was a study done to allow women, regardless of how far along they were in

their pregnancy, to go in and get treated. Some of them got treated only a week or two or a few days before they delivered. Evaluation of efficacy in subgroups, including duration of antepartum therapy.

And in the published results then was the phrase "The efficacy of zidovudine was observed in all the subgroups. Subgroups including those who got a short amount of treatment and those who got a longer amount of treatment." So this is known in 1994. Published late in 1994, reviewed earlier in 1994.

(Slide.)

Because of this phrase in the paper that there was no difference between the short and long, I sought to get the data -- can you just lower that slightly? Yes. -- the data from the researchers. Now these are data that were actually presented at a Data Safety Monitoring Board in February of '94 before the New England Journal article was published and before any of these other trials were designed.

This is what we have called a subgroup analysis but it was based on prior to a start of other study view of the researchers that they wanted to look at duration. What you can see here is in the left-hand pair of bars, those women who got less than 12 weeks of therapy, an average of seven weeks, had a reduction of

66.4 percent compared with the women who came in at the same time who got a placebo and conversely in the women who had more than 12 weeks of therapy there was about a 65 percent reduction. So this -- these were the data behind the statement in the paper saying that there was no effect of duration on -- there was no univariate relationship between duration and result.

An important result known before any of these other trials were published. It is of interest that in June of this year -- of that year, which is between the time that the trial was presented at an NIH Data Safety Monitoring Board and when it was published, there was a meeting of WHO and the convener of the meeting said, "Data from the 12-week subgroup analysis study and the data on the pharmacokinetics were not available."

This is being said four months after these data were presented at a meeting which was attended by a couple of people who actually were at the WHO meeting. So there is a serious failure to do the first principle of research, which is research what has already been done.

(Slide.)

Who was and who was not informed about this subanalysis? Informed, as I mentioned before, were the people who were there at the NIH Data Safety Monitoring

Board. Not informed -- because I spoke to the woman who -- the epidemiologist who led the discussion at that meeting -- were the people in June and, therefore, it was not utilized because all of the trial designs, except for the one that was done by the Harvard people in Thailand, were placebo controlled studies.

One can see that the hypothesis generated from that trial was -- and from the biology of the transmission was that a short course would work.

(Slide.)

CDC correctly in their protocol formulated the research question and this is the protocol from the Cote d'Avoir study, which was a placebo controlled trial, but in the protocol it said, "This study is proposed in the belief that short course oral therapy may be as effective or nearly as effective as the full ACT regimen."

Remember this is a design where they used short course, not compared with long course as the Thailand study did, but compared with the placebo and this is the kind of study that we criticize for this reason, more so even after we got the data that were available.

Let's go back a second to that.

The formulation of the question is very

important because whereas the question that was posed despite what you see here in the protocol was is there evidence that a short course is better than a placebo. The question that was asked by the other researchers, the other NIH funded -- the NIH funded study in Thailand was can we design a study in which we can find out whether the short course is as good or nearly as good, and someone can almost paraphrase it as this statement, "But they actually carried it out and designed a trial that way." It is a very different attitude in terms again of the benefit and risk to the patient as to which trial design is adhered to.

(Slide.)

Just moving on because my time is almost up, beyond the design of the study are issues obviously of IRB review and informed consent, and we point out, and I think that people generally agree that it is not enough as people have sometimes said, "Well, this study is okay because it went through the IRB review, here, there, everywhere, this study is okay because there was informed consent."

If the design of the study is flawed or if it is a study being done in a country where it is not going to be available you do not need to get to the IRB review and informed consent. It should not be done in the

first instance.

But let's assume that the study was well designed. We still need to look at these two factors and these are just some comments. One was by a virologist in Zimbabwe wrote -- writing to us after we had criticized these studies.

"An environment where the majority can neither read nor write is wallowing in poverty and sickness, hunger and homeless, where the educated, the powerful, the rich or the expatriate is a semigod, how can you talk of informed consent?"

(Slide.)

These were interviews done by a New York Times reporter, Howard French, in the Cote d'Avoir in the context of the study there. "They gave me a bunch of pills to take and told me how to take them. I figured that if one of them did not work against AIDS then one of the other ones would." Informed consent was obtained within five minutes of being told the person was HIV positive and one woman signed up, "Because of the medical that they are promising me."

(Slide.)

This on the issue of IRB's is again a letter written by a researcher to the New England Journal after the article that we published. "One of the major

problems in the Third World is the weak ethics in scientific committees that review scientific studies. The membership consists of interested parties such as investigators and they may receive incentives, including coauthorship or a ticket to an international conference."

That is all for the slides. I just want to conclude by summing this all up and pointing out that the benefit and risk to the patient, not the researchers, the funders, the country, the politicians and everything is first and foremost, and e are very concerned that in the developing world in the context of this massive globalization just as cheap jobs make cheaper products elsewhere, it is less expensive to do research and particularly the human experimentation corporations are taking advantage of this.

Similar to Doctors Without Borders, we believe that the NBAC has a duty to interfere with what may be otherwise going on in other countries by setting policies which reduce, if not eliminate, the extent to which human rights are being abused by unfavorable benefit/risk ratios to the patients in the studies in experiments in developing countries.

This is an important issue for NBAC to deal with at least to the extent that the studies involving

American funding are being done to seek approval of drugs by the FDA. There is, as Doctors Without Borders has shown, a duty to interfere. A principle of medical ethics without borders is one way of constructing the issues which you are considering.

Thank you.

DR. SHAPIRO: Thank you very much.

Let's go to questions.

David?

DISCUSSION WITH COMMISSIONERS

DR. CO: So, Dr. Wolfe, I have a very simple question for you and it is one which is just based on fact so it does not have to involve any suppositions.

With respect to the advertisements of a company like Quintiles it certainly raises the kinds of concerns that you mentioned. Okay. Are there any facts available that those kinds of abuses are going on by a company like that or others?

DR. WOLFE: We are currently and have been for some time trying to get some information on this by querying the FDA because to the extent that these clinical trials are submitted as part of a new drug application the FDA is exerting some kind of surveillance.

We just do not know. It has happened very,

very rapidly. There was a discussion of this in the context of the four reports issued by the Inspector General on Institutional Review Boards. These were issued in the summer of '98.

One of the concerns they had was that although institutional review boards, IRB, number one, are fixed to academic medical institutions, since these human experimetnation corporations are not academic medical institutions they have to have their own IRB's. They have named the independent review boards IRB's as well so as to confuse them with the institutional ones and one of the concerns was that people at one point sitting on these independent review boards own stock in the for profit IRB's.

These IRB's are for profit so that both at the level of the company wanting to race to the market as quickly as possible with their drug company partner and the ethical review, combine that with the increasing amount of these that are being done in foreign countries, there is at least a plausible biological hypothesis that there may be problems and it needs to be looked at very carefully.

DR. CO: So the answer to that first question is no, there are no facts right now?

DR. WOLFE: There are no facts either way. We

are in the -- we have been delayed somewhat getting information from the FDA on that.

DR. CO: So that is -- and then my -- the other factual question was do you believe that the results showing in the -- that those prior results concerning the efficacy of short-term versus long-term AZT treatments, which were not at that time published but were available to some, that that was scientific -- that was sufficient scientific proof to show that short-term versus long-term were equally effective?

DR. WOLFE: No. What I believe -- because the trial was not designed that way. It was designed to let anyone in whenever they chose to get prenatal care and then they were paired off more or less with someone with a placebo.

No, it simply presented information that should have said, "Okay. Let's see whether we confirm this." And the response should have been to repeat it but the repetition would be the kind of design that the Harvard-Thailand group are doing, which is an equivalency study comparing short-term to long-term in an out front completely randomized way.

No. I mean, one study does not ever prove anything but the point that we have made is that it is at least -- given how well controlled that whole study

was -- is at least suggestive enough to abandon any subsequent studies using the placebo.

DR. CO: Thank you.

DR. SHAPIRO: Thank you. We have got quite a few people who want to speak but Larry next.

DR. MIIKE: I am interested in both Dr. Whalen and Dr. Wolfe's answer, and you can answer this yes or no.

DR. WOLFE: Who would you like to answer first?

DR. MIIKE: Well, I would like to hear both of you but, first, just on the premise -- let's just assume that a trial has to benefit the population -- potentially benefit the population in which it is being done and then we can somehow resolve the issue about undue influence by providing care that is not available in a country versus best available care being provided on the control side where they are.

The study that you talked about said it was really an equivalency about whether it was equally effective for short-term versus long-term. I am interested to know whether you people would find it ethical to do a study in a population where the best available treatment is the control and you deliberately design a study that you are looking for efficacy but

deliberately at a lower level of efficacy than the best available study because that may be more available in that country.

You see what I am saying?

DR. WOLFE: I do.

DR. MIIKE: You deliberately design a study --

DR. WOLFE: Sure, I undersatnd.

DR. MIIKE: -- for something that is less efficacious but more --

DR. WOLFE: Right.

DR. MIIKE: -- potentially more available in that country. Is that ethical or not?

DR. WOLFE: I will try and answer.

I mean, the issue of -- I did not use the word "equipoise" but obviously, as you know, that is supposed to be present going into a trial. I think that the thinking -- let's just go to the specific example that I use. The thinking there was that one of the arms, as in the short arm, would be available in Thailand or wherever else because it was, in fact, used as the comparison group to the placebo in the other studies that we have questioned the ethics of.

I think that in that case there was a belief that they would be equally efficacious.

DR. MIIKE: Oh, but that is not the question I am asking.

DR. WOLFE: No, I understand. So I will now go to your question, which is if you go into the study believing that one is going to be better than the other that is -- raises serious ethical questions because you are -- I mean, that is --

DR. MIIKE: What I am saying is that the proven therapy --

DR. WOLFE: Right.

DR. MIIKE: -- is at a particular level. What you are trying to do is do a trial where you know -- your hypothesis is that the therapy is going to be less efficacious but it is going to be half a degree of efficaciousness. But the fact that I am looking at is that that may be more available in that population than the best available treatment.

DR. WOLFE: It may be. And that is a more difficult question. I mean --

DR. MIIKE: Oh, but in the hypothetical --

DR. WOLFE: Yes. In --

DR. MIIKE: -- would you say yes or no? Would you find it ethical or not?

DR. WOLFE: I do not know is the answer. Sometimes we have to say we do not know and this is

one which I do not know and the only thing that -- the question I would raise about your hypothetical is that how would you know going into it -- let's assume that the best available, that the most expensive therapy rather, the 076 equivalent for example, was --

DR. MIIKE: Well, you are ducking my question.

DR. WOLFE: No, I am not.

DR. MIIKE: You are ducking my question.

DR. WOLFE: No.

DR. MIIKE: You are ducking my question.

DR. WOLFE: No, I am saying --

DR. MIIKE: I am providing it --

DR. WOLFE: -- I do not --

DR. MIIKE: -- in a --

DR. WOLFE: I am saying I do not know. I am not ducking your question.

DR. SHAPIRO: Why don't we let everybody answer what they want?

DR. WOLFE: My answer is I do not know.

DR. SHAPIRO: His answer is what you want.

DR. WOLFE: I understand your question and it is a difficult one and I, therefore, say I do not know.

DR. MIIKE: Dr. Whalen?

DR. WHALEN: I know you want me to say yes or no.

If I -- I will try to answer yes or no but let me think out loud for a minute. When you do an equivalency study you are -- the hypothesis -- the null hypothesis and alternative hypothesis are flipped and you are looking for the fact that one treatment gives a result that is very close to the other one.

And when you do a study and your results confirm that two treatments are similar, you can move forward and you know that treatment A is the same or equal to treatment B. But when you -- when the study fails to demonstrate that, all you know is that one result is not as good as the other result. Okay.

So let's say -- and then in a developing country I can see a scenario where having done an equivalency study that does not demonstrate equivalency that you are actually left with no information to base public health decisions on.

DR. MIIKE: If you will indulge me, Harold, then let me ask the question this way: In the example that you are using where short-term versus long-term, suppose the evidence going into that trial had been the short-term was less effective but it was effective nevertheless. Would you have accepted a trial that tried to confirm that so that in -- that it would be left up to the country, for example Uganda, having been

given that information that they might make the decision to use a shorter therapy knowing that it would be efficacious but not as efficacious as the longer therapy regimens?

DR. WOLFE: Let me just expand on the first set.

Part of the -- and I am sure this will be addressed later -- part of the design of the equivalency is this tolerance. How much will you tolerate in terms of difference between the proven therapy and the other. And let's assume that the proven therapy was a 100 in terms of terrific and you would tolerate as little as 80 or 90 or whatever in your design and if it turned out to be less than that you would stop the study.

I think part of the answer -- I mean, I still say I do not know but I think that from the public health perspective the country in which a study is being done would then have to choose with some difficulty to announce that they are going to use the shorter course even though it is, let's say, 10 percent less effective. I mean, that is a difficult question both at the trial design level and at the level of implementing it around the country.

Let's assume -- which is what your question assumes -- that the more expensive one is too expensive

and that, if anything, they are going to only be able to do the less expense one.

I think that again one of the reasons for this design in the equivalency study was in the hope that it would be the same or close enough that they could persuasively from a public health perspective say, "We are going to give you something that is just about as good, not quite as good," and the gap of the not quite is obviously very critical. If it was only half as good there would be a question but again the biology suggests that it will be about the same.

DR. MIIKE: But again that was not my question. My question was there is a clear difference.

DR. WOLFE: Right. The clear difference -- then if there is a difference then why do the study? See what I mean?

DR. MIIKE: Well, that was my question. So your answer is no?

DR. WOLFE: No. I am saying if there is really a clear difference -- in other words, the short and the long have both been studied sufficiently that there would be a clear difference then there is no need to do a study. You do an implementation. I did not mention on one of the considerations on that slide about factors is sometimes the results are clear enough that

you do not need to do another study. You can just make it available.

There are certainly a number of sites around the world where after 076 they just made AZT available to HIV positive pregnant women whenever they came in the door even if they came in very late in the course.

DR. SHAPIRO: Okay. Tom?

DR. MURRAY: Thank you.

First I want to ask Sid for a brief clarification. Early in your presentation you cited this company, Quintiles, about which I do not know anything except what you just told us.

DR. WOLFE: Here is their ad for those of you --

DR. MURRAY: Okay. And you read something about drug naive populations and I thought you were imputing some significance to that and I just -- I wondered what you think they meant with the term "drug naive" because I interpreted it differently than you did.

DR. WOLFE: Well, I think it is -- it is a double entendre at the very least. I think what they meant was that there -- these are populations which have not had a prior exposure to pharmaceuticals and who, thereby, would not have some of the problems in a

population which is much more likely to have gotten pharmaceuticals. It is another advantage if you want to look at it that way of going to developing country. That is how I interpreted it.

DR. MURRAY: That is how I understood it.

DR. WOLFE: I just -- when I first read it, it was sort of appalling because I think that in a sense the other part of the double entendre is that these people are somewhat naive in that in many of these instances they are not in countries where one sees fifty ads a week in the newspaper about clinical trials.

DR. MURRAY: Okay. So we actually have a similar understanding.

DR. WOLFE: Yes, we do.

DR. MURRAY: That is comforting.

Now a question. At the end of your talk you spoke about informed consent and, in particular, you quoted a virologist who gave what I thought was a fairly despairing account of the very possibility or impossibility of obtaining informed consent in certain settings.

DR. WOLFE: Right.

DR. MURRAY: What lessons would you take from what you have told us? I mean, one possibility is since there are so many difficulties here imposed by poverty,

desperation, illness, et cetera, one should never attempt to get informed consent and one should never attempt research of any kind in these populations.

I guess I want to know what your interpretation and what advICH you would provide and then I want to ask Chris for his take on it.

DR. WOLFE: Okay. Is this microphone on or not? I think it is.

PROF. CAPRON: Yes.

DR. WOLFE: Okay.

Well, I mean, if you combine that with the findings not just in the Howard French, New York Times, Cote d'Avoir but other interviews with people in Uganda -- there was -- I think a Cleveland Planet reporter interviewed some people in Uganda in the TB study -- I am mainly an optimist and I do not believe that one needs to abandon entirely doing research in developing countries. I think that it poses a greater challenge. You people have dealt with a very difficult question of informed consent in vulnerable populations.

Let's just look upon these people as a different form of vulnerable population partly because of naivete of previous experience, partly because of education, and I think it is just a greater challenge to do informed consent in the right way, and one needs to

do outcome studies in informed consent. Simply counting up how many people sign is really not enough and you are dealing with this in some way in the studies that you have commissioned out.

What is the evidence that those people who signed the informed consent sheet actually understood it? I mean, instead of having newspaper reporters interview them, you can do it in a more formal way and actually see whether it gets through. So I think it is more challenging just as it is more challenging to obtained informed consent in vulnerable populations in this country.

DR. MURRAY: Okay.

Chris, do you have anything you want to say about -- you want to add to that?

DR. WHALEN: I think one must always obtain individual informed consent even -- I recognize the difficulties in some settings in Africa where the tribe leader may be able to acknowledge that anyone in his tribe can participate or a family leader may -- head of a household, for example, may indicate that what he says everyone can -- anyone can participate if he says so.

I believe we still need to get individual informed consent.

Recognizing that there are problems with

informed consent and making sure that people fully understand the nature of the research -- that is a real challenge of doing research and obtaining informed consent in a developing country.

I know that the procedures we used in the Preventive Therapy study were quite extensive with group and individual sessions sort of sequentially over three or four different time periods. And even in that scenario when you come back years later some individuals did not recall the informed consent process or had a different understanding of what that process was about.

So I think one has to attempt to get it and do the very best you can to inform the individuals in the study.

DR. MURRAY: Thank you.

DR. SHAPIRO: We are running into some time constraints here so I have four commissioners left who want to ask questions. That is Bernie, Eric, Steve and Jim.

One question each so that we do not last another half hour on this.

Bernie, we will start with you. Pick your most important question.

DR. LO: My question is directed to Dr. Wolfe

and Dr. Lurie. I am trying to understand a little bit more about how you operationalize these criteria you set out about when is it unethical to withhold an intervention in a control group.

And I am trying to -- again, my mind works better with concrete examples. I am trying to think of what I would be doing if I was designing a perinatal HIV prevention study in a country where most women do not get prenatal care except for prenatal care at delivery or shortly before delivery where I cannot give intravenous AZT during delivery because, you know, we do not have facilities to give intravenous drugs after the study is done on a sort of population basis.

Would those sorts of considerations fit under your rubric of is there a feasible plan to make an intervention available in a country after the study?

I can obviously do it in a clinical trial but if -- to operationalize the intervention after the trial will require changing patterns of presenting for prenatal care and making it feasible to deliver i.v.'s in the hospital.

Does that mean that for all intents and purposes that is not a practical intervention in that country?

The second question, again with your criteria,

has got to do with --

MR. HOLTZMAN: You got around your one question.

DR. SHAPIRO: Yes.

DR. LO: Well, it is subpart A and B.

(Laughter.)

DR. LO: We are very good at this.

MR. HOLTZMAN: He will say this is Part B of the first question.

DR. LO: Right.

(Laughter.)

DR. LO: Well, it has to do with --

DR. SHAPIRO: Some of your colleagues will get zero questions.

DR. LO: -- relevant biological differences and I guess I would like to know is a study that is done in a nonbreast feeding population -- is it a relevant biological difference for perinatal transmission that the country I am interested in has breast feeding as its cultural norm? Do I assume that 076 applies to a breast feeding populaton?

DR. WOLFE: Well, let me just answer the question. I mean, the first one at the time, -- and just using the concrete example since you correctly, as do I like to deal with concrete examples -- , there was

good pharmacokinetics data available back four or five years ago that one could just as well get the blood levels up with an oral dose.

So if you did not have that information it would be a different consideration and that would be something that you could not even do in the context of the trial. But, in fact, one knew at that point that oral, which would obviate the need of hooking up someone to an i.v. would suffice.

As far as the breast feeding issue is concerned, subsequently there have been studies in breast feeding and nonbreast feeding countries, and the magnitude of the reduction is very, very similar. Yes, that is different but one has again some other biological information about what kind of transmission can occur with breast feeding and I do not think that it is relevant in the sense that the country is or is not a breast feeding country but that does not mean you cannot do the trial or should not even expect to get the result.

Do you want to add anything?

DR. LURIE: Yes. If I might, I actually think both your questions have the same answer. How about that for parsimony?

The issue is can you find another way of

answering these questions short of getting into either a placebo control trial or even perhaps a randomized control trial? I personally believe that one needs a placebo controlled trial to establish the safety or lack thereof of INH in African patients, many of whom have been getting INH for many, many years. I am referring to Dr. Whalen's question.

In the particular case of the questions that you raised, though, as Sid points out, you could have answered the i.v. versus oral question by simply randomizing a small number of people to oral versus i.v. and measuring their blood levels.

And CDC predicted that the levels would be the same and, in fact, when a few years later they actually got around to doing the test, the levels of AZT in the blood were the same. You did not need a randomized control trial of efficacy, let alone a placebo control one to answer that question.

With regard to the breast feeding there were data available to the researchers at the time of the study that about 14 percent of transmission in breast feeding patients was -- I am sorry. That the absolute contribution of breast feeding transmission was 14 percent, the breast feeding point, and that the majority of it, probably 28 or more or so percent was, in fact,

due to the nonbreast feeding portions.

So the question is not are breast feeding patients different than nonbreast feeding patients. The narrower question is, is that difference of breast feeding versus not sufficient to likely wipe out the dramatic effectiveness of 076?

We predicted that it would not. We predicted as well that the oral versus the i.v. would not. It turns out that we were right. We predicted a long time ago that the short courses would be effective. It also shows that the so-called subanalysis was a good predictor of what was going to happen.

My point then to summarize is that there are very often data available, the same as trial ways of addressing questions that fall short of randomization, let alone placebo control groups.

And it is the responsibility of the researcher to pull together every bit of possible information existing or that can be readily obtained short of necessarily and reflexively resorting to placebo controlled trials, especially when that can result in better protection for patients.

DR. SHAPIRO: Thank you.

Now I can easily tolerate the fact that members of this commission have no respect for my views.

(Laughter.)

DR. SHAPIRO: What I cannot tolerate is keeping our guests waiting who have traveled to be here.

DR. DUMAS: That is right.

DR. SHAPIRO: So the last question is -- Eric, if it is short you can ask it, if not you cannot.

DR. CASSELL: It is short.

DR. DUMAS: I do not believe it.

(Laughter.)

DR. CASSELL: You had a statement up there that the researcher has primary responsibility for the well-being of an individual participant. And is that the same as it would be as if it were a clinician? Is there no difference between a researcher in relationship to responsibility to a participant versus responsibility for the knowledge from the trial or are they really the same?

Coincidently, "naive" is a word of art. In the OED you are naive when you are appalled.

DR. WOLFE: The reason that many people have said that the researcher needs to act as though they were a physician is because the benefit/risk ratio that one would subject your own patients in practICH to should not be arguably different than the benefit/risk

ratio that you would subject someone or a group of people in a trial.

So I think it is very similar, if not identical, is the answer. As a physician who is --

DR. CASSELL: No --

DR. WOLFE: Pardon? If anything, it is greater because there are --

DR. SHAPIRO: It is not a discussion, Eric. Thank you.

DR. WOLFE: Okay.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I think this is a quick question.

Moving apart from specifics and more to the general principle level, you advocated that it is a very good thought to say to yourself before I undertake this line of experimentation, would I do it to myself, would I do it to my wife, would I do it to my child.

DR. WOLFE: Right.

MR. HOLTZMAN: When I ask that of myself as an investigator, should I say would I do that, that is given I am Steven Holtzman with the following income level, with the following health care available, with the benefit of the fact that cost is no object, or should I ask it of myself and my children and my wife

imagining myself into the situation where those facts may be different?

DR. WOLFE: Well, I think that it is most relevant if you imagine yourself as being in Thailand or in South Africa or wherever knowing what the facts are, what the availability is, what the possible design alternatives are. I mean, I think that it is relevant in that country. That is not meant to support, which I attacked earlier, cultural relativism but it is really to focus -- and is one of the reasons why there are both U.S. based and local investigators. I mean, the local investigator who lives in the country and knows about it should ask themselves the question would I be willing to give myself or my mother or father or whatever a placebo.

So I think it is in the context of the country but I am not sure the answer would be a lot different. I mean, other than mentioning that cardiac bypass surgery centers are not available in some of these countries and, therefore, it is a nonquestion. You, therefore, do not do a study having to do with outcomes of that in that country.

DR. SHAPIRO: Jim?

DR. CHILDRESS: This question arises out of something Dr. Whalen had said toward the end of one of

his recent comments about questions about the adequacy of informed consent. You referred to recall studies but I am not at all convinced that studies of how much subjects recall months or years later can really tell us a lot about the adequacy or inadequacy of the informed consent in a particular setting at the time, say, the form was signed or the consent was given to proceed.

I just wonder whether you have any suggestions about ways we could get at the adequacy of informed consent. This is a problem in the U.S. as well as elsewhere.

DR. WHALEN: I know some people have proposed a brief set of questions shortly after the process of informed consent has been completed. We have not used that in Uganda to date, though. In the future studies, it is something that I would be interested in trying out certainly but I do not know how the Ugandans will respond to it.

They may feel as, though, why are you testing me, is this -- do I have to pass a test to come in this study and you are going to keep me out because I cannot answer these questions and even though they may fully understand them.

So I -- so even that in the culture -- in the context of Ugandan culture I would need to, you know, do

studies along those lines or do pilot evaluations along those lines.

DR. SHAPIRO: Thank you.

Let me finally thank both Dr. Wolfe and Dr. Whalen. Thank you very much for being here today. We very much benefitted from your testimony on this issue we will continue to struggle with.

Let me say to the commission we will take only a five minute break. I mean, you have your choice of no break or five minutes only.

(Laughter.)

DR. SHAPIRO: Because we do have -- some of our guests have to leave and they have made great effort to be here so I really will rely on you all to be back here in five minutes.

(Whereupon, a break was taken from 10:38 a.m. until 10:47 a.m.)

PANEL II: RESEARCH DESIGN METHODOLOGY

DR. SHAPIRO: I would like to get this session underway if you do not mind.

Let me extend my thanks to all of you for being here today. I know that everybody has extremely busy schedules and we are very appreciative of the fact that you have taken time to be here.

At this time, just to keep matters a little

uncertain, you are not listed in alphabetical order on the program and I will go by the program. I know that some of you may have to leave early. We will try to move on as quickly as possible.

We certainly appreciate that you have other commitments but let's just go this way. We will go from my left to right as one way of doing this so we will hear first from Professor Lagakos, who is a professor of biostatistics.

Welcome. It is a great pleasure to have you here.

DR. LAGAKOS: Thanks.

DR. SHAPIRO: We look forward to hearing your remarks.

STEPHEN LAGAKOS, Ph.D., M.P.H.

HARVARD MEDICAL SCHOOL OF PUBLIC HEALTH

DR. LAGAKOS: Thank you.

Hopefully, the microphone is on.

PROF. CAPRON: You have to get up close.

DR. LAGAKOS: Oh.

PROF. CAPRON: That is the rock star analogy.

DR. LAGAKOS: Okay.

PROF. CAPRON: For those people who thought that they had to play music while they were speaking.

DR. LAGAKOS: I want to actually begin with an

apology. I was not sure what the format would be and I did not prepare overhead transparencies so I will read my testimony.

DR. SHAPIRO: Thank you.

DR. LAGAKOS: Okay.

As a statistician, I am used to using them but you all should have a copy of my comments.

DR. SHAPIRO: Yes, they are here. Thank you.

DR. LAGAKOS: And I can provide somebody with a diskette if they want it.

So let me just start. I am pleased to have the opportunity to be before you today and present some of my thoughts about international clinical research and to answer questions that you may have.

Let me begin by saying something about who I am. I am a mathematical statistician by training but have really spent my entire career as a biostatistician. I am on the faculty of the Department of Biostatistics at the Harvard University School of Public Health. I have been there since 1978.

I am also a member of the Center for Biostatistics and AIDS Resarch, commonly called CBAR at Harvard. CBAR is involved in many HIV trials and most notably because it plays the role as the statistical center for both the adult and pediatrics AIDS Clinical

Trials Groups with whom I have been involved since 1987.

Prior to my AIDS activities I was involved for ten or more yeras in clinical trials for the evaluation of new therapies for cancer.

Most of my experience in clinical trials has been based in U.S. trials. However, through the WHO I also had the opportunity to help to design and implement a clinical trial of hepatitis B, of a hepatitis B vaccine in China in the '80s, and more recently have been involved in the planning, conduct and/or the analysis of HIV trials in Thailand, Botswana and Cambodia.

I am a member of several Data and Safety Monitoring Boards, DSMBs, for several international trials. In this capacity I have had the opportunity to review the interim results of trials to ensure that patient interests are being safeguarded.

In particular, I am a member of the DSMB for an HIV perinatal transmission trial based in Chiang Mai, Thailand, that Dr. Wolfe described as the Harvard-Thailand study, that I will discuss in some detail during this testimony.

These experiences have led me to think a good deal about issues of ethics and together with recent opinions, as expressed by others in the scientific and

medical literature, have shaped my views.

I also have benefitted greatly with my discussions with my colleagues at Harvard who are involved in trials, and with fellow DSMB members, and with investigators who I have collaborated, and with colleagues at the New England Journal of Medicine where ethical issues are sometimes debated during our weekly meetings to review manuscripts.

So that is where I am and let me just begin with an introduction. I was asked to provide -- in the words of someone, I cannot remember who it was now -- a ten minute primer on the ABC's of clinical trials.

So numerous ethical issues can arise in the design, implementation, monitoring and analysis and reporting of clinical trials -- clinical research studies, even those that do not involve therapeutic interventions.

In this session four of us will discuss our views and experiences in this area. Before presenting my own views I will try to give some background material on the main types of clinical trials that are undertaken and on several types of designs that are commonly used in randomized clinical trials aimed at comparing two or more treatment groups.

I will then focus on several issues that can

arise -- on specific issues that can arise in the conduct of Phase III comparative trials that are being conducted in developing countries but with sponsorship from an outside organization such as the NIH or a pharmaceutical company.

This setting, a trial being conducted in a developing country with external support, can raise additional ethical challenges because of, one, the different ethical views or standards of medical care between the host country and the country of the sponsor; and, two, the fact that the sponsor is providing funds to help support the cost of the study.

Okay. Basics of clinical trials.

Biomedical research studies involving humans can take several forms. In a cross-sectional study, for example, information about a group of subjects at one point in time is examined. This is to be distinguished from a longitudinal study, which includes information on subjects collected over a period of time. Among longitudinal studies it is common to distinguish those that collect information retrospectively such as a case control epidemiologic study that is aimed at assessing a possible association between some exposure and the subsequent risk of disease and a cohort study in which a group of subjects is followed prospectively over time.

Even within cohort studies one can further distinguish observational studies, which generally means that there is no therapeutic intervention, and clinical trials where there is a therapeutic intervention.

There are many types of clinical trials. One way of classifying clinical trials is by the type of design, namely uncontrolled trials, trials with nonrandomized controls, and trials with randomized controls.

An example of an uncontrolled trial would be a study in which all participants receive the same drug and efficacy is based on the results of just that study.

If, instead, the drug's efficacy were assessed by comparing these results with the results of a past study of another drug, say published in the medical literature, then the trial would be classified as one with nonrandomized controls.

Alternatively, if some of the patients in the trial were randomly assigned to receive a new drug and some were randomly assigned to receive a standard treatment or a placebo then the trial would have a randomized control group.

Much has been written about the use of randomized versus nonrandomized controls and the consensus view among clinical trialists is that the use

of nonrandomized controls can be severely biased and unreliable. Thus clinical trials with randomized controls and with blinding, when practical and appropriate, represent the gold standard for the evaluation of therapeutic interventions.

I strongly agree with this view and in the interest of time will not focus on the values of randomization and the use of a placebo pill as opposed to giving no treatment or blinding in my comments. However, I will return to the issue of how to choose a control group.

Another way of classifying clinical trials is by phase. Phase I studies, drug studies, are typically small and often used to determine the optimal dose of a new drug. These are often conducted in nondiseased individuals such as medical student volunteers.

Phase II trials tend to be somewhat larger and are often aimed at obtaining an initial sense, a preliminary sense of whether a drug may have clinical efficacy. If the results of these trials are promising then a larger Phase III trial aimed at establishing whether or not there is efficacy may be conducted.

Phase III trials are large, typically 50 to thousands of subjects, and comparative in nature with randomization with at least two arms, one of which

serves as a control or a reference arm and one or more arms involving new treatments.

The term Phase IV trial is often used to refer to post marketing surveillance studies aimed at assessing long-term effects. For example, rare but serious side effects of a new treatment.

In the interest of time I will hereafter focus on Phase III randomized trials as most of the ethical issues I am familiar with have arisen in this setting.

There are many types of designs that are used in Phase III randomized trials. For example, in diseases where an effective treatment is available and in use a common design randomizes trial participants to receive either a new treatment or the standard treatment. Even in this setting there can be different scientific goals. The most common is to determine whether the new treatment has superior efficacy than the standard or to the standard, I guess. If so, and if its associated costs and safety profile are comparable to those of the standard, then the new treatment would be preferable and may replace it as the new standard of care.

In other instances, however, the new treatment may have fewer side effects and/or be less expensive than the standard treatment. Here demonstration that

the new treatment is as or nearly as efficacious as the control may be enough to conclude that it would be preferable to the standard. Or when the standard treatment may not be well tolerated in some patients there may be value in demonstrating that a new drug -- in demonstrating that a new drug is equally efficacious, even though it may not be less expensive or have fewer side effects. Since this might represent a valuable alternative for patients who cannot tolerate the standard treatment.

Phase III trials which aim to show that a new treatment is more efficacious than a standard treatment are often referred to as superiority trials. While trials aimed at showing that the new treatment is as or nearly as effective as the standard are often called equivalence trials.

The latter name has been criticized by some arguing that it would be more accurate to refer to these as noninferiority trials rather than equivalence trials on the grounds that if having equal efficacy would make the new treatment preferable to the standard then having superior efficacy would also. I support this view.

Let me now comment on the choICH of a control group. In an equivalence trial the control group is usually a standard treatment that has been proven or is

perceived to have therapeutic value. In such a setting where demonstration of equivalence is the goal, use of a placebo control makes no sense.

However, in a superiority trial the control group could be an active treatment or a placebo. For example, if there were no proven effective treatments for a particular disease then the goal of the trial would be to demonstrate that a new treatment is beneficial. This usually translates into leading to a better response than a group of patients who receive no treatment. Thus the natural and appropriate design would be to -- scientifically would be to randomize patients to the new treatment versus a placebo.

One point I wish to make here is that I have heard some describe ethical issues in terms of superiority versus equivalence trials. In fact, the real issue is not this but whether a placebo or an active control group should be used.

The final general comment I wish to make about study design is that this should be dictated by the scientific question that one wishes to answer in the trial. While the goal of linking the design of the trial to the scientific question is hard to disagree with conceptually, the most appropriate scientific question is sometimes not obvious and thus the choice

among several clinical trial designs, including the choice of a control group, may not be obvious. I will return to this point later in my testimony.

Ethical issues: Ethical issues can arise in each of the types of studies I have just mentioned. Not just in Phase III clinical trials. For example, in a case control or cross-sectional study based on information already present in some database there could be issues of confidentiality or access to records or in an observational study in which there was no therapeutic intervention for any subject, ethical issues might arise if an invasive diagnostic test is used or perhaps simply because no intervention was used.

The latter situation is illustrated, for example, in an article that appeared in the New England Journal of Medicine last year where Dr. Prophan from the Thai Red Cross raised ethical concerns about a U.S. supported study of the natural history of HIV in pregnant Thai women and their offspring.

The underlying reasons why ethical issues can arise are numerous, but in my experience these are often related to issues of cost and expediency, conflicts between the scientific goals of a study and the best interests of the study participants, and differences of opinion about the relative importance of the scientific

questions that should be addressed.

As noted above, I will discuss ethical issues arising in Phase III clinical trials. Further, I will try to focus on issues that have commonly arisen in clinical trials being conducted in a developing country with support from an outside organization such as a pharmaceutical company or the NIH. This setting where the customs, cultural norms, standards, and extent of medical care may differ considerably between the host country and the country of the sponsor can lead to additional ethical challenges.

So now let me turn to some ethical issues arising in trial design. Ethical dilemmas can arise when there is an established effective treatment for a disease or a condition that is not routinely used in the host country because of cost.

For example, while ZDV is now well-known to be highly effective -- a highly effective way of reducing the risk of perinatal transmission of HIV, it or other antiretroviral agents are still not in widespread use in many parts of Asia and Sub-Sahara Africa. In this setting, is it ethical for us, meaning say investigators from the U.S., to undertake a placebo controlled study when effective therapies exist under the standard of care in the United States and other developed countries?

The fact that the care provided in every arm of a trial would be as good or better than what the subject would receive if he/she were not in the trial does not in and of itself make the trial ethical.

Ethical issues can also arise regarding the duration of treatment of study subjects. For example, again using the setting of perinatal transmission of HIV, what is the obligation for treating the HIV infected mother after her child is born? What is the ethical argument for failing to offer antiretroviral treatment to the mother after her child is born?

Similarly, is there an ethical obligation -- I should probably say, will there be an ethical obligation to provide antiviral treatment to participants who become infected during an HIV vaccine trial, assuming this represents the standard of care in the United States at that time?

Let me turn now to ethical issues related to the enrollment of study subjects, and I will be brief here. Many developing countries provide inadequate, at least by our standards, health care. Thus, for a potential volunteer there can be a strong incentive to participate in a clinical trial since all of the treatment arms, even if some fall short of U.S.

standards, would represent an improvement to the available options if he or she did not volunteer in the trial. In such opportunities the opportunity for -- in such settings the opportunity for unintended coercion might be significant. What safeguards should be taken in such a setting to ensure that proper informed consent is provided?

Perhaps I should just comment now based on some comments made in the discussions earlier that I have just finished teaching a course in clinical trials in Greece and the view in other countries about informed consent is not the same as the prevailing view here.

For example, concerns that -- the general perception that some people gave me in other countries is that we are too concerned with the bad investigator who tries to take advantage of a situation and we do not worry enough about perhaps the psychological harm that can come from informed consent. So I just throw that out there to make the point that the issues of informed consent can be particularly complicated in other settings.

Ethical issues arising in the monitoring of interim results: Clinical trials often require several years to complete. As a result, it is important that the trials be monitored regularly to ensure that the

best interests of participants are safeguarded. When I say "monitored" here, I do not mean site monitors. I mean interim analyses of the clinical trial.

This task is best accomplished by an independent DSMB, Data and Safety Monitoring Board, whose members have expertise in the disease area and in clinical trials methods and in who have no personal or financial interests in the outcome of the trial.

In addition to examining the evolving results of the trial, the DSMB should be aware of what advances in the -- should be aware of advances in the field and assess whether the study design, which presumably was ethical and scientifically valid when the trial was initiated, is still ethical and scientifically valid.

This is especially important for diseases such as HIV where progress in the development of effective therapies has been rapid. Trials that are no longer ethical because the control group no longer represents an accepted standard of care, trials that have no reasonable hope of leading to an unequivocal result, and trials that have already demonstrated a definitive difference between treatment arms should usually be terminated even if their continuation may have some benefit to the medical and scientific community.

Because the data sources used to assess these

conditions, unequivocal results, new standard of care, are never completely unequivocal themselves, the ethical considerations that arise in such instances are often not clear-cut and conscientious and knowledgeable experts on the DSMB can disagree in fundamental ways about the best course of action. In such instances, how does one ensure that the views and perspectives of both the host country and the sponsor are understood when deciding whether to continue or terminate or modify a study? What if there is not consensus on the proper course of action between members of a DSMB that represent the host country and those that represent the sponsor?

Resolving ethical issues: When I try to determine my own views on an ethical issue that may arise in a trial I tend to first use my own sense of values to determine whether I am ethically comfortable with a study.

Sometimes it is difficult to know exactly how I weigh the various considerations that are involved in thinking about the issue -- the ethical considerations -- but I will say that I firmly believe that any investigator in a trial, including members of its DSMB, assumes a responsibility to ensure that the best interest of the study participants are protected. I

will just comment now that that is not restricted to physicians in any sense. That is anybody who takes a responsibility. By buying in, one bears a responsibility for those subjects.

Sometimes the ethics of a situation are not so clear to me. I then try to identify the underlying ethical principles that may be at the heart of the concern. However, even this is sometimes a difficult task.

Much has been written about ethical principles for the conduct of research involving humans and the Declaration of Helsinki is often referenced as a key sort of principles. Individually the principles in the Helsinki Declaration seem reasonable and laudable. However, when it comes to certain specific issues the practical interpretation of a principle might be somewhat vague or appear to conflict with another principle. Thus it is not surprising that a thoughtful and competent clinical research often disagree -- that thoughtful and competent clinical researchers often disagree on the ethics of a specific situation.

As a result, I sometimes find myself unable to pigeon hole myself as being on one side or another of an ethical debate or to fully justify why a specific study is ethical even though I support its implementation.

Because of this recognition that the issues are not always clear-cut and clearly addressed by these principles, I try to remind myself that those taking the other view are not necessarily ignorant of the issues even though -- just becasue they disagree with me.

So that is my background on clinical trials. Let me say now a bit about my own views. I would now like to express some of my own personal views on the specific ethical issues that I raised in the preceding overview of clinical trials.

To maintain a link between the different issues I will use the example of perinatal transmission of HIV as a paradigm and, in particular, the example of the CDC supported placebo control trial of ZDV that was recently completed in Thailand. I choose this example because I find the ethical issues to be particularly challenging and because clinical investigators, whom I deeply respect, have taken very different views on some of these issues.

Let me begin with the issue of choosing a control group. The Thai-CDC study, as I will refer to it, compared a short course of ZDV to placebo in HIV-infected pregnant women in Thailand. Enrollment into this trial was undertaken after the results of ACTG-076 were made public in 1994. That study indicated that ZDV

appeared to reduce the rate of perinatal transmission of HIV by about two-thirds.

I will not provide the details of either of these to studies because I am sure you are well familiar with them. However, I will make a few general observations to set the stage for the ethical and scientific considerations.

The setting in Thailand when the Thai-CDC trial was initiated was as follows:

One: HIV was recognized as a serious problem in Thailand. It was well-known among Thai scientists that HIV can be transmitted in utero; that ZDV had been shown to greatly reduce HIV transmission in several studies; and that ZDV had become the standard of care in the United States and many parts of Western Europe.

Two: Pregnant Thai women known to be HIV positive were not, in general, offered ZDV or any other antiretroviral agents to reduce the risk of perinatal transmission of HIV.

Three: Previous studies showing that ZDV could reduce perinatal transmission of HIV were predominantly in regions where the B subtype of HIV-1 was predominant. In Thailand the predominant subtype of HIV is the E subtype.

By its design, the Thai-CDC trial hoped to

determine whether a short course of ZDV was effective in reducing the risk of HIV transmission relative to no treatment. If it were -- and now I am speaking as if we were designing the trial, this is before seeing any of the data -- if it were, then a more affordable and perhaps safer ZDV regimen than the ACTG-076 regimen would be available and perhaps could be implemented on a national basis more easily than the ACTG-076 regimen.

However, if the study were to show that ZDV were more efficacious than placebo, it would still not be known how much efficacy was lost compared to an ACTG-076 regimen by giving the drug for a shorter length of time.

What about the scientific and ethical justification for using a placebo group in this study?

One rationale for the use of a placebo group was that a two arm trial comparing the short course ZDV regimen to the ACTG-076 regimen could not reliably determine the extent to which the short course is better than no treatment.

Let me say that again and try not to mumble.

One rationale for the use of a placebo group was that a two arm trial comparing a short course of ZDV to a longer course could not reliably determine the extent to which the short course is better than no

treatment.

Two reasons for arguing that the use of a placebo group in the Thai-CDC trial is ethical are: And these are my reasons or my arguments:

Although the standard of care in the U.S. at the time was ZDV, ZDV was not given in Thailand. Rather HIV infected women were untreated. Thus the placebo arm reflects the "standard of care" -- and I put that in quotes -- in the host country. And no trial participant would be -- in this trial would receive a treatment that is less effective than what they would receive if they did not participate in the trial.

The second point was that previous studies had clearly demonstrated ZDV reduced perinatal transmission of HIV but these were mainly in parts of the world where the B subtype was predominant. Thus, how assuredly could one conclude that ZDV would be effective against the E subtype of HIV?

For example, if a study comparing the ACTG-076 regimen to a short course of ZDV resulted in similar transmission rates in the two arms, can we be sure that both were highly effective or could this simply be reflecting a situation where both were equally ineffective or only mildly effective? In the face of this uncertainty, use of a placebo group could be

argued.

An alternative study that was implemented in Chiang Mai, Thailand, at about the same time as the Thai-CDC study, compared a short course ZDV regimen to an ACTG-076 type regimen. This study was actually a two-by-two factorial design which attempted to answer several questions, but for the purposes of this argument I will proceed as if it were a two-arm study of short course ZDV versus a long course, ACTG-076-like regimen.

The scientific question being asked in this study was different than the one asked in the Thai-CDC study. Specifically, the Chiang Mai study, which Dr. Wolfe referred to as the Harvard-Thailand study, basically asked whether a short course of ZDV was as or nearly as effective as the longer course. If it were, and again I am thinking -- I am talking about the logic used when this trial was designed -- if it were as effective or nearly as effective, then it would be demonstrated that one could achieve similar efficacy with a cheaper and perhaps safer ZDV regimen.

If the short course proved to be less effective than the long course then, it would be, in general, difficult to know how much, if at all, the short course reduced the risk of HIV transmission

because there was no control group. Since no placebo group was included in the Chiang Mai study, the issue of justifying the ethics of a placebo group was irrelevant.

Note that the specific questions being asked in these two studies are quite distinct. Both questions bear on the general question of the efficacy of ZDV in reducing the risk of perinatal transmission. Both designs could lead to very useful scientific information for both Thais and other peoples, and both designs have limitations in their interpretation for certain study outcomes that I pointed out.

One additional note about these studies: Because one would not expect the efficacy of a short course of ZDV to differ as much from a long course as would a short course differ from a placebo, the Thai-CDC study was considerably smaller in size, approximately 400 mothers, than the Chiang Mai study, approximately three times as many mothers. This substantial difference in size has implications for the cost of the studies and the time needed for their completion.

I find some merit in the ethical arguments used to justify both studies and in the scientific questions that both studies attempt to address. For me, however, the sticking point and the justification of the

Thai-CDC study is the use of a placebo group even though the HIV infected pregnant women in Thailand were not, in general, offered ZDV at the time of the study.

While I appreciate and in some other settings concur with the use of a placebo group when in a more affluent country effective agents are available, I nonetheless also believe that the goal is to provide the best known treatment to the participants in a trial -- excuse me. I nonetheless believe that the goal of providing the best known treatment to participants in a trial is a laudable one.

In this particular setting, an alternative design was available -- something akin to the Chiang Mai study -- that addressed a somewhat different scientific question than the Thai-CDC study but without having to resort to a placebo group.

For me, the potential scientific limitations of the Chiang Mai Trial, that is the issue of whether ZDV is effective for the subtype E of HIV and the fact that this trial cannot demonstrate the efficacy of either short course or long course relative to no treatment, those limitations are real. However, the Thai-CDC study also had scientific limitations. Most notably, its inability to tell us about the relative efficacy of the short course ZDV regimen compared to the

longer ACTG-076 regimen. And, on balance, I find the practical scientific utility of this trial, i.e. the Thai-CDC Trial, to be less than that of a Chiang Mai type design from a scientific point of view.

Since the latter, the Chiang Mai type design, avoids ethical issues of using a placebo, I reached the conclusion that interests -- that the interest of the study participants would have been better served if a Chiang Mai type design without a placebo group had been used. Indeed, I feel sufficiently strong about this that I would not have been able to serve as an investigator or DSMB member in the Thai-CDC study.

Let me make some additional comments about the ethics of this situation.

One: After children in both of these studies were born, the mothers were not offered long-term treatment with combination antiviral drugs even though the value of these drugs had been demonstrated in scientific studies. Does this violate the principle of offering all participants in a trial the best possible treatment? How then do we ethically justify this?

I must confess that I find this a very difficult issue to come to terms with. Instinctively, I do not have ethical problems with either of these

studies as regards their failure to provide long-term combination antiviral therapy to the mothers. However, at the same time I cannot really identify a compelling ethical argument to justify this.

I say this to point out the real complexity of the issues that can arise in these studies and why I believe that it would be inappropriate for an organization such as NIH to adopt a dogmatic view such as never using a placebo when a known effective therapy exists when funding and sponsoring international trials.

Two: One issue that I have not raised is the ethics of including a ZDV arm in these studies. In my opinion the fact that ZDV is known to be effective is not a sufficient justification ethically for its inclusion in an international trial. As others have noted, it is also necessary that a new treatment has some realistic hope of being implemented in the host country if the study demonstrates its efficacy.

In the case of Thailand, which is a rather affluent country by many standards, use of ZDV on a widespread basis is realistic. Thus this is not the case, at least in the foreseeable future, in other countries such as the neighboring country of Cambodia where the total per capita expenditure for health care is extremely low. In this type of environment it is my

view that a case needs to be made for the value of a trial that involves ZDV or other interventions of a similar cost.

Three: The ethics of the Thai-CDC study have been debated in the medical and scientific literature and in many less public settings. I find it interesting that very little of the public debate has focused on the issue of how the ethics of a study can change with time as new information becomes available and standards of care evolve.

The DSMB for a clinical trial bears enormous responsibility in monitoring the study results and external developments to ensure that the best interest of the patients are being safeguarded. Based on my understanding, the Thai-CDC study was monitored in the U.S. by an NIH appointed DSMB that only included one Thai representative and this DSMB met in the Washington, D.C. area. It is not clear to me that the Thai government had access to or was closely following the interim results of this study. I just do not know.

While I have the utmost respect for the NIH, who has led the way in advocating the use of independent DSMB's for the interim monitoring of trials, I believe that we can make improvements in the monitoring of trials that are sponsored by the U.S. and conducted

elsewhere.

What is clear to me is that (a) the decision to terminate a study following an interim analysis also often involves ethical considerations; (b) it is important that the ethics be fully aired and understood by qualified representatives from both the sponsor and the host country; and (c) that if either group, i.e. the sponsor or the host country concludes that the study is no longer ethical then the study should not continue in its present form.

However, how to structure a DSMB or more generally the interim review of such studies to achieve these goals is complex and to me not clear. This is one area where I think a great deal of additional discussion is needed.

Let me end by making a few suggestions on steps that can be taken to assure that international studies supported by the NIH or other organizations have high ethical standards.

First, as specified in one of the Helsinki principles, rigorous external review of study design should be encouraged with special emphasis on ethical considerations and of alternative designs that might avoid certain concerns, ethical concerns. Such review should be made by qualified persons in both the host

country and the country of the sponsor.

Secondly, the interim monitoring of such studies should be done by a qualified DSMB with appropriate representation from both the host country and sponsor and perhaps others.

Finally, because some host countries will have little experience in the design and analysis of clinical trials and the responsibilities of DSMBs, training on the principles of clinical trials, including the ethical considerations involved, should be given a higher priority. And by "training" here I mean NIH supported training of investigators from developing countries where we plan to do studies.

In closing, I wish to say that I hope my comments have been helpful to you in identifying and framing some of the ethical issues that arise in international studies. I would be glad to discuss these further. Thank you again for inviting me.

DR. SHAPIRO: Thank you very much for coming and thank you very much for your remarks.

I think what we will do today, otherwise we will never get to Dr. Chase, is just hear from each of the panelists first.

And members of the commission just note their questions down and at the end we will question any of

the panelists.

Dr. Dixon?

DENNIS DIXON, Ph.D.,

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AND INFECTIOUS DISEASE

DR. DIXON: I thank the commission for the opportunity to participate in this important meeting. Ethical concerns arise often in designing clinical trials, whether the trials are to be conducted entirely in the U.S. and other so-called developed countries or are sponsored by the U.S. and carried out jointly with one or more so-called developing countries.

Some concerns appear to be harder to resolve in the international setting to be sure, and among those is choice of control group in a comparative clinical trial. Most of my comments will focus on that particular topic but time permitting I will mention briefly some other aspects of international trials that clearly have ethical components.

Whether an experimental treatment regimen will be tested against active control or placebo control can be a difficult and even controversial choice. In reality the focus should be on what is currently available in the population where the study will be carried out and whether the research goal will be to

improve the chances of a good outcome relative to available alternatives or to maintain current prospects while reducing the risk of side effects. Once those matters are clear, choice of trial design is usually straightforward.

The hardest case is when a treatment is already established for a condition related to but not identical to the one to be studied in the trial being planned or in a different setting. Then it may not be so clear whether the usual criterion that placebos cannot be used if evidence exists of an adequate treatment actually holds. The investigators must judge whether to extrapolate the previous results. Let me give a specific example.

Suppose a drug like ZDV in a particular regimen, like the long course, has already been shown to reduce the rate of transmission of HIV from infected mothers to their babies in a population in which breast feeding can be effectively discouraged. It is possible that the regimen will not be effective in a setting where breast feeding is the norm because transmissions through breast milk may offset those prevented up to and including the time of delivery.

Thus evidence of benefit in a nonbreast feeding setting may or may not constitute evidence in a

breast feeding setting. Other factors also have to be considered in deciding what the appropriate control intervention should be.

Similarly, elective cesarean section appears to reduce the risk of mother-to-infant HIV transmission. In many parts of the world this information has no relevance because of the lack of access to suitable surgical facilities.

If an established treatment is available in a given setting any proposed new treatment must ultimately be compared to that established treatment. Success for the new treatment does not necessarily mean better than established treatment in terms of the primary outcome, however.

To attempt to show that an experimental treatment causes fewer side effects than an established treatment without compromising the efficacy of the established treatment, an appropriate alternative to the superiority trial design is the equivalence trial.

The basic idea is that it is desirable to reduce the frequency of side effects but this should not entail more than a modest reduction in efficacy.

Although equivalence trials have an important role in appropriate settings they have two drawbacks.

First, simple failure to reject an

experimental hypothesis of equal effects is not sufficient to demonstrate equivalence of two treatments. It is necessary to rule out by means of highly precise estimates the possibility that the experimental treatment is much worse than the established treatment.

When rejecting an equality hypothesis, it is better to do so quickly after studying a minimum number of volunteers so that the better treatment can be made available widely. In other words, one does not need to know whether the advantage for the new treatment is slim or substantial so long as it is clear that there is an advantage. To obtain the precise estimate needed in an equivalence trial to rule out large differences requires a large study.

Second, in using an equivalence trial, the investigators have to accept a degree of risk that in the new trial the established treatment will show no benefit due to sampling variability even though it was shown in a previous trial to be efficacious. In that case, it is not helpful to show equivalence of established and experimental treatments becasue neither will have been shown to be beneficial in that trial, in the equivalence trial.

Perhaps more relevant in the context of international clinical trials the equivalence design

does not seem useful if the goal is to reduce the cost of a treatment. If the putative established treatment is in reality not generally available in the population of interest, an equivalence trial of that treatment compared with a less expensive alternative treatment may demonstrate that the expensive treatment really is better but the expensive treatment is still unavailable and the inexpensive one will not have been shown to be better than no treatment leaving no practical option for general use in that locale.

Turning now to some other aspects of clinical trials that need special attention in the international setting, let me begin with procedures for monitoring the interim trial results.

Randomized trials begin at a point of equipoise regarding the relative risks and benefits of the treatments under study. That is no consensus exists that one of the competing treatments is superior. As the study proceeds, accumulating study data or new results from other research may produce strong evidence in favor of one of the treatments overturning the equipoise and leading to a recommendation that the study be stopped. Because such a recommendation goes beyond a preplanned statistical calculation, responsibility for review of interim data is often given to an independent,

of the investigators, group of experts in the clinical problem, biostatistics and bioethics called a Data and Safety Monitoring Board, whose job is to examine interim data from all the participating clinics and make a judgment about whether the study should continue as planned or change in some way.

Full host country participation in monitoring committees is a challenge only partially addressed thus far. There are conceptual issues such as the need to establish that all participating countries agree on the ethical and statistical basis for monitoring and early stopping of trials; increased communication and training among partner countries are likely to be the solution in this area.

There are also logistical challenge such as identifying host country representatives with suitable backgrounds to participate knowledgeably in the process. Many individuals with appropriate credentials will have participated in trial preparations and thus not be independent.

A third issue relates to the distinction between compensation and manipulation of trial volunteers. Even in clinical trials with a reasonable prospect of direct benefit to volunteers compensation for burdensome follow-up contacts, clinic visits, data

collection and so forth seems appropriate, especially when follow-up extends beyond the period of delivering study medications. Particularly in multinational trials it can be difficult to judge the point at which reasonable compensation reaches the level of manipulation.

In a recent example the investigators needed details of the circumstances of death to meet the primary objective of their study of tuberculosis treatments. To maximize access to the information they offered to pay for some funeral expenses and so indicated in the informed consent document. This kind of inducement would rarely be acceptable in a clinical trial in the U.S. It is difficult to assess how it would be perceived in a different country. In this instance it appears that no ethical or scientific review committee raised any question about it until it came before the NIH Data and Safety Monitoring Board for the study which asked that the payment offer be dropped.

Another difficult issue arises when methods of dealing with known side effects of an experimental treatment are unavailable in a place that otherwise would be a suitable locale for conducting a trial. Recombinant Interleukin-2 or IL-2 is under evaluation as a way to stimulate immune function in persons with

HIV/AIDS. One side effect is a transient burst of HIV repilcation, which is thought to be of minimal consequence provided there is concurrent administration of antiretroviral drugs.

After extensive discussions it was decided that IL-2 should not be studied in countries in which antiretroviral drugs are not generally available. Although the antiretroviral drugs could be provided to trial participants, of course, without the expectation that the general population could obtain such drugs, trial organizers deemed it unethical to study IL-2 in those countries.

The last situation I want to discuss is referred to as potential social harms. Participation in a clinical trial can occasionally expose individuals to nonmedical adverse consequences. Trial organizers have a duty not only to make potential volunteers aware of these but to take steps to ameliorate them.

Persons who receive candidate HIV vaccines will sometimes test falsely positive for HIV infection using standard serologic screening tests. These individuals would thus be vulnerable to stigmatization and other forms of discrimination from potential employers, insurers and others unaware of their vaccine trial participation.

In U.S. trials, various forms of documentation are provided to those volunteers who request them. In other countries documentation may actually have little utility, and other ways of addressing this problem have to be found.

In some places serious social harms would result from the mere fact of participation in a clinical trial for persons with HIV. The trial organizers may then propose to enroll and follow a cohort of similar but uninfected volunteers, who cannot contribute any information relative to the primary scientific objectives of the trial, just to preserve some degree of confidentiality about the HIV status of volunteers. While this devICH creates difficulties of its own regarding the informed consent process, it does seem a reasonable attempt to deal with the confidentiality issue.

Once again, thank you for the invitation to come today and I look forward to the discussion.

DR. SHAPIRO: Thank you very much and thank you for your contribution.

Professor Dickersin?

KAY DICKERSIN, Ph.D.

BROWN UNIVERSITY

DR. DICKERSIN: Good morning.

Thank you again for asking me --

DR. SHAPIRO: You have to talk close to the microphone.

DR. DICKERSIN: Thank you for asking me to be here this morning. I am also going to give you a little background about myself and then get into the material that I submitted to the commission.

I am at Brown University in the Department of Community Health. I am trained as an epidemiologist and I focus my research on performing and studying randomized clinical trials.

Of relevance to our topic today, I have been involved in trials using placebos and no treatment controls, as well as an equivalence trial. Although I have not personally conducted any international trials, I have served on a number of Data Monitoring Committees. One for a long term treatment trial coordinated from the U.K. and involving numerous countries.

It should not be surprising then that I basically believe in the concept of randomized trials so I am showing my biases.

Nevertheless, I have struggled -- thanks.

Nevertheless, I have struggled in each study I have conducted, monitored or reviewed with ethical issues. Trial investigators have been granted a public

trust that I take very seriously.

I have also served as a consumer advocate. While a graduate student I was diagnosed with breast cancer. I subsequently cofounded a breast cancer support group here in Baltimore, Maryland, and was a founding member of the National Breast Cancer Coalition.

I tell you this because these experiences with other patients, almost all of them nonscientists, have allowed me exposure to the patient perspective that I otherwise probably would not have had and my own views about the ethics of trials have consequently changed.

One of them is that, for example, I am no longer comfortable using the word "subject" in talking about participants in research becasue of the connotations of that word and it just surprises me -- I hear it over and over again -- why I do not hear this discussed more often.

So now I am going to read from the background paper that I gave to the commission and in the interest of time I will omit the examples that I gave. You asked for examples as well as a discussion of study design and I would be happy to go back over the examples in the question time. Mainly they point out ethical dilemmas in existing trials that are relevant to the question

that I am posing.

I have prepared a series of questions and responses that address the issues you have asked me to address and they do not cover issues specifically important to international research but are important wherever research is conducted.

A major point of what I will say is there often is no right or wrong opinion. Good scientists, doctors, consumers and policy makers are often justified in having very different opinions. Just as a clinical trial conducted multiple times will have multiple results, groups of investigators and ethical advisors will come to various conclusions about the optimal study design and ethical approach for testing a given intervention. Some of the proposed designs will be wrong but most will be all right.

In addition, it is not possible for us to judge a study design completely fairly post-hoc. Without realizing it, our own society -- our own and society's views have changed over time and influence our judgment.

Twenty yeras ago trials -- when I first began my training as an epidemiologist, trials with soft outcomes such as quality of life were widely denigrated by the scientific community and today the patient view

is considered sufficiently important that we are including patients on study sections and trial steering committees.

So the first question is when is it appropriate to conduct a randomized clinical trial? Scientists who conduct clinical trials, the Food and Drug Administration, and others probably agree that when there is insufficient evidence that a new or existing intervention is efficacious a randomized trial is appropriate. Even within these groups of people, however, it is unlikely that general widespread agreement could be reached regarding under what conditions a new trial of the same intervention and the same disease would be warranted. That is when are populations, settings, dosages or outcome measurements sufficiently different to merit a new study?

Randomization is necessary to ensure that two or more groups to be compared are similar in every known and unknown way. It has been well established that comparisons of two nonrandomized groups tend to show much larger treatment effects than randomized populations.

Doctors and patients are less likely than scientists to agree on the appropriateness of a randomized trial since their perspective is oriented

towards the individual and not populations. I think that can be the fundamental difference that we are hearing today is this orientation towards individual rights versus the society or community view. Thus only sometimes would one expect there to be widespread general agreement about when a randomized trial is ethical.

I give an example about an ongoing trial in the U.S. and one that has been conducted in men already but it was decided it needed, also, to be conducted in women, and that is one issue. And it is also being -- the Data Monitoring Committee has agreed to carry this trial past an expected endpoint of myocardial infarction, which is well-known to be better in one group than the other, to a cardiovascular mortality endpoint because this is what they want to learn about.

When is it appropriate to compare a test intervention to a placebo or no treatment? It is well established that persons given a test intervention will experience both positive and negative effects of that intervention according to their expectations. Thus when there is no established intervention for a health condition an investigator will typically compare the test intervention to a placebo assuming both groups will experience similar positive and negative effects related

to their expectations, that is a placebo effect, and allowing the true effect of the test intervention to be measured.

Sometimes it is not possible to use a placebo. For example, in the case of a trial testing a new surgery. Regardless of whether one uses a placebo or a no treatment as the comparison group, the major area of disagreement is whether another intervention has been established as efficacious. Even when randomized trials have been unable to establish a clear benefit of an intervention, many doctors, patients and others will insist that it is unethical not to offer it.

I give an example of a new method of detecting lung cancer and there is a current debate ongoing as to whether the comparison group should be no method of detection or an x-ray which has not been shown to be beneficial, but people still consider it the standard of care.

When is it appropriate to compare the test intervention to a standard intervention? When it is clear from randomized trials and other studies that a given intervention is beneficial compared to placebo or intervention it is appropriate to compare a test intervention to it.

Some would argue, however, that when the

established intervention is not standard in a given setting it is ethical to compare the test intervention to a placebo or no intervention. In addition, some interventions become standard without adequate evidence and some may consider it unethical not to offer the standard of care even if the standard has not been shown scientifically to be beneficial.

I give the example of breast self-exam compared to mammography even though in studies in China in randomized trials breast self-exam has not been shown to be useful. We could never do that trial here and yet its results are very useful here.

When is it appropriate to conduct an equivalence trial? Sometimes one wants to know that two interventions have similar benefits, not that one is superior. This might happen if one of the two interventions has fewer side effects, is less costly, involves a simpler regimen, or is more likely to encourage compliance.

Typically one is searching for small to moderate effects in randomized trials and thus it is very difficult to differentiate between results showing no difference between two interventions because there is truly no difference, that is they are equivalent, and possibly unreliable results showing no difference, that

is the sample size may have been too small to allow a reliable estimate of a true beneficial effect.

Typically an equivalence trial would define equivalence as a difference between two interventions that would be clinically unimportant or unimportant to the patient. Again it is unlikely that general agreement could be reached as to when such a difference is unimportant.

I give an example of an equivalence trial that we are conducting, which to tell you the truth we have given up on it being an equivalence trial because it is really so difficult. There are multiple outcomes that are of interest, not just the primary outcome and it is a very difficult kind of trial to do although I do not think it has -- I disagree with some of the statements about the sample size implications and so forth.

When should we not conduct a clinical trial? Again, scientists, doctors and patients are likely to disagree about when there is sufficient evidence to warrant interventions being considered efficacious. This is probably related to differences in understanding of and weight attributed to population versus individual needs and the relative value of data and experience.

Even within a group of scientists, however, there is often ample disagreement about whether it is

appropriate to conduct a randomized trial. This may be because of variations in standards of care in a community, individual and community uncertainty about an intervention's value, and the practicality of administering the test intervention even if it is shown to be efficacious.

I give an example that is rather famous now of thrombolytic therapy where trials were carried on well beyond the time when thrombolytic therapy was shown to be efficacious in preventing secondary myocardial infarction. Nevertheless, because there was uncertainty in the minds of some people and some communities it was deemed ethical by some to continue doing these randomized trials.

So I would like now to present a series of principles that are guided by design issues for conducting clinical trials internationally for your consideration.

First, trials should be conducted when investigators believe but do not have reliable evidence that one intervention will be better than another. In the case of a planned equivalence trial one intervention would be deemed better because it is less costly or have fewer side effects.

Research should only be conducted in a country

if the results will potentially directly benefit the population.

Trials should not be conducted in a country just because it is easier to obtain approval by an ethics committee or informed consent or because there are cost savings related to a particular system of health care.

They should be conducted in a given country because the investigators have good reason for testing the intervention in the population and it is expected that the intervention will be used in that population.

Research studies comparing treatments that are nonstandard in the sponsoring country, and we had the example today of placebo control versus the short course of zidovudine from maternal transmission of HIV, are possibly -- are acceptable in a host country if there is general agreement by the investigators in the host country that the control represents a standard of care or typical care in the population.

The test intervention -- sorry -- in the population if the test intervention is one that is feasible or in use in the host country and individuals in the host country make a commitment that the test intervention will be applied to the trial participants and more generally over the long term if it is found to

be beneficial, that is the test intervention should be applied to the people who have been in the trial and to the general community over the long term.

If the intervention -- that is the regimen as a whole, not just the drug -- tested is feasible but is too costly for it to be generally used in the host country once it has been shown to be efficacious, the sponsoring country should bear some responsibility for supporting its subsequent distribution and use.

Research conducted internationally should involve local investigators and ethics committees at all stages of planning, decision making and implementation in a meaningful way.

Health advocates representing a constituency should be involved in all stages of the planning and decision making for a research study, including Ethics Committees and Data and Safety Monitoring in a meaningful way.

Patients in trials should not be denied care they would otherwise have had.

Patients have the right to participate in a well designed research study where an intervention they seek is offered.

And, when possible, products used in the research studies and in subsequent distribution programs

such as drugs should be manufactured locally.

Similarly, local staff and support should be included as much as possible and as acceptable to the local decision makers.

I am grateful to you, the commission, for devoting your time to these important issues and look forward to your report.

DR. SHAPIRO: Thank you very, very much.

Dr. Chase?

GARY CHASE, Ph.D.,

HENRY FORD HEALTH SCIENCES CENTER

DR. CHASE: Thank you. I am pleased and honored to be able to appear before this commission.

I am a medical statistician from Southeast Michigan and I have about 29 years of experience in a hospital based environment. I want to mention a little bit about my background because I think it is relevant both to my point of view and to the fact that I am taking a slightly different approach from my three colleagues in presenting my views about this problem.

I have been a chief statistician at two institutions, Georgetown and Henry Ford, and my principle professional duties for the last six years have been to coordinate, hire and recruit other statisticians and epidemiologists.

I served for four years on the Recombinant DNA Advisory Committee. I was Acting Chief Statistician of the Armed Forces Institute of Pathology. I have served on my own IRB at Henry Ford hospital and I just completed a three-year term as a civilian advisor for the Military Health System's MHS-2025 Planning Group for Military Health Systems in the 21st Century.

I want to talk about four points, all of which I think reflect the structure of biomedical research as viewed by statisticians serving on IRBs and the implications of these new -- this new information about international clinical trials in terms of what we know or what we need to know about the processes of approval for these kinds of experiments.

I want to dwell on four points:

One: I want to talk about the optimal treatment language of the Declaration of Helsinki, and I am going to give you a little bit of local information about how it works where I come from.

I am going to talk about the argument that placebo controlled studies are good science and, therefore, it is okay to do them even with these reservations.

I am going to talk about my desire that the controversy about this 076 equivalence trial and placebo

trial in Thailand be reframed.

And I am going to talk about -- a little bit about the scientific validity of placebo trials.

So first about the optimal treatment clause of the Declaration of Helsinki. I have never seen this violated and in attempts to do so by investigators where I have reviewed their protocols all the groups that I have ever been on have extremely forcefully addressed attempts to violate the best treatment language of the Declaration of Helsinki.

I do agree -- my framework is different from Dr. Wolfe's but I do agree with his general point that in a hospital environment, which is what I come from, the distinction between a patient and a research subject should be practically nonexistent. There are only a few circumstances where that really makes sense and so we treat these folks as patients who are entitled to the best treatment.

Furthermore, my IRB, and I inquired extensively about this, treats the optimal treatment clause of the Declaration of Helsinki as law even though it is not binding. It is not legally binding on them. They do treat it as law.

I looked at -- I asked some staff members from a neighboring IRB at a very prestigious institution

about the same issue -- this is still in Southeast Michigan -- and again they treat it as law.

Why is this important? Because obviously to accommodate to these international situations it has already been proposed to bend the optimal treatment language of the Declaration of Helsinki.

I think the main argument that people made that I talked to is that it protects the integrity of and people's confidence in biomedical research. It is very difficult to export a standard of treatment of human subjects that is not ultimately going to come back home to the United States. I think many of the trials that have been the subject of these controversies, as has been mentioned from my colleagues, would not have been performed in the United States and, indeed, could not be.

I actually do not like the term "clinical trial" that well. I prefer the term "medical experiment" and the reason is that despite my earlier point that a patient in a medical experiment or clinical trial should be treated as a regular patient, we need to make it clear to the subjects that it is an experiment and that what they are doing is helping us to develop new knowledge.

Now on the argument that good science

"justifies" the use of placebo such as in the CDC-Thai experiment, I am not sure it is good science and I will come back to that later but even if it is good science I think I need to make two points.

One is that as a statistician I have always believed that good science is secondary to the rights of subjects in medical experiments. There is just no conflict in my mind because in my view the biomedical community that I belong to has already made a ranking of those principles that is inviolable so there is no need to discuss whether you want to bend this principle to another principle because as my bioethics chief that I talked to said at my institution:

"Is there a principle that is more important or should outweigh in any circumstance the optimal treatment clause of the Declaration of Helsinki?"

She said, "No, there is no such principle."

I said, "Yes, I am glad you told me that because that is what I wanted to hear."

I do not think I have ever had to do bad science or not do good science because I held that as a supreme principle.

My second point about that is that I am viewing this good science argument again from a hospital-based perspective. I interact with physicians

on a daily basis. I drink their coffee, you know, and as Kay had well put that she understands what it is like to be a patient, I think I understand what it is like to be a doctor.

I am not a medical doctor but I think I understand what goes through their mind and also the kinds of pressures that my medical colleagues may be put under, whether diplomatic or commercial or otherwise or academic, to engage in an experiment that would violate optimal treatment guidelines. I know those pressures exist but we resist them and I think what we come down to is, yes, this is our patient, a Henry Ford patient, and our IRB chair stated to me very specifically, and it is in my written statement, 'that, "The venue of a medical experiment is not the deciding criteria for withholding or administering the best effective treatment. It is the treatment that we would give to our own patients."

That is the standard we want to use and even that standard is not always obtainable in a city like Detroit where we have many poor patients and we have agonized over treatments whereas, Dr. Lagakos has mentioned this is even in the United States, the good drug is not necessarily available to that patient after the trial is over and it has been approved efficacy. I

think that is a significant ethical problem in American medicine but I do not have the solution to it.

Thirdly, in terms of reframing the controversy, a number of people that I talked to, and I agree with this point of view, would like to know more about the process of how this placebo study got approved in the first place because I and a lot of people I talked to did regard it as pretty far beyond the usual. I had never seen anything like it. I was very surprised that anybody agreed to it and so I want to know how it happened.

I would like to know about the Common Rule and whether the Common Rule covers a situation like this. Does it need to be amended or strengthened because as I understand it, the Common Rule is more binding on American IRBs than the Declaration of Helsinki. I could be wrong about this but you will obviously know the answer.

I also think empirical information about this would be very useful. IRBs could be surveyed. Maybe they already have. They could be queried through the use of vignettes. Historical experience could be sought through documentation of placebo trials that have been proposed when efficacious treatments have been available and the arguments of IRBs could be researched.

Obviously we have to respect the privacy of institutions but, for example, our IRB audio tapes its meetings and we could recover the discussion and reply. Probably we would have to review it, but could supply salient details of an oral debate about a proposed placebo trial.

My fourth and last point is that I do not know really enough. Even though I am a trained statistician I do not really know whether the information obtainable from a placebo trial is unique or qualitatively different from other information that might be obtainable through a route which provides more protection to the human subjects.

I just do not know the answer to that question but I also think that some of the people that approve these placebo trials did not know the answer and that in some cases there may be a reflexive or knee jerk response on the part of people who review proposed medical experiments, because I know from being a medical statistician that truth or orderly procedure in medical statistics is sometimes very highly codified to the extent that new knowledge available from other branches of statistical inference does not readily penetrate into the literature or into people's thinking.

A classic example is this over emphasis on

hypothesis testing and the p value that is kind of like something that we are burdened with and we can never really shake.

I agree with Dr. Lagakos' point also on this that I think there has to be enough flexibility left in these rules to allow for departures from normal. I think the departures we are talking about may be a bad case to make rules about it because they are so far out of the ordinary.

There are other cases such as the ones cited by Dr. Dickersin that really do bring up dilemmas such as the problem of setting the agreed amount by which an equivalent treatment could be different from the standard and, you know, I think Dr. Lagakos is correct that IRBs and investigators need enough wriggle room to be able to design a good trial.

However, getting back to my first argument that does not weaken my point that the optimal care provision of the Declaration of Helsinki should be a strong principle. A principle is almost never obeyed 100 percent of the time by everybody but sometimes it is just important to say we value this principle and we want to export it as well as using it here.

About this issue of exporting a clinical trial, I have been struck by a lot of the arguments

about the standard of care and about the difficulty of taking one piece of biomedical research, that is the controlled clinical trial, and putting it in another context where the other pieces such as the infrastructure are just not available.

And the analogy I came up with was, what I call the flutes and oboes, that if you asked a symphony conductor to perform a Beethoven Symphony in another country but then the inviting person said, "Well, we only have room for the flutes and oboes on the stage. So bring the flutes and oboes." And he said, "Well, I cannot do the symphony." But the person would say, "Well, these people have never heard a concert. This is better than nothing." Clearly it is not.

So, you know, I -- and again I do not know the answer to this but I do not -- I really think that some of these dilemmas might come from the problem that you are trying to take one bit of biomedical research, which is an integral whole, highly developed with your hospitals, your labs, your ethics part, your statistics part, all of the parts of the policy, public policy review.

If you try to disaggregate one piece of it and then plunk it down in another country with all these different cultures and languages and the standards and

role of public officials, I do not know whether what you come up with is science or is it good science or even if it is science because to me it is almost as if you took one bench of test tubes in the lab and you put it somewhere else but you did not take the centrifuge or you did not take the -- you know, the pad that you wrote down the results on. So I just -- I think that is an open question but I think it deserves a little more discussion.

So, in summary, I think my views here really have to do with the impact of these unusual examples on the structure of review of experiments, the role of statisticians and other American scientists, the need for more empirical and historical information, and finally, of course, use of information to form policy for the future, which reflects our values as a nation.

I understand cultural relativism but we have a culture, too, and I want to be able to be happy about that culture when I go to another country and say this is what we stand for and this is what we want to export even if in all cases we cannot bring it to your country.

Again I want to thank the commissioners for listening to my comments and I hope that they will be useful.

DR. SHAPIRO: Thank you very much and let me thank all of the participants this morning.

Let me now open it up to questions.

Dr. Lo?

DISCUSSION WITH COMMISSIONERS

DR. LO: First, I also want to thank all four of you for your very thoughtful and stimulating presentations.

In listening to you I was struck that a number of you raised the theme that there can be honest disagreements between reasonable people and you talked about how scientists may disagree and so forth.

It also struck me that participants, to use your term, Dr. Dickersin, may disagree with clinical trialists, IRB members or ministers of health in developing countries. I would like to come back to the question of how can we find out what the views of participants in international clinical trials are and my issues are how can they be involved in the design of studies in IRB review and in DSMBs.

I know this is done, and perhaps Dr. Dickersin can talk about this, quite often in AIDS clinical trials here, but is this a feasible procedural model for sort of trying to make sure we do not end up designing a study or proving a study that is just ethically

unacceptable and we just have not heard from the participants who would tell us very clearly that it is so because we are so sort of blinded or limited in our vision?

So if you could sort of address that issue, actually all four of you, it would be helpful. That would be useful, particularly in the international context, which I think is the biggest challenge.

DR. DICKERSIN: I am very optimistic about it. My particular experience relates in two areas to the breast cancer advocacy community but also with the Cochrane Collaboration, which is an international collaboration trying to pull together the results of randomized trials for all of health care, all fields, and has a consumer network as an integral part of the whole design of that collaboration.

In the context of breast cancer, and we have now over the last four years expanded to international advocacy, we have something called Project Lead in this country that we have trained people from all over the world and they have started their own programs like that. It is a science program that is four days long and held four times a year in this country and, as I said, other countries as well that does not aim to train advocates to become scientists. It just gives them a

grounding in the language and concepts.

For example, we have one day of epidemiology, one day of basic science and so forth so there is some grounding and these people go on to serve on study sections and committees and so forth.

In terms of the Cochrane Collaboration, now the breast cancer and AIDS model, of course a very special situation where advocates have been much more active than other fields. But the Cochrane Collaboration is really promoting a consumer network and, for example, the AIDS advocacy community is in full force there especially from Africa. And this year there were, I think, 10 to 12 African AIDS activists there who were training themselves, learning about scientific concepts, and even more importantly since the meeting is predominantly investigators and those -- and policy makers, they are bringing their views very forcefully to us and so there is an exchange of ideas.

I do think it is possible but I think we have to form partnerships with mutual respect for something to happen that is useful.

DR. DIXON: I have very little to add to that except that it is something we struggle with. It has been our practICH for the Data and Safety Monitoring Boards that oversee our trials to involve host countries

but it has been a difficult process and I am not sure that we have any idea of how to involve those beyond the scientific or political communities in those countries.

I mean, the paths of communication that are there immediately available to us go through the investigators in those countries or the Ministries of Health and that is problem we need some new ideas about, I think. I do not -- I certainly do not have the answer. I agree that it is a very important obstacle at the moment.

DR. SHAPIRO: Jim?

DR. CHILDRESS: In some ways this is just a faint echo of Bernie's comments and question.

First of all, high praise for all of the panelists and their contributions to our deliberations.

But then the question moving beyond how we can get views of participants, given the recognition of disagreement among the people of good will, how can we from a standpoint of process in deciding whether to go forward with a trial or how to design a particular trial, how can we resolve that disagreement or decide how to proceed in the face of the disagreement?

And so moving beyond the participants, and how we might get their input, what kinds of thoughts do you

have about the larger process and the kinds of procedures we might follow in the face of this disagreement? Any thoughts you have there would be helpful.

DR. CHASE: I like that question. I think this is an unusual controversy because, as I think Bernie suggested, I found that a lot of people that I really have a lot of respect for, like Varmus and Satcher and a couple of bioethicists who are involved with AIDS research are on the completely opposite side of the spectrum that I am and I guess I am moving from confrontation to collaboration.

I think when you have people that are obviously well-trained and well-educated that have a totally different point of view and you have spent 30 years agreeing with them on everything else of this magnitude, you have to sit back and think about a process for resolving it.

I am a negotiator. I feel like that I will go to the table with a principle that I think is very important and I want that principle to remain primary. They are going to the table with other -- and I also might say that I -- although I agree with Dr. Wolfe's starting premises, I do not agree with his approach that sort of tends to cast this as heroes and villains. I do

not think drug companies are these corporate thieves who are out to rip you off.

They have -- are starting from a different set of assumptions but in our IRB we often have to work with a drug company to get them to change a trial design and sometimes they will do it.

So I think when you sit together if you have this climate of people respectfully disagreeing and you preserve that each person brings his or her own issues and, you know, hopefully, you get to a consensus.

DR. DICKERSIN: Yes. I guess I would say that to some extent some of the process is already happening in that we have more than one study and so we have many different opinions out there and it is being expressed in different ways and that is natural. I think the process should always be public and that has also been true of things for the most part that happen in this country and we should be keeping things public and all the information out there that we can get out there.

And then, finally, I think there may need to be new principles established in addition to those that we already have that deal with these complex issues having to do with international studies but, also, I think the idea of these multinational drug companies has raised some new issues.

DR. SHAPIRO: Anything further, Dr. Dixon?

DR. DIXON: No.

DR. SHAPIRO: Ruth?

DR. MACKLIN: I, too, want to thank the panelists.

I had a question for Dr. Lagakos but since he is gone -- wait. Am I permitted a different question to more than one person rather than one question to all?

DR. SHAPIRO: Yes.

DR. MACKLIN: Because it will not take any longer. Okay.

Let me ask then -- start with Dr. Dickersin because you used similar words to those that Dr. Lagakos used in his presentation and it is of some interest to this commission because we are going to be working on some recommendations.

You used the phrase "a treatment that has been established as efficacious." Dr. Lagakos used the word "established effective treatment." Later on today this commission is going to be looking at some similar wording.

So if you could --

PROF. CAPRON: Where are you reading from?

DR. MACKLIN: Pardon?

PROF. CAPRON: Which of the points are you

reading?

DR. MACKLIN: I am now asking Dr. Dickersin.

PROF. CAPRON: Which page?

DR. MACKLIN: I am sorry. On page one.

PROF. CAPRON: Thank you.

DR. MACKLIN: Page one. No, I am sorry. I am sorry. It is page two in the first paragraph. You referred to an established intervention and also an intervention as established as efficacious. Now, of course, we know that if it is an approved drug the answer is simple but there are a lot of other interventions other than approved drugs and, of course, you gave the example down below of the self-examination for breast cancer as something that is "standard" but not "proven" and then you showed the Chinese trial.

So my question to you, given that background, is you say that trial could never have been conducted in the U.S. as it would be seen as unethical. Now it may have been seen as unethical but I take it from your argument it would not be unethical.

Now would it be seen as unethical because it was established as a "standard" and yet without adequate testing and, if so, is there a way of doing the trial in the United States, for example, or would this destroy the science, which goes back to Dr. Chase's question,

for example, choosing women who do not undergo self-examination of breast cancer or is that a biased sample and, therefore, would be unacceptable for scientific reasons?

DR. DICKERSIN: Well, first, I am a trialist so I think almost all trials if they are ethical are possible and that would include the self-exam trial. I would like to try it.

I do not think that it -- just because you have a select population in that trial, say of women who do not already do self-exam, does not mean the trial itself would be biased. All trials include a select population. The first concern is does the trial itself have internal validity and randomization helps with that. Then how applicable are the results of the general population is a second question but the first has to do with the internal validity.

I was just there and elsewhere talking about the difference between standard treatment or standard intervention, something that is considered standard medical care versus somethng that has been established. I also used x-ray to identify lung cancer, say, in smokers. It is considered the standard of care. We probably will have to use it in an upcoming trial looking at this new type of scanning method but it

certainly has not been established as efficacious.

DR. MACKLIN: So not everything that is a standard has been established is efficacious?

DR. DICKERSIN: Right.

DR. MACKLIN: A quick question of clarification to Dr. Dixon. I did not understand this and it is my ignorance so forgive me but on page -- on the first page of your written testimony down -- it is about a quarter of the way up the page, the paragraph that begins "Second, in using an equivalence trial the investigators have to accept a degree of risk that in the new trial..." and this is the part I did not understand, "...the established treatment will show little or no benefit due to sampling variability." Again it is my ignorance. If you could just --

DR. DIXON: No. It is just the issue that the purpose for including the so-called established in the trial is to have concurrent controls.

Sampling variability may produce in the new trial a circumstance in which the results with the "established treatment" do not really look very impressive. Maybe there would not even be a placebo in that particular study. That is the essential reality of sampling variability.

In that case this trial was not designed to

establish the benefits of that treatment but if it is, itself, not clearly better than placebo in that study then establishing the equivalence of some other treatment to it in that study does not get you anywhere.

DR. MACKLIN: Okay. I think it is clear.

DR. DIXON: I am sorry it is --

DR. SHAPIRO: Alex?

PROF. CAPRON: Well, I wanted actually just to suggest that that may be a point which comes out in the article by Robert Temple, which we have in our books, where he discusses, beginning at page 269, the problems in interpreting active control equivalence trials and it is my understanding -- and I would like a response on that but this is not the question, this is responding to Ruth -- whether the -- whether it does not just come down to sample size and cost.

In other words, with an active control one would -- to have statistically powerful results -- would probably need a larger sample size and it would be a longer more expensive process. Is that a fair characterization or not? Is it just impossible? That is how I read Dr. Temple's piece.

DR. DIXON: I think that that -- it is a tricky business to try and focus just on that narrow an issue. It does turn out to be the case that equivalent

studies are larger generally than superiority studies but the reason is because they are not addressing the same question.

PROF. CAPRON: Right.

DR. DIXON: The reason is that in the equivalent study it is necessary to get a tight estimate, a much more precise estimate of the relative effects than it usually would be in the superiority study.

So I do not -- I would not say that equivalent studies are at a disadvantage just because they are larger. It is just a fact that an equivalent study would be generally larger because it is trying to address a different question.

PROF. CAPRON: This is worth exploring just a little bit it seems to me.

Your present answer, as I undersatnd it, is that where you are looking for smaller differences or where you expect to find smaller differences, you are going to need a larger number simply to have statistically measurable difference, whereas if you are comparing to placebo the thought is given the 30 percent placebo effect that we seem to get no matter what we are doing or something, you will be -- if you have something that is going to be efficacious you will be able to see

it with smaller numbers, that the effect -- the expected effect is just larger. Is that wrong?

I mean, you would need a very small trial to see whether penicillin was effective in 1950 against pneumonia or something. I mean, you do 10 people and -- anyway it is something in which you have a dramatic effect --

DR. DIXON: Yes.

PROF. CAPRON: -- the number of subjects you are going to need is just very much smaller. And when you are doing the equivalence trials you are likely to be finding very small differences so you are going to need a large number. Is that a wrong headed view?

DR. DIXON: No. That is basically correct.

PROF. CAPRON: Okay. That is fine.

DR. DIXON: That is basically correct.

PROF. CAPRON: I had -- I actually had --

DR. _____: But that is a different --

(Simultaneous discussion.)

PROF. CAPRON: Yes, it is.

DR. DICKERSIN: Yes. And you have chosen the exact example where there is a huge difference between penicillin and a placebo. There is a really big difference. And in most clinical trials your standard treatment probably is not much better than placebo.

PROF. CAPRON: Yes.

DR. DICKERSIN: We are looking for small differences most of the time.

PROF. CAPRON: Right, okay.

MR. HOLTZMAN: You forgot the other question, Alex.

PROF. CAPRON: Do you want to ask it then?

MR. HOLTZMAN: Yes. You framed it. And that key question is: in the case of those drugs where there is not a huge difference between placebo and the standard of care, if you then go to do an equivalence trial, is it the case that invariably, forget the size, that because of sample variation even if you show that X is equal to Y so to speak, you will not have shown that either is better than the placebo.

PROF. CAPRON: The placebo, right.

MR. HOLTZMAN: And that is not a function of cost or size. It is just epistomologically a fact of the nature of the case.

PROF. CAPRON: I wanted to explore one of the issues that has emerged this morning, which is this question of the obligation of the researcher as opposed to the research project to treat participants as patients or with the equivalent level of concern for their welfare that you would have for a patient.

I know -- and someone will tell me who this is but there is a -- one of the sages tells us that the measure of a fine mind is the ability to hold at one time two contradictory thoughts. I tend to think of this in fashion terms that it does not look good for most people to wear two hats at once.

I come to the question of whether it is a criticism of a research trial that the researcher in charge of it places as her or his primary objective the discovery of knowledge. The answering of the hypothetical, the issue, answering the hypothesis, which lies behind the trial.

And, if so, if the issue is not asking that person to instead have the welfare of the individual subject as his or her primary goal, which might cause them to do things that are going to undermine the experiment but rather to say somewhere in the design there should be someone who has only the subject's concern and not the research as their primary concern who is available to the subject and who plays that role.

Now I just want to get your response as to whether you think the former view that -- I think Gary Chase was agreeing with that quote we saw from Dr. Kim that Sid Wolfe put up that it is the obligation of the researcher to have the subject's welfare as its

principle objective.

DR. CHASE: Well, I would agree with -- I agree --

PROF. CAPRON: You are going to have to use a microphone.

DR. CHASE: I agree with -- I agree that that is my point of view. However, I would phrase it slightly differently because I would phrase it more as that the primary duty to the subject is a constraint in which the need for science operates. Analogously, my goal in working may be to obtain money and professional satisfaction but I do not do it by robbing banks.

In other words, so if you take the optimal treatment provision or the responsibility of the patient as a constraint rather than saying this is a conflict of principles, this is a boundary condition. So within that boundary condition -- and in my view it is the role of IRB's to socialize researchers so that they keep that upper most and treat it as a constraint, within that constraint then go for the knowledge. But I would not like to see it happen where you have to weigh those in conflict, which this situation is going to engender. That is -- you know, I hope that is helpful.

DR. SHAPIRO: Other comments?

DR. DICKERSIN: I guess I did not agree with

that comment and I certainly do not agree with the principle that the investigator should say, "What if it were my wife or whatever?" I actually find that fairly offensive because the patient can speak for him or herself and it is -- and the doctor's role is to be the doctor.

And I think that is why you need a group at the table so we each bring our specialty. Often I have been asked to sit on boards as a consumer advocate, NIH, whatever. I say, "Well, at NIH, you know, maybe in the early days of the advocacy movement I was a consumer because that is all they would let at the table was someone who was also a scientist." But now they let real consumers at the table and that, too, should be there. Someone who is not coming with her clinical trial hat. So we will wear more than one hat but we have to -- we have to wear that one hat when we are representing that role in the research we are doing.

DR. DIXON: I am not sure I have a great deal to add here either. I would just say that part of the purpose -- part of the rationale for having Data and Safety Monitoring Boards to, in a confidential way, examine the emerging data from a clinical trial is so that the individual investigator does not have to deal with a situation in which trends are beginning to emerge

not strong enough to settle the issue but maybe strong enough to disturb that individual's degree of equipoise.

And the -- in effect, the investigator agrees for the purposes of this study he will delegate -- designate the responsibility for monitoring the emerging results to this other group of experts so it is a tough situation.

DR. SHAPIRO: Thank you.

Eric?

DR. CASSELL: Well, I have a couple of comments.

First of all, Dr. Chase, you have got to be careful about analogies. They always reach up and bite you.

DR. CHASE: I feel one --

DR. CASSELL: The orchestra that Beethoven composed his symphonies for was considerably different and by our present standards primitive so I do not think he would object to our bringing our orchestra back to Beethoven's time. I think he, while he could still hear, would be very pleased and when he could not hear he would have been glad at the applause.

DR. MACKLIN: If it were just oboes?

DR. CHASE: Yes, that is a good point. I

mean, the whole -- for example, with today's horn you would not have to change horns during the -- when the key changed.

DR. CASSELL: Yes.

DR. CHASE: That is right.

DR. CASSELL: So I am a little concerned -- I am still concerned about this issue of the investigator -- oh, no.

(Simultaneous discussion.)

DR. CHASE: Those cell phones can really get to you.

PROF. CAPRON: That thing is reaching up and biting you, Eric.

DR. CASSELL: That is the way it goes. Sometimes they cannot be answered.

DR. CHASE: Mine is turned off.

DR. CASSELL: That is my wife calling.

(Laughter.)

DR. CASSELL: I am still concerned about the problem about the investigator versus the clinician. We could think of numbers of examples. One commonly used one is the 20th patient in a trial where it looks like the trial is not coming out right and the clinician would be -- would not generally be as eager to get somebody to participate and finish because otherwise the

trial is no good at all. So, I mean, I could think of some other examples.

But I am more concerned about your feeling that the transfer of placebo controlled research into a different country would not be good science. Now I undersatnd it might not be ethical but the question is does that mean that the factual result that you got out would not be valid, would not be internally valid? I mean --

DR. CHASE: I think what I said is that I do not know if it would be good science because I think when a piece of something has been taken out and moved somewhere else it does not then come back with the integrity of the whole that was behind it.

There is an infrastructure that exists to support clinical biomedical research and in my world that involves hospitals that have dialysis machines and, in fact, referring to a letter -- I believe it was a letter to the British Medical Journal that this point was brought up that, you know, you were not required to build a renal dialysis facility just because you were conducting a trial in some country that did not have them.

So I think you have to look at the circumstances. There might be some circumstances where

it did not matter that you did not take the rest of biomedicine with you when you went to this country and did an experiment. If it was a clear-out result that did not depend on these supporting activities then fine.

But from the trials that have been discussed this morning and the other ones I have read about, it seems to me there were many side aspects and covariates and other treatment possibilities, and there was a dynamic environment where the treatment available was constantly changing, and so I am just raising the question as to whether this transplanted methodology by itself gives you the same currency essentially or the same validity that it would when it was carried out in the circumstances for which it was really designed.

DR. CASSELL: And I understand that and I appreciate that but when you are helping other people design research, and leaving out international research, are you always so careful about transplanting everything from one site to another site, the kind of people, the hospital environment, all that?

DR. CHASE: It is a very big issue in my environment because in Southeast Michigan, which is where I come from, there is a vast heterogeneity in the availability of medical resources to local subjects and,

in fact, in discussing these Third World trials with my colleagues, many of them brought up examples that were less than three blocks from my hospital where children who have epilepsy do not get antiseizure medication.

So I think there is -- yes, at our hospital and our IRB we do pay a lot of attention to the ecological resource and also the racial and ethnic context of the studies that we carry out to try to make sure they are as valid as possible. You cannot guarantee total success but, I mean, we have a whole branch of one of our centers, for example, that develops questionnaires that are targeted to people who come from ethnic groups that have different attitudes about end-of-life treatments.

We have --

DR. CASSELL: Well, the question there is the different kind of data than we are talking about.

Dr. Dixon or Dr. Dickersin, would you comment on that?

DR. DIXON: I am not -- I do not think I really have anything to add to what Gary has said on this question.

DR. DICKERSIN: I think that I undersatnd what he is saying about it but I think maybe I am understanding incorrectly that it is back to the

the local public health officials on the assessment of the trials.

One official said that, "Senegal did not choose the vaccine as their primary means of control.

around. To limit the problem of schistosomiasis you first need running water, taps in the homes, latrines, less contact with water."

This was the litany. They needed basic, basic health control measures.

A nurse in -- who worked in the health post of a small, small village of 4,000 people that lived along the Senegal river was saying -- she said, "Even me, I go to the river." She educates people on how not to get the disease. "Only four flasks a day. That is not enough water for sure. You have no choICH but to enter the river. It is the financial means that we are missing above all the means."

What came up again and again and again when I was conducting the research was that they wanted to have care for the population. They wanted to be able to provide the standard of care anywhere else in the world that we just take for granted.

They do not have the means but international research groups that enter the area in order to conduct research do have the means and seeing this incredible amount of money being put towards research being put towards the laboratories frustrated them. They wondered why they could not take just a little bit of the money that was coming into the region for vaccine trials which

did not have the informed consent of the population really but nobody worried about that because that was not the issue.

The issue was where do you get the money to provide the basic health control programs that the populaton needs and then you see this incredible amount of money, as I said, coming in with the research programs and think can't we get a little bit of that maybe to go towards the needs that we feel are health priorities. It is a good question.

DR. SHAPIRO: I have to ask you to draw your comments to a close.

DR. JONES: Yes. I am sorry.

I would also like to point out -- like to draw attention to a conflict of interest that the local researchers have. In this particular case the man who is now the director of the research program on the Senegalese side is also the representative of the Ministry of Health.

I think that when American researchers begin to set up partnerships and begin to set up the research programs they need to be careful not to put people in the local communities into situations where there is a conflict, an inherent conflict of interest between -- between who does what.

Can I have two more quotes?

I am sorry.

One doctor in the region who had been trying to find out for a long time what the research was that was being done in the population, when he found out that there were going to be vaccine trials not necessarily with informed consent, he just shrugged his shoulders and said, "It is Africa. People can do whatever they want. Nobody is going to stop them."

And then another man who is a university professor who has taught in America and teaches at Senegal and very -- understands development, understands the differences in culture -- simply says, "You cannot do that in America but in Africa you can. The rights of men are not as well developed here. The population is not sufficiently well educated to make the decision for themselves so the doctor makes the decision for them."

As I pointed out, the doctor who makes the decision is also the man who is in charge of the research and in charge of the health of the population. There are conflicts of interest that go much deeper than anything we imagine here in the states.

Thank you.

DR. SHAPIRO: Thank you. Thank you very much also for your written comments which we have distributed

to everyone on the committee. Thank you for the trouble in coming down here today. We very much appreciate it.

MS. JONES: You are welcome.

DR. SHAPIRO: Any questions from any members of the commission?

Okay. The next is Mr. Terry Rhinehart on human experimentation.

Mr. Rhinehart?

MR. TERRY RHINEHART

ISSUE: HUMAN EXPERIMENTATION

MR. RHINEHART: Mr. Chairman, members of the commission, my name is Terry Rhinehart and I appreciate the opportunity to address you today.

My purpose is to inform you of a nonconsensual research project and encourage the strengthening of government oversight on human subjects research and the protection of human subjects.

My situation began as a contract employee where I was conducting Ph.D. research with the Army Corps of Engineers in Vicksburg, Mississippi. I have attached a summary of my situation, what I have experienced, literature related to my experiences, medical evaluations which I have undergone which have not explained this situation which I am experiencing. What I would like to do is highlight some of the aspects

of the summary to you.

Essentially I have been exposed to microwave technology which allows vocal communication and electrical stimulation of the brain. The technology was placed on me without my consent or knowledge, which is easily accomplished considering the size of the technology in its present state.

From review of the scientific literature: fiber optics are commonly used in microwave transmission technology. Fiber optics currently are about the diameter of a human hair or about the size of a fishing line and easily placed on a person without knowing it.

The microwave auditory effect is well-known in research in the scientific community but less well-known by the general public and the medical community. However, the microwave auditory effect has been known for at least fifty years and is also part of the basis for limiting the exposure to humans in microwave frequencies, including those used by cellular telephones.

It is known that the microwave frequencies will induce what is known as the microwave auditory effect. The microwave auditory effect has been used to -- for vocal communication as well as being discovered that vocal communication can be used with the microwave

auditory effect to direct a vocal signal directly to the brain bypassing the normal hearing route through the ear.

The medical community tends to consider the form of communication as an auditory hallucinogen with a common diagnosis of schizophrenia.

From what I have been told through the vocal communication system the material was placed on me for a matchmaking effort and since that effort failed the Army was going to use the technology as they normally do. Had I cooperated with their matchmaking effort the Army had informed me they would remove the technology.

Based upon a psychological profile the Army had stated they had developed from those working with me it would be easy to screw up my brain. The psychological profile indicated I had academic problems and was an isolated person.

My academic problems were that I had taken a course from a professor who was essentially retired. I repeated the course while I was in Vicksburg.

I was isolated because one individual that I was familiar with had not seen me socializing in Vicksburg.

It was obvious to me from what I had found through the vocal communication system that the person

who is doing the psychological profile must not be well-trained in developing psychological profiles or in data evaluation. Obviously generalities are used in developing psychological profiles but those do not always completely define a situation.

I also question why it was necessary for the Army to be involved in a matchmaking effort especially since I was informed near the beginning of their effort that their effort was guaranteed to work.

Through the vocal communication system I have discovered that those who are doing the communication are 20 to 21 year old males with the rank of private first class and not essentially researchers.

The communication system is a two-way based upon EEG communications. Interpretation of the EEG signal enables the interpretation of words and sentences and has been referred to as talking off the top of your head.

EEG communications are the basic for paraplegics to communicate by "thinking" a word or sentence and allowing it to be seen or heard on a computer screen.

Interest in the remote transmission of the human EEG signal has been around for fifty years, as indicated by the 1949 article referenced in my summary.

While exposure to microwave radiation may be less damaging than ionizing radiation, the effects are still negative and have an adverse impact on a person's life.

My concern is that if my exposure is due to a matchmaking effort how many others have been or will be exposed and not understand what is happening or are able to do what is necessary to get the exposure stopped?

Needless to say, the vocal communication system could be used as an influencing method if the subject allows themselves to be influenced.

The Army has also informed me that I am involved in the current situation due to my willingness to seek a legal solution to the matter and the fact that I should easily be irritated since I had more to lose.

There have been questionable situations with doctors initially willing to believe what I am saying and to work with this situation only to have them decline to work with me and not return my phone calls.

I believe that the government should be held accountable for improper decisions and complying with laws and regulations for human subjects research, especially those with potential negative impacts on human lives.

I encourage the National Bioethics Advisory

Commission to review regulations and research projects and the project approval process for human subjects research ensuring that all federal agencies comply with laws and regulations related to human subjects research.

I also believe it is important that the arrogance which can be used to inhibit a person from seeking a conclusion to nonsentual (sic) research and competence for damages incurred be addressed or overseen.

Thank you very much.

DR. SHAPIRO: Thank you very much. Have you provided us with a copy of your remarks or would you like to provide us with one?

DR. DUMAS: We have a copy.

DR. SHAPIRO: We have a copy. Let me see it. I did not get a copy.

MR. RHINEHART: Yes.

DR. DUMAS: I have an extra.

DR. SHAPIRO: I appreciate that very much. I did want to, and we will certainly look at the material. However, I do want to make a point that as a commission we do not investigate any individual cases. That is not in our purview but I understand the general point that you are trying to make, which is broader than your

particular case.

Thank you.

Any questions from members of the commission?

All right. Next we have Dr. Peter Lurie.

DR. PETER LURIE

DR. LURIE: Back by popular demand as a member of the public.

I actually have a couple of slides which turn out to illustrate points raised by people on the commission this morning.

Can we get that down there so that people can see? Would you mind?

(Slide.)

I am going to make two methodological points and one historical point.

The first methodological point responds to a comment by Dr. Murray that the idea of noise in an equivalency study will result in one concluding -- reaching improper conclusions.

Actually that is not true. What noise does in a clinical trial is bias the results towards the null hypothesis. In a placebo control trial the null hypothesis is that no one treatment is superior to another. The alternative is that they are different so noise in a placebo control trial biases one to

concluding that the to treatments are equal.

But as Dr. Dixon pointed out in an equivalency study the hypotheses are reversed and the null hypothesis is that one treatment is superior to another. In that respect I recommend that you all read the article by Dr. Walter Houck, who is the person who first established that, in fact, the hypotheses are switched in an equivalency study.

The result is that noise in an equivalency study will bias one towards the null, which is that one treatment is superior to another. Quite the opposite of what Dr. Murray asserted.

The second point -- can I have the next slide, please?

(Slide.)

That is the first point.

The second methodological point: Sample size.

Let me explain what I have done over here and I am trying to illustrate the point that it is not true by a long shot that the sample sizes needed for placebo control trials are invariably substantially smaller than those for equivalency studies.

What we have here is a perinatal trial type situation again in which the transmission rate in the

placebo group we have taken to be 25 percent and the transmission rate in the 076-like group is 10 percent. And then along the X axis we have the rate of transmission in the so-called short-course AZT group across the bottom in numbers ranging from, I guess, 12 up to 19 or so.

The dark line is the number of subjects that will be needed in an equivalency study and the dotted line is the number of subjects that would be needed in a placebo controlled trial.

What you can see is that in certain areas the placebo control trial requires more subjects. In other areas, the equivalency study requires more subjects. It all depends on where on these curves you are.

Now in the Thailand study that Dr. Lagakos spoke about, which he ultimately concluded was more ethical than the placebo controlled one, they used an event rate in the short-course group corresponding to 16 percent, which happens to be about the crossover where the equivalency study sample size is about the same as that in the placebo group.

Indeed, with other examples you can come up with circumstances where it is more efficient, if you will, to use the language people seem to like, to use the equivalency study.

So the other point to take home from this is that the differences for most of the places that are reasonable -- these are the areas that you would most likely be looking at -- especially in developing countries -- are, in fact, quite small. These are not very large numbers of subjects and that must be taken into account as well.

It was stated that the so-called Harvard-Thailand study -- you can turn this off now if you like -- that the Harvard-Thailand study had taken longer than the Thai-CDC study, the one that used the placebo group. Well, there are a number of reasons for that.

The primary one is that NIH reviewers held up the study for a full two years while they were insisting upon the use of a placebo controlled trial and there was submission and resubmission over and over again, and that is what delayed the study. Not because it is an equivalency study.

It is also unfair to say that there were three times as many people in the equivalency study as in the placebo controlled study in Thailand because the Thailand study that the CDC did with the placebo group had two arms but the equivalency study had four arms. That is why the numbers were different so we really must get away from those ideas.

With the small differences in sample sizes that are often seen, a clear solution to this problem is to recruit more aggressively, not simply to abandon a whole kind of study that has a whole literature supporting it.

And I think that that could happen. The 076 study was done in two countries and at several dozen different centers and the same thing could have been done in many of those studies in Africa.

Fundamentally, though, the whole idea that the sample sizes would really matter is a naive view of the implementation aspects of these studies.

In fact, in South Africa, for example, where I am originally from, there -- we still do not have AZT short course or nevaripine put into place for reasons that have nothing to do with science whatsoever. So the notion that somehow there is an automatic transition from science to policy is a really naive view.

Some of those studies, I will point out, were actually conducted in South Africa and they still do not have the intervention even though it is probably the wealthiest country in Africa.

I guess the final -- I did say I would make two methodological points and a historical point and the historical point relates to the depiction by Dr. Whalen

of the study that he did in Uganda -- right? He failed to mention four important things.

One, in addition to the studies that he mentioned there is, in fact, a randomized placebo control trial in Zambia of HIV positive people using INH prophylaxis that was positive and reported in 1992 in the abstracts of the Amsterdam AIDS Conference and that is another -- that was not mentioned by him in his presentation.

He failed to mention that in 1994 during the time that he was still recruiting patients there was reported an equivalency study or at least an active control study at the 1994 AIDS Conference conducted by Dr. Neil Halsey, who is no great fan of placebo control trials having criticized us for our criticism of his placebo control trial but he was conducting -- at the very time that Dr. Whalen was still giving placebos to patient, he was reporting the results of an equivalency study on INH prophylaxis.

Dr. Whalen also failed to report -- to point out that even after his study was positive his group mounted a concerted campaign to deny treatment to the placebo group. There were people sent down to CDC to try and convince them that there was no need to treat the placebo group even though the INH prophylaxis had

been proved effective not only in the previous studies but in his. For thirteen months this campaign resulted in the denial of the effective treatment in his study to the placebo patients.

All of this I can document with documents that we have obtained through the Freedom of Information Act.

The final point, and I think in some ways the strongest, is that I found during the literature review a study from the Journal of AIDS in 1995 conducted at the same hospital as Dr. Whalen's hospital dealing with INH prophylaxis in HIV positive people.

Astonishingly, this is not a study of INH efficacy, let alone versus placebo. It is a study of the feasibility of using INH prophylaxis in people who are HIV positive. So at the same time that Dr. Whalen was denying it not only to the people in the placebo group but then to the people in the placebo group after it proved to be inferior to INH had long been, in fact, had been reported a study conducted between 1991 and 1992 in which these people were asking the right questions. How do we get the drug to people? Not wasting time with irrelevant, redundant and predictably positive studies of INH prophylaxis.

Thank you.

DR. SHAPIRO: Thank you very much.

Any questions from members of the commission?

Is there anyone else in the audience who wants to address the commission?

Yes, please.

It is Dr. Goodman.

DR. STEVEN GOODMAN

DR. GOODMAN: Right.

Hi. My name is Steve Goodman. I am on the faculty here at Hopkins in oncology, epidemiology and biostatistics and I am a member of their Bioethics Institute.

I am just going to make three very short points. One is I heard in many of your questions a tremendous concern about hearing the perspective of the participants in the trials and people who were involved in trials in the Third World countries where these trials are going on.

I will say that my own views on the subject has been profoundly affected by exposure to investigators from the countries in which these trials are going on.

I hope that in the course of your deliberations you make a special effort to invite -- to

spend the money to bring the people here and talk to them face-to-face and not read reports and not, you know, do it second hand.

I think it has a tremendous -- it will have a tremendous impact on your own thoughts about -- on the values that are being considered in these countries and some of the things that your comments showed so I hope you take that very, very seriously.

The other thing I wanted to comment on was to focus -- there is a lot of, I think, misstatements about -- and misfocus related to the issues of equivalency trials and difference trials. I think the only way to cut through the fog is to just look at the measure of effect at the end of the study. Just look at the precision of the difference that you are seeing.

All this stuff about equivalency and differences is -- I do not want to say it is nonsense but it obscures the central focus of these trials, which is to look at a comparison between two therapies and estimate it with a certain degree of precision. It is absolutely true that if you had more endpoints to the system then it biases towards a null effect.

The -- what Dr. Lurie showed was sort of an abuse of the word "null" in the sense that you, indeed -- it is -- in these equivalency studies you, indeed,

flip what is called a null and alternative hypothesis so the word "null" becomes -- means something else. But I think we all -- you were using it in the sense of "null" meaning zero effect. If you add more noise to the system you tend to bias towards zero effect so let's get away from what is the null and what is the alternative and all this sort of stuff.

Related to this magnitude of effect I also want to point out that it can help clarify the issue of the value of doing placebo controlled studies. I am not taking a stand either for or against but I just want to point out that from the perspective of the developing countries the comparison between short course and placebo was not just an issue of deciding is it better but how much is it better by and is it worth spending the extraordinary amount of resources that might be necessary for that country even in a short course for that degree of benefit.

So the actual degree of benefit is sometimes a central question. Not is it better by epsilon or is it better by one percent because even if it is better even a cheaper short course can -- diversion of resources in a country towards that sort of therapy can take it away from very efficacious treatments of other conditions and other modalities so it -- I just want to point that out

as a factor in the equation and we should get away from language that says does something work or doesn't it work because it is a more complicated thing.

It is always an issue of balancing and you cannot do balancing unless you use language about how much does it work and how sure are we that it works by that much.

The final thing I will just comment on was the original, I guess, barometer of the ethicality of a trial, which was suggested to be whether you would enroll, I guess, either yourself or some loved one. I think an alternative question that we also need to ask is whether we want to live in a society in which we are -- medical choices are informed and governed by the results of clinical trials.

Sometimes the answers to those questions will be different, that is we, ourselves, would not want to enroll and yet we want to live in a society where they are done. And I think a lot of what this is about is about how to best resolve that conflict and it is something that we cannot get away from.

I think if we are going to live in a world where clinical trials are done we are going to have to live with some very, very difficult choices and, of course, that is what you are all here to discuss and

debate.

Thank you.

DR. SHAPIRO: Thank you. Thank you very much for your comments and for taking time to be here today.

Any others? Anyone else who is in the audience here today that would like to address the commission?

Bernie?

DR. LO: Could I ask Dr. Goodman a question?

DR. SHAPIRO: Absolutely.

DR. LO: Your first point sort of encourages us to sort of talk directly to investigators from developing countries and you said you had learned a lot from doing so, you tantalized us and I cannot help but asking, can you just give us a sentence or two of what you found from those discussions that you did not know before and presumably we might also learn?

DR. GOODMAN: Well, my most extensive exposure actually may have been as part of a project. I am not sure if it as commissioned by NBAC. It was done by Dr. Nancy Kass where what she did several months ago -- and this is in addition to other discussions I have had but this was the most formal setting in which she brought together actually on very short notice investigators and public health officials from about ten different Third

World countries actually in this room about six months ago and discussed their own problems with the process of reviewing studies and IRB's.

So I actually -- I do not -- I am not the best person. If you want to know the results of formal meetings like that I would actually encourage you to talk to her who I know you know.

But I would say in a general qualitative sense what I learned is that there is -- while it is easy for us to here to talk about the fact that these -- that many of these people have competing interests and have interests in getting money from the U.S. and in going to international conferences and may not have the interest of their own people at heart, I think when you talk to them at length, even though many of those things may be true in general, one sees an extraordinary dedication to the interests -- what they see, what they perceive is the interests of their people. A very, needless to say, rich understanding of the social and economic context in which these trials are done. And it is -- it is that sense and that sort of information which I find very compelling.

Now, you know, from speaking to them you can make the decision yourselves whether you can -- whether it is possible to go the extra step and whether it is

meaningful to actually try to get a hold of trial participants, I do not know, that will inform you.

But I think it is that general qualitative sense which is the -- which is what I will leave you with but there are transcripts of that particular meeting but I -- as I said, I think that speaking to people one on one and looking them in the eye, I think, there is no real substitute for that. So on some level I would almost hesitate to say anymore because I think that there is nothing like that particular process.

DR. SHAPIRO: Thank you.

Eric?

DR. MESLIN: I am sure the commissioners are all aware of this but just to confirm Dr. Goodman's suspicion for the audience, Dr. Kass is one of our consultant contractors on this project and the focus group that Dr. Goodman referred to is part of the project that Nancy and her colleagues are doing so we are well aware of her work and are making good use of it as well as the follow-up survey that she and her colleagues are going to be undertaking.

So thanks for reminding the group that we are already benefitting from Nancy and her group's work.

DR. SHAPIRO: Thank you. Any other questions from members of the commission?

Okay. Thank you very much. Let's go on to the next item then on our agenda. We are going to hear from Dr. David Lepay from the Food and Drug Administration, who is Director of the Division of Scientific Investigation.

I think you are going to be using the overheads, right?

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

OVERVIEW OF FDA

DAVID LEPAY, M.D., Ph.D.

FOOD AND DRUG ADMINISTRATION

DR. LEPAY: That is correct, yes.

Well, I would certainly like to thank Dr. Shapiro and the commissioners for the opportunity to speak here today. My focus may be just a little bit different from your discussions this morning, although I think perhaps it is all part of one continuum.

(Slide.)

What I am here to talk about today is FDA's oversight of international research. In particular, our roles, our responsibilities, the limitations we have and, in particular, also the harmonization efforts that we have undertaken on a global level to try to put into place good clinical practices.

I would also like to, to the extent time

permits, talk a little bit about our experiences in the oversight of international trials. I may not have sufficient time to do so and we might be able to address that in part of the questions and answers as well.

So with that I think I will move to the first slide.

(Slide.)

And I want to start off by saying to everyone, first off it is important to recall that, one, FDA does not in itself fund clinical trials. FDA does not in itself conduct clinical trials. There are a few exceptions. People are involved within the agency.

Our role is in the oversight of clinical trials and in the oversight under very particular circumstances.

Our authority to oversee clinical trials, domestic and international, derives from the Federal Food, Drug and Cosmetic Act. And probably the most important passage or the most important paraphrase that exists here today is that research -- that any movement of products, that is pharmaceutical products, any of the products FDA regulates, biologic, medical devices, veterinary products, food additives, in interstate commerce requires an FDA approved research permit or marketing permit.

It is the movement across state lines that gives us our authority to be able to regulate research and that is an important point to bear in mind as we talk about international considerations.

(Slide.)

Well, of course, pharmaceuticals can move across state lines during two stages of human use and we are talking here, in particular, in the United States. They can move across state lines during the research phase itself prior to approval and what we are talking about there is the requirement for a research permit in the area of pharmaceuticals. This would be an investigational new drug exemption or IND. And drugs can also -- pharmaceutical products can also move across state lines after they are approved during marketing and in order to market in the United States we require a new drug application and the approval of that new drug application.

(Slide.)

We have regulations in the United States. FDA regulations that govern clinical studies in both of these conditions. What is going to be overseen in the course of undertaking a research permit? What is going to be required in putting together a new drug application and getting approval of that application?

In terms of the conduct of clinical studies we are really talking about three principle regulations here. Those are the first three that are listed. All part of Title XXI of the Code of Federal Regulations.

Part 312 describes the requirements of a study and the requirements of an applicant to obtain an investigational new drug exemption.

Part 50 describes the requirements for informed consent during the course of human research.

Part 56 describes FDA's requirements for IRB's that are overseeing clinical research. These are our in-process or real time controls over clinical trials in the United States.

Part 314 deals with the issue of new drug applications. What must be submitted as part of that application.

(Slide.)

Well, let's move then to non-U.S. clinical studies. Studies conducted completely outside of the United States. A sponsor, a pharmaceutiacl company, can come in and can voluntarily state that they want to conduct this study under a U.S. research permit and investigational new drug exemption, for instance. This is voluntary on the part of the sponsor if this is not a study being conducted in the United States and it is a

very rare circumstance. We are talking at most maybe a percent or two of studies, if that.

If, indeed, a study comes in under U.S. IND regulations, of course, regardless of where it is conducted if that is the choice of the sponsor, and they have voluntarily submitted such, all U.S. regulatory requirements would apply, all of our informed consent regulations and all of our IRB regulations.

(Slide.)

By far, of course, the more common scenario is that studies are conducted outside of the United States independent of a U.S. IND. We have, of course, accepted there is a limitation to hear of what we can actually regulate during the conduct of this sort of clinical trial. This may be the more common scenario but clearly we are not moving drugs across state lines within the United States so, therefore, FDA itself has no authority to regulate these clinical studies during the course of their conduct.

What we have control over, however, is if these studies are to be submitted as part of a marketing application to the United States that is part of a new drug application. Then again we have some controls over how the study was conducted but we are not necessarily talking in real time here. We are talking about having

some oversight, if you will, as to how the study was conducted when this information is submitted to us.

Our authority here really relates to whether we will accept or not accept that data for that study for FDA review. And the word "review" is, of course, very important here. We are not accepting point blank any of these studies in support of a U.S. drug approval. We are accepting them for FDA review.

(Slide.)

These are our criteria under the regulations to accept non-U.S. data for FDA review. These are, in fact, imbedded within our Parts 312 and 314. The ethics of the trial have to be acceptable to the world's community and, in effect, we have defined that there be protection for human subjects that are equal to or greater than those protections provided in the Declaration of Helsinki.

The Declaration of Helsinki, of course, requires informed consent. The Declaration of Helsinki requires institutional review but, in fact, specifies the nature of this informed consent and this review in very open language.

It is not extremely explicit so when we are talking about, in fact, protection greater, what we are talking about here is whether there is any standard

within that country perhaps that will provide more explicit information about informed consent, more explicit information about the oversight by an IRB or the constitution of an IRB that is embodied in the Declaration of Helsinki and, of course, our own regulations are much more explicit in this area as well.

Our criteria also include that the trial has to be well designed. I am not going to get so much into trial design. I know that was your topic this morning. The trial has to be well conducted. The investigators have to be qualified and those qualifications are typically expressed in terms of qualifications within the country in which they are conducted. The medical qualifications within that country are acceptable to us.

Similarly, the trial has to be approved by an IRB or Independent Ethics Committee. For our acceptance as well, the data that is being provided to us has to be applicable to the U.S. population to clinical practice in the United States, which is not necessarily a good clinical practice standard but is a requirement for our own acceptability for review.

And, finally, we do maintain the provision -- and given my own position within FDA is overseeing

Bioresearch Monitoring, this is a very critical element to us. Not only do the above conditions have to be met, the trial has to be available for us to go out and inspect and inspect anywhere in the world for us to be able to accept this information.

(Slide.)

So let's move on here. A little bit about GCP's then. Good Clinical Practices. What we have been takling about all along is, in fact, the whole concept of good clinical practice. The ethical and scientific quality standards that affect all aspects of the clinical trial involving human subjects. This is the definition of good clinical practice from the International Conference on Harmonization's GCP Guideline.

(Slide.)

Well, the -- one of the issues that I was asked to discuss today is, in fact, the whole concept of harmonization, where we are in terms of the International Conference on Harmonization, what this particular group has been involved in, what their role is, what their responsibilities were.

So let me spend a few minutes on that.

What we are talking about here is harmonization of standards for good clinical practices

as we define them and standards of harmonization between the European Union, Japan and the United States.

There were other participants involved in this conference and those included the World Health Organization, the European Free Trade Association, as well as Canada. There were certainly many other countries that were watching from a distance and certainly have become involved in trying to incorporate some of these standards into practice as time has gone on.

This process was initiated quite some time ago back in 1990 and it has, as its origin, trade agreement legislation. The goal here was to reduce unnecessary barriers to trade but I think the last point is the more important; that, in fact, in coming into a harmonization effort we had as a criterion for harmonization that there would be no lowering of safety or quality standards in the process.

It is also important to remember what we are trying to harmonize here. We are trying to harmonize the technical requirements for application to regulatory agencies. This is not necessarily an attempt to harmonize ethical principles or a harmonization of all aspects of trial ethics.

(Slide.)

This was not purely an effort or not at all an effort, in fact, that was restricted to government regulators from these different regions. Industry was very well represented here and, in fact, the steering committee that oversaw all of ICH had six cosponsors. Two each from the European Union, Japan and the United States.

And in each case representing the government and the European community, the MHW in Japan, the FDA in the United States, and our industry counterparts within each of these regions. The Secretariat was represented by the IFPMA, the International Federation of Pharmaceutical Manufacturing Associations.

There were a large number of expert working groups that developed out of ICH and, in fact, I cannot say that I could probably list all of these at this point because this is very much an ongoing process.

There were four areas of focus, though, for ICH. There is safety and safety here when you see this, we are talking about preclinical or animal toxicology, carcinogenicity and so forth.

The "S" series of ICH harmonization efforts is, in fact, animal safety.

"Q" for quality. We are talking about manufacturing practices here.

Regulatory communications, the "M" series. Looking at areas of harmonization for terminology for adverse event reporting. For communications, electronic communications to regulatory agencies, and so forth.

And then a very large series of harmonization documents or efforts that have come out in the area of efficacy and here we are talking about efficacy in human subjects, which includes human subjects safety and, in particular, what we are referring today is the E guidance, the good clinical practices guidance.

(Slide.)

Now we all, of course, entered ICH with differing levels of GCP standards and regulation. In the United States the concept of good clinical practice goes back to the 1960's and the regulations that followed from the Federal Food, Drug and Cosmetic Act at that -- that was developed at that time.

I have already given you the four regulations. These are, in fact, the -- our actual GCP regulations as we are talking about in the United States. These are legally enforceable requirements. They remain in effect with some amendments to today. So we have a long standing practice of good clinical practice in the United States.

(Slide.)

GCP in the United States also embraces guidance documents. The guidance documents help to articulate certain issues that may be brought up in our regulation but where we figure more amplification is necessary. Some of these include guidance in the area of monitoring clinical studies as well as guidance in the form of information sheets. Many of these deal with question and answer format and other additional information pertinent to Institutional Review Boards or clinical investigators.

The other point, I think, in our coming to ICH is the whole concept that we -- our ability to oversee clinical trials. Within FDA and, in fact, starting with the division that I currently direct, we have had a formal GCP inspection program back to 1967. We have been going abroad to look at clinical trials that were conducted outside of the United States since 1981.

(Slide.)

Well, standards, of course, coming into this were perhaps a bit different in each of the areas involved in ICH. In the European community, of course, we have to deal with standards that were developed within each individual country in the European Union and some of these are listed here.

The drug laws in Germany and in Spain dealt very early on primarily with issues such as manufacturing for purposes of putting these drugs into clinical trials.

More comprehensive guidelines involved ethics and conduct of trials in France and Germany came into being in '87.

The United Kingdom in '88.

The Nordic States in '89.

And in '91 the European Union developed a voluntary guideline prior to ICH and issued a directive again indicating that this voluntary guideline should be or could be followed.

So this is again the extent of GCP standards. There was no single international inspectional authority within the European communities. Different of these governments had levels of oversight, again, varied one to the otehr.

(Slide.)

Within Japan, as well, we are talking again about very different standards. They, themselves, have their own development of a GCP guideline. Back in '85 they announced that they were going to draft such a document.

Over the course of five years of debate, in

fact, in Japan they were finally able to get such a guideline finalized but what came out by 1990 was, in fact, quite different from the U.S. standard. It allowed oral informed consent.

It was a whole different -- a system for allowing oversight by a senior clinical investigator and what their responsibilities were and limits to how, in fact, a drug sponsor could oversee this particular clinical investigator. So there was quite a bit to be able to -- within Japan -- to look at as we started to talk harmonization.

(Slide.)

By 1991, again one year into the ICH process, it was realized that good clinical practices was a viable area for harmonization. An expert working group was convened and the U.S. was part of this, of course. And our harmonization strategy was very clear. We wanted a standard that was going to be adopted from and consistent with FDA regulations. So we are talking about consistency with Parts 312, 50 and 56 of Title XXI of the Code of Federal Regulations.

We wanted to make sure that we put forward a strategy that would avoid any type of dual standard for U.S. versus non-U.S. studies. Again we did not want to promote studies simply going abroad because the

standards may be lower. We wanted an acceptably high threshold standard and that is what we believe we achieved within the ICH process.

(Slide.)

It took several years again, much as with earlier guidelines that were developed country by country. By August of 1995 a consolidated guideline was submitted to the regions. By 1996 this was signed off by the steering committee. And in May 1997 the ICH guideline was published as official U.S. guidance.

(Slide.)

So what are the contributions of ICH GCP? Well, I think in some sense right from the start, much like the Declaration of Helsinki II, it starts out by developing and declaring 13 basic principles of good clinical practice and I provided these. These are listed in a handout that is part of your notes for today without going through those specifically.

It also provided clear assignment of responsibilities. Who was responsible for what, what duties did each party in the trial process have to undertake. And, indeed, in the United States we look at clinical trial oversight as a system of checks and balances involving components such as the IRB, the clinical investigator, the sponsor and the regulatory

agency. For this system to work effectively each of these components has to operate optimally.

It is standardized to some degree, and we will come to this, the IRB or IEC membership. There was agreement on what essential documents had to be kept as part of a clinical trial.

Also, I think very importantly, we have said that our GCP standards up until the ICH document existed in multiple areas, that is within our regulations, within a series of guidance documents. Here we had it articulated, in fact, in one guidance document for the most part.

(Slide.)

ICH is also important as we talk about harmonization as we move forward to areas not only within the European Union and Japan but outside that there is a recognition of national laws and regulations within ICH, the GCP standards themselves.

The standard states, in fact, that local requirements may be even more specific or more stringent than what is stated within the ICH GCP guideline but, in fact, very importantly, what we have done is we have tried to provide flexibility but we have tried to again maintain that high threshold standard that we still believe is, in fact, a standard that is acceptable and

is achievable.

And integrated into all components of ICH GCP, much like in U.S. regulations, is the provision for verification through inspection.

(Slide.)

So this is basically the table of contents of the consolidated guideline. It spells out in a glossary many of the definitions that we have also provided within our own regulations. It provides the 13 basic principles.

It articulates in Section 3 the roles and responsibilities of an IRB or independent ethics committee.

Within Section 4, the investigator section, it articulates requirements for informed consent. What the investigator is expected to include in an informed consent document as well as the process of informed consent.

Section 5 indicates the sponsor responsibilities for oversight of clinical trial monitoring and auditing.

As I indicated earlier, there is a section that deals with what are the components that need to be included or should be included in a clinical trial protocol and amendments. What should be in an

investigators brochure. This is, after all, the information that is going to clinical investigators who are interested in carrying out a clinical trial. The kind of information has been specified in the GCP guidance.

It also specifies essential documents that need to be developed and retained as part of the conduct of a clinical trial, where these documents need to be retained, at which site and for how long.

(Slide.)

So very quickly I -- obviously I could spend a lot of time going through a step-by-step comparison of these two. Some of this is articulated again in more detail in the slides that you have in your notebook but I am going to try to abbreviate this a little and say, first off, as far as informed consent standards go, the parallel is very striking between FDA regulations and ICH GCP guidelines. We consider this certainly a triumph for our own involvement in the ICH process.

Compliance with FDA regulations will meet ICH GCP standards. To that effect, we, in fact, amended our own regulations to require dating of informed consents and this was put in place in November of '96.

(Slide.)

We have not within our own regulations yet

put into place the requirement that the person conducting the informed consent discussion has to sign and date the form itself. This is contained within ICH GCP's but not within our regs at this point yet.

But, fundamentally, the informed consent standards are essentially the same.

The common -- no, could you leave that up, please.

The common features are shown here. We have the same general requirements for informed consent. We recognize that informed consent is not only signing a document. It is a process and it is articulated what that process should include. Within FDA's regulations there are listed eight basic elements of informed consent. These are all found within the ICH GCP guideline.

Both documents provide, in fact, that there could be or would be access to a subject's original medical records by regulatory agencies and ICH also specifies for sponsors and auditors to be able to ensure, in fact, the integrity of the information that is provided or developed as part of the case report form.

Both provide, in fact, or recognize that there may be emergency situations where prospective consent

may not be feasible and put into place some controls for that.

(Slide.)

Now I will say FDA has been more explicit in this area and this is probably the only area in informed consent where, in fact, we may be more detailed in our regulations. We have specific guidelines for the emergency use of a test article, including the reporting within five days to an IRB the fact that the article should be administered only once before IRB approval has gone into effect.

We also have within the last couple of years put into place regulations for emergency care research as our Part 50.24. This is not something that is articulated within ICH.

(Slide.)

As far as ethics committees, generally speaking there are a lot of similarities and I really want to stress the similarities but where there are differences the ICH GCP guideline tends to be just somewhat less proscriptive and less detailed than our own regulations, and this was really based on a harmonization effort because many IRB's are, in fact, subject to local laws and those laws, as I mentioned earlier, are built into the ICH process, that

recognition.

ICH, however, did introduce for us no new IRB provisions that were not already contained within our regulations. So again as trials conducted according to U.S. regulations and standard are acceptable internationally.

(Slide.)

Common features as far as IRB's. Certainly the most basic. A requirement for IRB or Independent Ethics Committee Review. That an IRB has authority and the authority includes that of approving, disapproving, terminating a study or requiring additional information about a study. That there will be initial and continuing review of research. The periodicity in ICH is similar to that in the United States.

At least every year and more frequently, according to the level of risk if that is determined as appropriate. The IRB composition was generally standardized. The concept that IRB's need to hold and convene meetings and need to follow written procedures. There are certain standards for their own -- what they need to keep as records and how these records need to be kept.

(Slide.)

Both our regulations and ICH GCP do provide

for expedited review procedures, as well as special attention to vulnerable populations.

(Slide.)

So I will spend just a minute -- I am going to try to go again very quickly through some of the areas when I say we may be a little more detailed in terms of our regulations than ICH.

One area is on the diversity of IRB membership. We specifically talk about nondiscriminatory efforts. We want to make sure that no IRB is entirely men or entirely women; that there is a racial and cultural consideration and sensitivity in the formation of the IRB in their deliberations, and attention to community attitudes; that no IRB may contain -- be composed entirely of members of one profession and that, in fact, if protocols are being reviewed for vulnerable categories of subjects that the IRB also have that kind of representation.

So these are, in fact, not specified within ICH but more explicitly within FDA's regulations.

(Slide.)

Expedited review is permitted by both FDA and ICH. ICH just defers this according to the applicable regulatory requirements. FDA does have applicable regulatory requirements and these include expedited

review for minor changes in approved research as well as for certain kinds of research that involve no more than minimal risk and we are under regulation obligated to publish these within the Federal Register and they have so recently been revised.

(Slide.)

Criteria for IRB approval of research. This is very interesting because even though the ICH document talks a great deal about what needs to be looked at in the process of IRB deliberations there is no -- there are no specific passages that say these are the criteria you need to consider for IRB approval of research.

FDA does, in fact, have a regulatory section that describes such responsibilities and there is a list again included within your package that defines what we say needs to be taken into account before an IRB approves its research. These are not specifically spelled out in ICH.

(Slide.)

Very importantly, as well, our IRB regulations do have a provision for waiver of IRB requirements. That is that sponsors or sponsor investigators may apply to the FDA to waive any of the requirements. This is a very rare circumstance.

I will add that in for any who wish to ask me

and, in fact, in my years in overseeing Bioresearch Monitoring the only circumstance that I can recall our giving a waiver for it is for a sponsor who is coming in and saying, "We are meeting all ICH GCP requirements.

We know that there are subtle differences in IRB composition between U.S. regulations and ICH guidelines. We would like to be a subject to U.S. IND. We cannot meet it if we cannot get a waiver that allows us to use the specifics of ICH requirements as the basis for IRB composition. Will you give us that waiver?"

And we have granted that waiver because we do believe in circumstances that controls an oversight of the whole clinical study under the U.S. IND process gives us, in fact, much greater control over the process than we would otherwise have if we did not provide such a waiver so we think that is an important use of such.

(Slide.)

The final points that I want to get to as far as IRB provisions that may not be included: ICH was not intended, in fact, to develop compliance or enforcement of harmonization. These were to harmonize technical requirements for application. So our regulations specifically provide enforcement provisions that are otherwise not contained within the ICH guideline.

We can refuse to consider data and information

in support of an application under circumstances shown here: That is when there is -- when we do not have IRB approval or, in fact, if the institution or IRB would refuse to allow us to do an inspection of a site if we so requested.

We also have the ability within the United States to take clear enforcement actions. We could put in place administrative actions stopping an IRB from enrolling new subjects, stopping an IRB from moving forward with new clinical trials. We can take an IRB to task to the point of administrative action of disqualification, that is closing down an IRB effectively from an administrative standpoint. We also have civil or criminal judicial proceedings.

Again these are U.S. regulation and not part of ICH.

(Slide.)

Well, as far as implementing ICH, our implementation, of course, includes its publication in the U.S. Federal Register as official guidance. I want to reiterate the point.

Part of our involvement in ICH, and it was my division that represented the Center for Drugs in this process, Center for Biologics was also part of this process for FDA, we wanted to come up with a system, as

we said, where our existing infrastructure would be generally consistent with GCP requirements, would fully support their implementation, and ultimately --

(Slide.)

-- such that we could say, in fact, that studies that were conducted according to ICH GCP will meet our GCP standards as we have defined them in our regulation for acceptance of data for review.

(Slide.)

And, again, we have seen this slide already but certainly all of these provisions with the asterisks, the acceptable ethics protection, in fact, greater because it is more explicit than the Declaration of Helsinki, issues about trial conduct and design, the qualifications of investigators, the approval by an IRB, the ability to inspect. All of these are ICH GCP standards. All of these would, in fact, meet our criteria under the regulations for acceptability.

(Slide.)

Implementation outside of the United States. Well, in the European Union ICH has thus far been adopted as official guidance, the GCP standard, and they are moving at this point towards a GCP directive that will, in fact, require each of the member states to make ICH GCP law that will be law across the European Union.

So it will not just be guidance. It will become a legal standard that will become enforceable. This has not happened yet. We are expecting this will occur some time in 2000. Again, of course, we watch this with great interest.

We, also, can state, of course, that in the process of putting this into place, the Europeans have also recognized the need to be able to ensure compliance with ICH. They have developed working groups among their own individual member states, inspectorates, individual member states' regulatory authorities, and they meet periodically again until law is put into place implementing.

(Slide.)

In Japan, ICH was very quickly adopted as law. So it is, in fact, a legal standard. It is legally enforceable and much as with the European Union this is a reciprocal process. Since ICH has come into place, both the European inspectorates and Japanese inspectorates have come to the United States to inspect our conduct of clinical trials according to ICH GCP standards, much as we have gone to inspect European trials and Asian trials according to FDA's regulatory requirements.

(Slide.)

We continue to work within ICH. This is an ongoing process. Many of these guidelines that I mentioned earlier, the whole series of many of the efficacy guidelines are still in the process of various draft stages, are going in through the finalization process, but as far as the Good Clinical Practice Guideline, we are in the process -- they are -- the European Union, Japan, they are still in the process of implementing the guideline themselves since it has become law.

They are also in the process of ensuring compliance. We are in contact with them about inspection programs. We are providing them with technical knowledge and expertise with our own experience in having inspected since the '60s internationally to help them develop programs that will oversee clinical trials within their jurisdictions comparable to the way that we are doing this within the United States, both domestically and internationally.

Certainly we know within the framework of clinical trials, even within the framework of the conduct of clinical trials, there are many new and emerging issues. We are going into increasing areas of electronic data capture, for example, computer systems use in clinical trials, computerized medical records,

all of these are areas that certainly we have to make sure there is preservation of data integrity in human subject protection in process.

So at this point this is really where I wanted to close my discussion of FDA's role and responsibilities and ICH standards. I do have some additional materials. We can put those into place as people are interested in terms of our own oversight, our own experience, if you will, of the extent to which we have overseen international trials but I will leave that as a point for discussion as the Commissioners would care.

Thank you.

DR. SHAPIRO: Thank you very much.

If we could get the light switch that would be helpful.

Thank you very much and thank you very much for an obviously very carefully prepared presentation. I very much appreciate it.

Let's see if there are questions from members of the Commission.

Ruth?

DISCUSSION WITH COMMISSIONERS

DR. MACKLIN: Thank you. This was a lot to absorb, some of which I knew and others I did not.

I have a specific question about the application of the criteria for acceptance of non-U.S. data and then I want to ask very briefly for you to elaborate a bit on the thing that you said is never implemented or never applied.

My question is this: We have the handout and it is on page 2, the first slide.

DR. LEPAY: Okay.

DR. MACKLIN: Protection equal to or greater than the Declaration of Helsinki. Now my question goes now to the much discussed AZT maternal-to-child transmission studies that have been brought up here and elsewhere and the specific provision that causes a lot of trouble, which is the "best proven diagnostic and therapeutic method" in the Helsinki Declaration.

Now according to the criteria for acceptance, the protection -- the trial protection has to be equal or greater than the Declaration of Helsinki. If a U.S. researcher who conducted, who was one of the investigators in those maternal-to-child transmission studies that were placebo controlled in Thailand, for example, or in Cote d'Avoir, came for approval of the short course AZT in this country based on those trials but, of course, those trials could never be done here, would that meet this criterion for FDA acceptance?

DR. LEPAY: I -- again, I am going to hedge on this a bit because again it is not within our purview to make that decision. It is within the purview of the reviewing division that receives the application to make that determination. So again --

DR. MACKLIN: Could you guess about what they would do?

DR. LEPAY: No, I really do not want to guess in terms of what they would do but certainly they would, in fact, very carefully look at the conduct of the study in light of Helsinki and I would imagine that they will or would consult not only within their own operation within that reviewing division.

They would certainly also discuss with us the provisions of Helsinki. We would also, of course, be in a position to inspect that trial to make sure that the other provisions, not only the trial design provisions that we are talking about here, were also properly executed.

And I would imagine this is an issue that they would possibly take to an advisory committee and, indeed, this is why FDA has developed advisory committees to address just these sorts of issues.

Clearly, we have had meetings within the past few days, in fact, of advisory committees looking at

pediatric clinical trials and conduct of pediatric trials for anti-infectives. So I do not want to second guess, in fact, and I think it would be very dangerous for me to take that position.

DR. MACKLIN: It might not be dangerous but it may be not wise.

The other question, if you could just say a word more about it, IRB provisions in FDA regulations but not ICH GCP. This was the waiver. This is page 9 of the handout at the bottom left. The waiver of IRB requirement and here it says, "On application of a sponsor or sponsored investigator, FDA may waive any of the requirements contained in these regulations including the requirements for IRB review."

Now that seems to be in contradiction to the requirement of equal to or better than Helsinki provisions. So what is this here? Is this a kind of rare exception? Could it be implemented? I know you are going to tell me it would have to go to the committee but, I mean --

(Laughter.)

DR. MACKLIN: -- I am trying to understand the logic of it here given what -- given all the other things that you have laid out for us.

DR. LEPAY: Well, again, of course, we are

talking now about regulations as they pertain within the United States when we are talking about this waiver provision.

Part 56 applies to the conduct of clinical trials within the United States where we regulate. This is not going to answer your question well but, in fact, this is built into our regulation but the Commissioner and/or the Secretary has the ability to waive IRB requirements.

To my recollection, as I say, this has certainly never been done in the form of waiving IRB -- an IRB -- the entire requirements for IRB review, although the regulation states, in fact, that that provision could, indeed, be a possibility.

DR. MACKLIN: And how would that then square with the role of OPRR? In other words --

DR. LEPAY: I would expect -- again there are certain provisions within 45CFR46, and I would have to consult with my colleagues over at OPRR, that, in fact, do provide some level in which the Secretary does have the ability to look at specific requirements under that regulation. So again the Secretary and by delegation the Secretary's authority within FDA is delegated as well to the FDA's commissioner.

But I think as we are talking about this you

are -- you are really -- you are looking at a regulation, of course, and I think that is a very valid point. I think that the counterbalancing point is, in fact, the application of this regulation and the fact that in these sorts of circumstance this ha never actually occurred.

It is a useful regulation from certain standpoints and I think I articulated one of those where we do, in fact, have protections in an international setting where a sponsor would like to come in and otherwise put themselves in -- under a regulatory umbrella of a U.S. application and we think again that that level of control is just -- justifies making some minor provisions, if you will, to implement the ICH guideline as a standard that will -- where there may be certain specifics that can be waived but we will accept the ICH provisions as equivalent.

DR. SHAPIRO: Thank you. Let me ask a question. I am trying to ask it carefully.

First of all, I think the effort as I understand it obviously has taken a lot of time and commitment to get more harmonization here and I understand the very worthwhile effort given that there are so many people operating in so many different countries to have this more harmonized or even

completely harmonized at some stage. It is certainly a very worthwhile effort and you and your colleagues deserve our thanks for working hard on this.

On the other hand, when I think of the issues that this committee is struggling with, the ethical issues that have come up, they seem hardly touched by all this effort. And that while this is a very worthwhile effort, I want to say that again because I am not trying to be critical of the effort at all, the issues that we are dealing with just are, I guess, in some other category or dealing with some other aspect of this.

I do not know if you -- you were probably not here this morning to hear the discussion but do you think in all of this harmonization -- maybe I have to ask it a more positive way. Do you think in this harmonization that there were important ethical issues as you see them addressed and resolved?

DR. LEPAY: Well, I think that the concept, in fact, of certain standards in informed consent and informed consent process are very important and very valuable standards. Helsinki, as we say, is not very explicit as to requirements there and, in fact, this, indeed, was a major achievement.

Another major achievement really deals with

the whole process of institutional review and what kind of requirements would be put into place there. I think those are very basic protections that, in fact, provides a level of oversight during the course of a clinical trial.

Obviously, we are all limited in terms of what we can see individually within a clinical trial as regulators with the resources we have available to oversee any or every particular clinical investigator, every particular clinical trial site.

Much of what we have to rely on are systems -- a systems focus, a process focus, and I think that is the very valuable achievement of the ICH GCP work thus far. It is a harmonization effort that has successfully put into place across three very large areas, certainly three very large economic areas, principles of ethical conduct of clinical trials that are largely harmonized from a standpoint of oversight of those trials and processes in place.

DR. SHAPIRO: Let me ask the question in a different way. I really do respect very much the work that has been done and I do not mean for anything I am saying to you to reflect otherwise. But have -- investigators who are working in this country requiring FDA approval for their work before, is anything

different for them now than before?

DR. LEPAY: From the ICH process itself, no because again, I think, that that was part of -- the goal again was to develop very basic standards that, in fact, could be applied internationally.

DR. SHAPIRO: Thank you.

Steve, do you have a question?

MR. HOLTZMAN: Yes. Maybe it gets at what you were getting at in a specific example that beyond just process kinds of aspects of harmonization, the goal ideally from the industry's perspective is that whatever will be sufficient for registration of the drug in one market would be true for registration in all markets.

DR. SHAPIRO: That would be valuable.

MR. HOLTZMAN: Right. That is the thought.

I think the following statement is true: The FDA's view in certain kinds of cases of requiring placebo control trials will not necessarily square with how Europe will take the view all the time and some of those studies which the FDA would require for registration would not be considered ethical in Europe, okay, because they would say, "We cannot use a placebo control."

So the question there in terms of harmonization, when you guys ran into that kind of

issue, which does raise an ethical concern, was the decision that, well, we will just continue to not be harmonious with respect to what kind of trials will be necessary and sufficient.

DR. LEPAY: Again, you know, this is a process that goes on within our review end of the house and I want to kind of emphasize again that one of the processes that we try to put in place in encouraging international trials to come in under the IND process is to be able to discuss with them prospectively up front the kind of trial design, the issues of trial design, the issues of conduct of study.

But I want to emphasize again within our own authority when a study is conducted outside of the United States, outside of the IND process, our authority to oversee the design of that trial only comes after that trial has been conducted and is submitted as part of an application for our review. It is not within our scope of authority.

MR. HOLTZMAN: That was not the question.

The question was when you guys were sitting and talking about this and you were staring at the fact that for this drug this study would be necessary and sufficient in Europe for registration but would not be in the U.S., conversely this study in the U.S., which

was placebo controlled would not be allowed to be done over there, and hence would not be -- because it would not be considered ethical, hence they would not accept the data from it. Did you look at it and say this is an issue we need to think about?

DR. LEPAY: These are issues that are still -- again, the ICH is an active process. There are many areas that we are still looking at harmonization on, including ethical issues, including ethnicity issues and this is not -- this is a process when we are focusing here or at least what I am trying to focus on here is an oversight process. ICH is by far not completed.

DR. SHAPIRO: Thank you.

Laurie?

MS. FLYNN: You may not know the answer but I was interested to see that somewhere in that material it seemed to me you indicated that there were differences in various places and, for example, in Japan they had been used to oral consent. Am I correct?

DR. LEPAY: That was the one.

MS. FLYNN: Has that now been changed? Are we now seeing a move towards another standard or another practice there or how do we understand the impact now of this harmonization effort on some of those?

DR. LEPAY: Absolutely. Oral consent is no

longer part of the Japanese system. This is no longer allowed under law in Japan. ICH is -- the GCP standard is law.

MS. FLYNN: Is now law, and when did that occur?

DR. LEPAY: In Japan -- what did I say? '98?

MS. FLYNN: '98. Recently then?

DR. LEPAY: Recently, yes.

MS. FLYNN: So we have seen at least some movement through this process to try to institute some more basically understood protections?

DR. LEPAY: Absolutely. And that is one area -- again I did not really touch on -- is what we are seeing from the standpoint of experience in clinical trials. We are starting to see from an inspectional standpoint. We have always had more difficulties with international trials in terms of the acceptability of data. There being data integrity problems and problems with informed consent, problems with IRB oversight.

We are starting to see a decline in the percentage of seriously violative inspections coming from areas where this harmonization is occurring. We are starting to see much greater compliance, complete compliance among clinical sites and clinical -- among clinical investigators and I think that is a positive

certainly that we have seen in the past three or four years to come from this.

DR. SHAPIRO: Bernie?

DR. LO: I want to thank you also for your very detailed and thoughtful presentation.

I am trying to think through the issue of research in developing countries as opposed to research in international settings, which may involve, you know, Britain, Germany and such.

We have heard a lot of allegations that the informed consent process in the developing countries in clinical trials is often not the ethical standards we would like to see. Concerns that people do not understand that this is research and not clinical care. They do not understand a placebo, that people elsewhere in the world might be getting standard treatment that is different than what they would get, et cetera.

I notice in the slide on page 11 when you look at the -- when you give the sites of foreign inspections, it seems that most of the sites of foreign inspections are actually industrialized countries as opposed to developing countries.

Do you have any -- or do you or any other branch at FDA have experience actually going to Africa, Asia, where some of the allegations of recent trials

have been made, to look at the informed consent process and sort of provide some independent confirmation or rebuttal of charges that the consent process there is inadequate?

DR. LEPAY: Well, there really -- this is a two part answer really.

First off, again you have to remember where our authority lies to look. We can only look at international trials when they are submitted to FDA as part of an application.

So the question is are there trials, in fact, that are not meeting ethical standards that may be performed that a sponsor appreciates these problems and never comes forth to submit to these to a regulatory agency and, therefore, nobody is looking at these? Certainly that is something we cannot answer and it is outside of our authority to be able to do so.

Among those studies that are coming in as part of an application and -- admittedly these are going to be studies that are submitted probably fairly late phase studies, they are going to have more intensive monitoring and auditing by a sponsor. These tend to be large pharmaceutical companies. They will invest heavily in them because they want these studies certainly to be acceptable to regulatory authorities

from the start.

Those are what we are able -- those are what we inspect. That is what we are able to go forth and look at. Even among that type of study, of course, what we do see, we do see a gradation and historically the gradation used to be U.S. and Canada versus the rest of the world.

As the harmonization process has taken place, as we have gone through the late '80s and early 's, the European Union or at least large parts of the European Union are beginning to look more like the United States in terms of what we are seeing.

We still see a gradation, though, as we are going into new areas and virtually every time we go into a new area we usually find some kind of problem there that recapitulates historically what we have seen first in the United States when we stated in the '60s and then in the European Union in the '70s and '80s, and as we are going, you know, into other areas now, into the Far East, into Africa, into South America.

I think what -- we do see more problems there, yes. And, of course, that does impact on our ability to accept data. We certainly do reject data. Twelve to fifteen percent of studies from developing areas. That is not an unusual rate of rejection of sites and studies

for FDA at this point in time versus maybe three to four percent from the United States.

The other part, I think, of your question is, yes, we are moving into areas. We move to where the applications are coming to us from and I think that is the slide that follows.

If you look -- what I am showing you in that following slide are areas where we have gone for the first time, which means it is the first time we have received data as part of a pivotal -- that is an NDA application for that drug sponsor and you can see in '96 it as tending to shift into South America; '97, '96, '97, a little bit into Eastern Europe; the beginnings again in Central America, the Pacific, Africa, more so in '98 into Eastern Europe; and now we are starting to see again some increase in Africa; and in the Far East in China. Our first inspections in China itself.

Some of these are very well conducted in what we are receiving. In others again we do see significant problems. But our expectation, again, is that it is very important for us to be able to continue looking. This is part of our process and so it is an ongoing process.

DR. SHAPIRO: Thank you.

Other questions?

Well, once again thank you very much for a very careful -- I am sorry, Bernie.

I am sorry. I did not see your hand.

DR. LO: As long as no one else wants to ask. One of the suggestions was made -- that was made to this Commission several meetings ago was to try and distinguish between the process of informed consent and the documentation of informed consent.

And a number of people whom we had commissioned to do sort of qualitative studies of research again in the developing countries as opposed to international research said -- gave us examples of situations where requiring written informed consent from participants was culturally inappropriate in that society and they thought that it would be preferable to focus on whether the consent process had taken place rather than the documentation.

Now assuming that that is sort of a valid sort of ethical policy point, I note that in your slides in both the FDA and the harmonization it is written informed consent is required.

In your discussions in this process did this issue of trying to distinguish between the consent process versus the documentation and the possibility there would be situations in which written signed

consent may not be appropriate, did that come at all and was that resolved?

DR. LEPAY: Certainly that was a discussion point and I think again in Japan that was probably the most -- a fairly important issue in discussion on harmonization. And I think as the dialogue evolved in process there was a gradual appreciation or a gradual interpretation that, in fact, this may be culturally difficult but it was certainly something that was achievable.

And I think that this is the dialogue that we are having as we are going from areas within the ICH and outside of the ICH. In the last year this is certainly taking place on several fronts.

We have had discussions in the past several months with the Pan American Health Organization so across Central and South America.

We have just had -- I just returned from a series of meetings over at the Hong Kong Academy of Medicine, which were attended by representatives from China as well, and there were discussions there about again the same sort of issue. This may be something that we are going to have a problem with but I think the general belief is that it was something that they could incorporate and certainly there was an incentive to do

so.

DR. LO: Okay.

DR. LEPAY: The process -- again when you are putting together a guideline the best you can do, of course, is to articulate your experiences and what your objectives are in both the concept of a written document as well as in terms of process.

This is again why we have put such emphasis within FDA on the on site observation, the bioresearch monitoring process, both domestically and internationally. Part of our inspection program is focused not only on assuring that there is written documentation.

Obviously one cannot easily return to the subjects themselves after the fact and sometimes these can be months or years after the fact. But you can spend time interviewing the research nurses and the physicians to discuss with them, to go through the process of how they obtain consent and at least to get information at least as to what their understanding of the process was and what they actually at least are stating that they put into place as a process.

DR. LO: If I could just follow up. I mean, as I recall, some of the ideas that were presented to us were along the following lines: That there were

countries in Africa where there is a history of repressive totalitarian regimes and subjects feared that signing a consent form might somehow link them with an official government agency in a way that might come back to haunt them if the government changed.

So there were concerns, although they had understood the consent process and had agreed, they would not feel comfortable, the subjects, actually -- participants signing a consent form and that, therefore, so the argument runs our requiring written consent would actually be ethically inappropriate in that situation and not respect sort of the dignity of the participants.

It seems to me that is -- I do not know if that is a different kind of argument than what you might have faced, for example, in Japan where I do not think that kind of argument would necessarily come up.

Has that been an issue in your harmonization discussions or do you think there is any validity in that kind of argument as it was presented to us at earlier meetings?

DR. LEPAY: I think it is an important issue because remember we are starting harmonization process at several levels. I think -- I will not put it in quite the same terms of ICH. Again ICH -- you can see by the representation the interest there was to discuss

within -- procedures and practICHs within their own jurisdictions, not necessarily outside of those jurisdictions.

Well, we are going into these sorts of conversations now more and more as we are starting to evolve these. Again we have not had as much dialogue yet with the WHO. This is beginning. It is beginning on several fronts and I expect that that will be an area in which we will certainly have increasing interaction as time continues and other major organizations or outshoots of the WHO such as the Pan American Health Organization.

There are areas certainly for very active consideration and debate but again there is no comparable harmonization document within these areas that exist that resembles the ICH process or is far along in process as ICH.

So I think we are talking toward the future and I will say I think the future for harmonization is a very positive one. I think it is the direction that we all want to go because I think it is important to at least have a better understanding of ethical standards and to be able to come to some mutual appreciation, if you will, of what is happening and what, indeed, we are receiving in terms of information here.

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

MR. HOLTZMAN: Yes. One of our speakers this morning pointed out that we are seeing more of a globalization these days of clinical trials, in particular, seeking test subject populations in undeveloped nations.

As one thinks about the ICH process if you are a drug company looking at a big Phase III you want to be able to support your U.S. application, your NDA, which means you would prefer to see ICH sort of standards, you would prefer to see therefore that study in China conducted according to the ICH standards, and there is a good side to that. It means the likelihood you will have better conditions of consent, et cetera, et cetera.

But the other implication of the speaker this morning was that you would be testing in a population which was unlikely to ever receive the drug itself and hence have a benefit. I believe in the Declaration of Helsinki are notions that you ought when you test in subjects that they are likely to get a benefit from it.

So as part of the saying it has got to conform with at least Helsinki, does the FDA say given the test population, assuming consent, et cetera, was done according to GCP, this is acceptable, this study if and

only if that population was likely to be able to benefit if the drug is approved?

DR. LEPAY: Certainly there is no such policy statement on the part of FDA. We do, of course, recognize the Declaration of Helsinki's addressing of these issues. And it is certainly something that comes up for consideration and it has certainly been a topic for discussion. It has been a topic for debate at advisory committee meetings as well as within review divisions themselves. So that -- you know, that is the extent to which I can really answer your question.

DR. SHAPIRO: Thank you.

Any further questions from members?

Ruth?

DR. MACKLIN: Well, one factual clarification. That provision is not in Helsinki. It is in CIOMS. And, I mean, it is just important to know where these things appear because --

DR. LEPAY: That is correct.

DR. MACKLIN: -- as we heard, it is Helsinki that is referenced and not CIOMS, and this is in CIOMs and, in fact, it appears as a commentary in CIOMS, not as a principle but it is there.

DR. LEPAY: I have to redirect because there was a very recent meeting, I am sure many of you are

aware, in London dealing with the Declaration of Helsinki as a workshop and this subject also was broached at that time as well.

DR. SHAPIRO: Comments, questions?

Once again, Dr. Lepay, thank you very much for being here today. We will -- I propose that we take a ten minute break now and let's try to reassemble at 3:15.

(Whereupon, a brief break was taken from 3:02 p.m. until 3:22 p.m.)

DR. SHAPIRO: Okay. We now want to proceed to have some discussion. I will turn to Ruth in a minute to give us some introduction but it is primarily centered around the document we all have under Tab 2F in our books, which is entitled "Assessing Risk and Potential Benefits: Ethical Aspects of Research Design," in which you have set out there a number of propositions which we are asked to choose amongst.

We are being asked to actually make some decisions and defend them here as opposed to making statements and let them hang out there so that, itself, is a discipline.

But if you notice, this is set out in four different categories. The first one has to do with

availability of treatment and so on. One, two, three and four. And in the first case we are supposed to choose from two, the second from four, a third from two, and a fourth from two.

Now what really is important in order for Ruth and Alice to make some progress here is that in the next hour or so that we really get to discuss -- have some discussion, even if it is not final, just an initial discussion on all four of these.

So the way I propose to proceed is to spend about 15 minutes on each one and then go to the next so we get at least some shot at all four and then we can come back with whatever time is left and rediscuss items one through four and so on.

I want to do that since that will be most helpful to our colleagues who are going to be writing this material as opposed to spending all our time on item one, which we could easily do, and not get to two, three and four.

Larry?

DR. MIIKE: Looking at those four, it seems to me that we need to discuss one first -- I am sorry, four first because if you make the particular choICH in that item it is going to affect one, two and three because it says that if we say, no, it should not be done then it

totally affects our decisions on the other three there.

DR. SHAPIRO: Four is the undue inducement.

DR. MIIKE: Right. But if we say that providing that treatment is undue influence, what do we do with those other three categories?

DR. SHAPIRO: I did not -- I certainly understand that although I did not have that reaction myself but I want to do what I think Ruth would find most helpful. So you can tell us if we -- it is important to you that we go in order here or can we go and take them up?

DR. MACKLIN: Well, since I do not think we are going to conclude that any of this would be an undue inducement, this is just a prediction and, therefore, we do not have to get to one, two and three, in any case our report is going to have to say something about all of these. So even -- whatever the consensus of the Commission turns out to be, we will have to address in the report all of the items.

DR. MIIKE: Oh, I understand that. I am just saying that the way that they are laid out you sort of end up and we would say, "Hey, wait a second now, we have been discussing all of these things and now all of a sudden I am faced with a choice which I should have made before I went on to one, two and three."

DR. SHAPIRO: I have no objection myself to starting with four. If Larry thinks -- if you think that will help us go faster --

DR. MIIKE: It just seems --

DR. SHAPIRO: I think we are going to have agnosticism here.

(Laughter.)

DR. SHAPIRO: We will spend 15 minutes only, though, on each one of these and then we will come back and see whatever else has to do be done.

So why don't we take Larry's suggestion, which is this on page three --

DR. DUMAS: From the back forward?

DR. SHAPIRO: From the -- well, from the back anyway.

(Laughter.)

DR. MACKLIN: Can I just get a couple of preliminaries out of the way before we leap over to four?

DR. SHAPIRO: Yes.

DR. MACKLIN: The Commissioners may want to know where these propositions come from anyway. I am sure someone is going to ask that. The answer is that Alice and I made them up but we did not make them up out of whole cloth.

We made them up based upon statements, arguments, articles, some of which you heard this morning actually, and we were pleased, in fact, to see that some of these propositions that we developed for consideration at this meeting were quite relevant to the six presentations that we heard this morning. So think of that as the background for these even though we devised these propositions even before we heard the good panels and the speakers from this morning.

The second thing to point out is the two assumptions that we start with here and there is a little asterisks. Let me just say something very quickly about the assumptions and the asterisks.

First, let's look at the asterisks. You see these words: "Established effective treatment." The asterisks says this term was chosen. It is a tentative. It is a provisional term for our purposes but it was chosen because it is less controversial than the various terms currently in use.

Now we saw from the presentation this morning, Sid Wolfe and Peter Lurie, not only the current wording of the Declaration of Helsinki, which is the best proven diagnostic and therapeutic method but also another phrase, the "highest attainable or the best -- the highest attainable method that is otherwise available."

These are the existing words and some proposed words.

In order not to leap into that, and this is not necessarily compromised wording, it is different wording, but in order not to leap into that fray we chose tentatively these terms and again I was pleased to see that two of this morning's speakers used these words.

Actually Steve Lagakos' presentation, which I had not seen before this morning, used these exact same words "established effective treatment" and in Dr. Dickersin's presentation she talked about an "established treatment that is efficacious."

So I know that there will be a push to define this and to say more about it but if we could -- and we will. We will have to do that. But rather than spend all the time doing that at the beginning, just to note that a treatment can be considered established in the obvious way, namely if it is an approved drug, or if it is not a drug there are a lot of other interventions of various sorts that are considered established.

And once again the underlining here says it is intended to refer to a treatment that is established and effective anywhere in the world. That is just to make sure there is no ambiguity and it does not mean established and effective in the country, in the

developing country where the trial is to be carried out.

So we could, if Commissioners want, at some point come back to this phrase but I fear if we start with it we will never get beyond it.

DR. SHAPIRO: Okay. We will try to accept that discipline as well and see how long it lasts but we will try.

(Laughter.)

DR. SHAPIRO: Let's go again to item four and we will spend, as I said before, about quarter of an hour on it.

Larry, you must discuss this discussion.

DR. MIIKE: Well, clearly if we pick anything we might as well go home. So I obviously would pick D except that it is a little curious because the discussion around this issue has been more like it is a moral obligation to provide that and in this list they are going sort of like, well, it ain't so bad, you know. You get the gist of what I am trying to say.

DR. SHAPIRO: Thank you.

Other comments on proposal four?

Bernie?

DR. LO: Well, I think I am going to fall into the trap that Ruth was hoping we would not fall into. I guess one thing that struck me about our four person

panel this morning right before lunch, our four epidemiology clinical trialists, was that in a given case there is going to be disagreement as to whether something is established effective treatment or not.

So I think a hard issue is not when everybody agrees it established effective anywhere in the world. It is when there is some controversy of equipoise almost where some people are saying, yes, it is established and other people say you are crazy, it is not established at all.

And it seems to me that is the harder issue. If everyone agrees that it is established and effective it is going to be relatively easy to get to an agreement but in the controversies we have been hearing about that is exactly the issue, is it or isn't it.

DR. MIIKE: To respond to that, Bernie, I think that is a separate issue all together from what they are trying to get at because when I am looking at this it is really in the context of people saying it is okay to withhold treatment if it is not available in that country and I hear strong opposition to that statement, you know, from our panelists as well as among ourselves.

So I think what you raise is a totally separate issue from what is on the table.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I totally agree with that.

DR. SHAPIRO: Tom?

DR. MURRAY: (Not at Microphone) I would probably opt for 4B with modification because it is possible that under some circumstances -- an alternative can be established -- might be -- but I would say there also may be many circumstances of where there would probably be exceptions and a lot would depend on the particular facts of the specific case.

So if we put language such as line 22 on that page does not necessarily or perhaps in all cases or routinely would probably --

DR. SHAPIRO: Jim?

I am sorry. Ruth?

DR. MACKLIN: Just a small point. Again these statements, these propositions are stated in the starkest of terms. Now I think what you are doing and suggesting is probably the way they are going to come out, right, because there are few, if any, absolutes outside of absolute zero in some propositions in mathematics. Therefore, there will always have to be some kind of modification.

So with the understanding that the starkest or most extreme form might be unacceptable, what our report

will have to say is this is the presumption. Okay. When you say not necessarily or there is a presumption that or in most cases with the understanding, and then there would have to be some kind of exception. So, I mean, that is a well taken modification.

DR. SHAPIRO: Jim?

DR. CHILDRESS: I am basically in agreement with Tom and say basically that what we would end up saying is it is not in principle ethically unacceptable but we would need obviously to look at the kinds of circumstances that might be involved. The class (sic) is that tentatively is being made I certainly sign on to it as well.

DR. DUMAS: But which one are you signing on to?

DR. CHILDRESS: 4B.

DR. DUMAS: I vote 4B too. Going, going --

(Laughter.)

DR. SHAPIRO: It is not required to --

(Simultaneous discussion.)

PROF. BACKLAR: (Not at Microphone). I am sorry I am late because I am particularly interested in this, as Ruth knows. I feel like this is -- why is this part different from any other? Are we supposed to vote on this?

DR. SHAPIRO: No, no. This is --

(Simultaneous discussion.)

DR. SHAPIRO: We are not at that stage yet.

PROF. BACKLAR: All right. Good.

DR. SHAPIRO: We are just trying to get some feedback to help Ruth understand where we are coming from on some of these issues and so on.

Eric?

DR. CASSELL: Well, just to make it easier --

(Simultaneous discussion.)

DR. SHAPIRO: That is a word we --

(Simultaneous discussion.)

DR. CASSELL: If we take away the word "undue" does it constitute an inducement?

DR. MACKLIN: Yes, it does but -- it may but the usual distinction in research is the distinction between an inducement and an undue inducement.

DR. CASSELL: Yes, I understand that.

DR. MACKLIN: Yes.

DR. CASSELL: I understand that.

DR. MACKLIN: So, I mean, if we say it is an inducement it does not yet tell us whether or not it is acceptable or unacceptable.

DR. CASSELL: Exactly. Exactly right. So what we have done -- what we know first of all is it is

an inducement.

DR. MACKLIN: Yes.

DR. CASSELL: And that, therefore, we would have to lay down some of the rules. What would make it undue? Would it make undue if in the face of an epidemic the only people, the sort of chance in their eyes, of surviving would be the people who were part of this project? Would that be an undue inducement? Or an epidemic which is already attacking -- which has already involved 65 percent of the population and this offers some promise and so forth, would that be an undue inducement?

So there we go, right? I was once asked the question testifying in the Army whether a boot could do this injury. I mean he kicked some poor guy in the head and knocked him silly. Could a boot traveling 65 miles an hour --

(Laughter.)

DR. CASSELL: The very relativity of it, I think, is the important point. I think that is the important -- that is one of our things we are going to get to, I think, when we are on the other side of this issue. The black and white is going to disappear.

DR. SHAPIRO: Bernie?

DR. LO: Is there an empirical issue here as

well? I mean, we have certainly heard allegations from newspaper stories that quotes from people saying, "Of course, I was going to sign up, you know, that is medical care and I really had no other option. I was going to die of this disease everyone dies of."

So would it make a difference how many potential participants in research viewed it as they really did not have a choice if they wanted to do what was best for them or is this purely a philosophical argument we are making? I mean, to what extent is this going to get tied back to the actual beliefs that impelled participants in the country to decide to sign up for the study or not?

DR. MACKLIN: Can I respond? I think this is a good example of the need to get some of those data about -- from trial participants in other countries. What we have now is at best anecdotal but I just -- you know that you have seen -- is it in this briefing book? Forgive me if I do not remember -- but the work that Elisa Eiseman is doing with the existing -- you know, the five part study of the views of participants in research in developing countries.

And although what we have are some comments here and there, we have a number of items that are already in the studies. I just finished rereading

reports to WHO by a researcher in Chile and one in Brazil. The one in Brazil is a very long detailed study.

The other one is a little shorter but also documents in a -- this was a carefully designed study of research participants in those two countries. And it is quite clear that from these two, which I just reread over the last several days, there is clear evidence that one of the motives but not the sole motive but possibly the prevalent, the predominant motive, for people is to have access to something they would not get outside the trial.

And again how much evidence we would need? I mean, this just is attempting to answer your question briefly that there is some evidence for it.

DR. LO: Yes. So my only question is should we be looking at the evidence before we make up our minds on proposition A versus B?

(Simultaneous discussion.)

DR. MACKLIN: It is not contingent for the following reason: There are some people who have said if we offer this it would be an undue inducement and, therefore, as that hypothetical -- I mean, we have heard that argument in various places at various times. Some of the very people quoted this morning that Chris Whalen

referred to, Edward and Beatty, and other people have written and said, "If we were to offer triple therapy in the course of an HIV preventive vaccine trial it would constitute an undue inducement." So prospectively as an argument one could use that as a reason not to even consider it.

So I think we can work both with the empirical information we have but also with the hypothetical because it is relevant to what one would think of doing.

DR. SHAPIRO: Trish?

PROF. BACKLAR: Also, I hope you have not discussed this before I got here --

DR. CASSELL: Do not worry. There is still something to discuss.

PROF. BACKLAR: There is something in this that I find a little bit complicated still and I go back to the fact that if this is a trial that is a randomized controlled placebo, you do not know whether you are going to get this anyway. Right?

DR. MACKLIN: Right. But it is giving someone 50/50 chance of getting it.

PROF. BACKLAR: Not necessarily 50/50 depending on how many arms --

(Simultaneous discussion.)

PROF. BACKLAR: A percentage of a chance.y

DR. LO: No. I thought 4B was for the control group so presumably --

DR. DUMAS: It is the control group.

(Simultaneous discussion.)

DR. LO: Right. So it is not the issue of 50/50 randomization. It is the minimum that anybody on the trial is going to get.

DR. DUMAS: Can get, yes.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: I guess this is directed to Ruth and people like Alex who have studied this stuff and have thought about it for a long time.

When you talk about -- particularly about undue influence and coercion, what do you mean and how do you think about it? What I mean by that is that -- is someone doing something that could be in their rational self-interest? Can that fall within a concept of being coercive or being undue influence?

DR. DUMAS: I do not think so.

MR. HOLTZMAN: So I am really -- when you guys use these words they have a rich history and meaning that some of us who are not familiar with the literature and had not thought about it do not really know we would be agreeing to or not be agreeing to.

I understand what coercion means where I can

think of it in terms of coercion and the paradigm there is maybe doing things where I do things against my self-interest but I am forced into doing them.

So I am trying to understand how you guys think about it. Is that reasonable?

DR. SHAPIRO: Alex?

PROF. CAPRON: I am sure Ruth and I have different responses, not that we are going to disagree but probably just come out of somewhat different backgrounds on that.

A lot of the discussion of all consent issues in research talks about the fact that we are talking about constrained choices. I mean, the notion of putting one's self into a Phase II trial, for example, of a cancer chemotherapy is the sort of choice which when we talk about it being made freely or something we are obviously talking about it being constrained by the circumstances.

So then one of the questions arises what do you make of a circumstance such as the one we are talking about here where a person who goes into a trial and ends up either getting that active agent or the control agent is in either case going to get something which is unavailable for them and depending upon the gravity of the illness something which may be "their

only hope" if the prevailing treatment is merely palliative.

Some people in these circumstances in applying the notion of undue inducement focus solely on the person's -- the subject, the participant's own thought processes and what he or she would have to weigh. Others focus on whether or not the action of the individual offering that is offering it in order to manipulate the choice.

In other words, that -- is this mal (?)or mal prohibitive? Is it something that is so wrong in itself or is it something which is only wrong because we choose to say in certain circumstances that it is wrong?

Offering someone more treatment than they can otherwise get could be viewed as something which we would usually regard as a good and not an undue inducement to accept that treatment.

Is it an undue inducement to make one's self a research subject? And there it does not seem that the choice is this intervention risky but, of course, is participation in the research and ending up in the other arm of the research risky, unduly risky?

And I -- I mean, I do not know there is a perceived view -- clearly the phrase "usually" deals with context quite separate from this where one is

simply treating it as the offer you cannot refuse, which has that sense of almost -- it is the good version of an onerous extraction.

It is something which overcomes the will and so, as I say, it is usually looked at the viewpoint simply what does it do to the freedom of the person to make a rational choice.

And offering the only cure for your child is equivalent to saying I have a gun to the head of your child. If you do not do something else that I want you to do I will kill your child if you see what I mean. In other words, undue inducement is seen as a bad because it may -- it becomes a choice which you cannot refuse. You just cannot choose other than what you would do.

MR. HOLTZMAN: But what is important in that is that cannot choose otherwise and you would if you could.

PROF. CAPRON: You would if you could but that is what I am saying about the additional --

MR. HOLTZMAN: But in the case of the terminal patient with no known treatment they rationally choose the experimental treatment precisely because it is the rational alternative yet it is the only choice available.

PROF. CAPRON: Well, no, but see that is --

MR. HOLTZMAN: That is what I am asking, how that is thought about?

PROF. CAPRON: See the thought here is that the experimental treatment is actually not the only course of available. It is the course that is available in the developed world which is the -- is the choice that is available. It does not happen to be available to them now so do they choose to take the unknown risk of getting the experimental intervention versus nothing, which is what they are getting now, over -- because they are being offered the possibility that they will be in the control arm and get the good thing.

Of course, this becomes additionally complicated if the good is, in fact, delivered to people in both the control group and the other, that is to say if the good is a level of medical care, this is one of the arguments about prisoners being used in circumstances in which the general prison population or the general population at an institution like Willowbrook in the 1960's is at a very low level and the offer to go into a treatment -- excuse me, an experimental arm offers a much higher level of care and release from certain abuses or detriments to life.

DR. SHAPIRO: Okay. We are going to have to -- but, Jim, and then Tom very briefly, and then we will

move --

DR. CHILDRESS: Actually mine is a little different. I have a question for Alex. I guess the way I have tended to think about this and have thought about the literature over time, I was a little surprised that you put -- and you may be quite right interpreting this in the law and in the general discourse that sort of the undue inducement and the coercion for you are relaly closely tied together and it is just simply a positive or negative version but it seemed to me to be sort of stronger than we often think about undue inducement but I may be just quite wrong about that.

PROF. CAPRON: No, that is why I say is this something which seems wrong in itself or is only wrong as an act which we prohibit in this context. And as I say, usually giving someone -- offering someone a good treatment that they could not otherwise get would be seen not as a wrong at all and so we would not -- we would not usually class the offering of that as something which would overcome your will and be inappropriate. It is only in the context where is what we are asking you to do in the process something which makes it that way.

If being a participant in a particular kind of research -- I mean, if you were offered $1,000, you are

a poor person and you are offered $1,000 to allow a little blood to be extracted for an analysis where the analysis does not get into any of these kinds of things that have terrible social consequences for you, it is just a cholesterol measure and they are doing -- they want 100 college students or something.

We say, well, the researcher is spending a lot of money but we do not call it an undue inducement because he is -- in the context he is not putting somebody in a circumstance where a rational person probably would not want themselves to be in absent this kind of extra push.

I mean, that is where the thing would be it is as though they held -- there you would not say it is equivalent to holding a gun to someone's head because what you are asking them to do is not so terrible.

Is taking this particular research intervention in that category? That is part of what -- it seems to me it goes into evaluating whether we call it an undue inducement.

DR. SHAPIRO: Tom?

DR. MURRAY: Very quickly. If I may coin a phrase, I think we engage in a little biological archaeology here and go back and look at what people thought they were getting at when they proposed the

language and the concept of undue inducement. That is not the question --

PROF. CAPRON: Oh, no, I mean this is an old concept in the law. It invalidates contracts.

DR. MURRAY: Not the law but in particular --

PROF. CAPRON: Yes.

DR. MURRAY: -- in the particular context of the debate about the research on human subjects, what people thought that was capturing and I think we could do that and also what Eric and Bernie were sort of suggesting to think more about the empirical circumstances under which we would count something as an undue inducement. So I am asking for both some conceptual work that is a little bit historical and some at least look at the empirical.

DR. SHAPIRO: Ruth?

DR. MACKLIN: I was only going to say here that I -- this concept goes all the way back, I guess, much earlier to the claim that we -- that the voluntariness for enrolling in research, the subjects would be recruited or enrolled without force, fraud, deceit or undue inducement. It is not called undue influence actually in the U.S. Federal Regulations.

I am not sure that will help though, Tom, and

the reason is this is a judgment that has to be made all the time by IRBs almost always in the context of offering money to normal healthy volunteers or to people who are coming in for focus group discussions.

The question how much is too much when the researcher says, look, you have got to offer these people something, otherwise you are not going to get anybody to come. We will pay for their car fare. So you have to offer them a little.

So when an inducement becomes an undue inducement back to what Eric says is something that has to be grappled with in the individual context and it is precisely what IRBs do so even if we look back and find out what -- the motives were simple, you know, you do not want to coerce people into being research subjects. It has to be voluntary.

But whatever the history was, any IRB has to look at this probably protocol by protocol knowing as much as one can know about the background conditions as Alex pointed out the constraints.

DR. MURRAY: I think it would be useful.

DR. SHAPIRO: Okay. We are going to go on now even though we did not quite stick to my announced time constraints on this one. We can come back to it later if there is time.

Let's just look at item three.

DR. CASSELL: Item three. Are we really going backwards.

DR. MACKLIN: No. We really should -- I think -- excuse me if I may. We just -- we really should start then at the top because three is a very specific. It is almost a subclass of what is otherwise.

DR. SHAPIRO: So you want to start --

DR. MACKLIN: Yes. If it is okay with Larry.

DR. MIIKE: No. I would -- one through three is reasonable.

DR. SHAPIRO: Okay. Eric, and then Larry.

DR. CASSELL: Well, I had as much difficulty with these things as I think everybody else does except -- and my -- I looked at this and I thought, well, what about the times when we say was it ethical or not ethical to provide medical care to a group of people who would not otherwise get medical care. There were some specific examples.

The medical care project that went into Mississippi at one time during the War on Poverty. There was poverty money. It went in there and brought in all kinds of stuff. The money folded and out they went and there was a great deal of discussion at that time of whether they did more good than damage by what

they did because they raised expectations and then they left.

DR. DUMAS: Who made the judgment?

DR. CASSELL: Well, that was the argument. It was not -- that is -- I think my point about it is not that it was the wrong thing to do but that what seemed like an obvious good, they are going to go in and give medical care to a bunch of people who otherwise would not have any turned out at least to be open to question because of the consequences of it. And that is -- as I look at these, I have the same problem.

My own sense of it is if you take care of somebody for that period of time, whatever you did at that time, you did some good and it is easy to walk out and then you pay no attention to the back and no attention to the front, and if you do that then I think the answers are easy but the minute we begin to get into the consequences, the longer term consequences, the nature of the disease that we are in and so forth then it begins to change.

And that is really my point about it, that it is affected by those variables that are very real, the nature of the disease, the population you are in, the consequences of treating and then walking out.

DR. SHAPIRO: Larry?

DR. MIIKE: I have a suggestion to make. I have to give in to a temptation. I guess what we are going to do is our usual method of obscuring our way to a clear answer rather than starting with a clear answer and making it obscure.

(Simultaneous discussion.)

DR. MIIKE: Number three, I would suggest the following change.

DR. SHAPIRO: Number what?

DR. DUMAS: Three.

(Simultaneous discussion.)

DR. MIIKE: No, 1C. 1C. But from the last phrase "when the availability of a treatment following the trial has not been determined..." I would suggest changing that to "whether or not the availability of the treatment following the trial has been determined." It is a -- it is not a -- it is a substantive change.

It should make no difference whether or not the availability is determined, has been determined, rather than just one side of that.

DR. CASSELL: Clarification of a very small point.

DR. DUMAS: Well, it is in the first one.

DR. SHAPIRO: But if one made that change what would your views be on these propositions?

DR. MIIKE: What?

DR. SHAPIRO: What would your view be on the proposition of 1A and B?

DR. MIIKE: I would pick C.

DR. SHAPIRO: You would pick C.

DR. MACKLIN: Could I just ask -- you said it is a substantive change. It is really 1D. It would really be a different item, that is one might then have to choose between 1C and the one you propose.

DR. MIIKE: But what I am saying is that to me it does not make a difference whether or not the treatment is available.

DR. MACKLIN: Well, that -- because that is a new proposition that we did not put down here that you now do agree. It would make a difference to some people, namely if you look at 1B and 1A those are the people who say it makes all the difference in the world. So you are actually now proposing a fourth one. Is that right? Am I getting this right because 1A --

DR. DUMAS: Yes.

DR. MACKLIN: -- says it is ethical -- it is unethical if it would continue -- if it is unavailable and would continue to be.

B says it is unethical to withhold it even if it is unavailable.

And you are saying whether or not it is going to --

DR. MIIKE: No. A and B is -- A and B is different from my C because -- they are. They are not the same.

PROF. CAPRON: Yes, she is saying that. She is saying your's is a fourth choice. A fourth way.

(Simultaneous discussion.)

DR. MIIKE: But what I am saying is that I do not care about a fourth choice because I would put my voice to it and it would make no difference to me.

(Simultaneous discussion.)

DR. MIIKE: Well, I mean -- but I am just offering that.

DR. MACKLIN: You are proposing a 1D. You are proposing 1D.

(Simultaneous discussion.)

DR. MACKLIN: We just have to keep them separate.

DR. SHAPIRO: Other comments on three or four of these different propositions? Nobody has any views on them?

DR. CASSELL: Three and four?

DR. SHAPIRO: Or one and two, 1A and 1B.

DR. CASSELL: Oh.

DR. SHAPIRO: Do you like 1A?

DR. CASSELL: Well, I have come out with the --

DR. SHAPIRO: Okay. With all of them?

DR. CASSELL: Yes.

PROF. CAPRON: And can we start enumerating the --

DR. CASSELL: Yes. I think that there is an element -- the element of uncertainty in this is not -- is not inconsequential as my colleague on the left here, who will not speak for herself, although I have noticed she does on occasion, and that the issue of uncertainty is a very important one because there are diseases in which it is so crucial to save any life you save if you are a clinician that it would not matter what happens, whatever you do you could point to it and say at least I saved X number of lives, and therefore providing the treatment to a control group would be an ethical thing to do. I mean, it does not matter about the consequences. I can think of diseases like that without too much trouble.

And on the other hand I could also think of diseases of longer term consequences that go on for a much longer period of time. There is a period during the trial while it might be important for the question

specifically being asked like the transmission, the disease goes on so long that the intervention really does nothing much for that population there. I do not think it is unethical to withhold -- you are not going to --

DR. SHAPIRO: Let me ask you a question. I mean this is -- the assumptions here is that we carrying -- some country like the U.S. is carrying on the trial somewhere else. It is not carrying this on at home. It is carrying it on somewhere else. Okay.

And the question is you have -- as I understand 1A, for example, that if you provide the control group with some effective treatment that is -- will not be available ever again, which I think is what 1A is.

DR. CASSELL: Yes.

DR. SHAPIRO: Then it is a question of what on earth are you doing there? Why on earth should you be there? Why is that -- if it is us, why isn't that taking place in Princeton, New Jersey?

DR. CASSELL: Because Princeton, New Jersey already gets it.

(Simultaneous discussion.)

PROF. CAPRON: It is a new experimental treatment. The question is not the control substance,

the substance used in the control arm, it is the experimental arm. You want to test out A. B is not available in the country. Is it unethical --

DR. DUMAS: No, it is not going to be available --

PROF. CAPRON: -- and would not be in the foreseeable future according to point A. It is and would continue to be unavailable in that country. This view is it is wrong to do the research there. You are merely exploiting people to do the research there. You should not be there --

DR. DUMAS: Well, see, I --

(Simultaneous discussion.)

DR. DUMAS: -- I would argue that you are taking a big risk but there is always a possibility that there may be -- that this treatment might be available in the future.

DR. LO: But then why not do the study some place else?

DR. DUMAS: No. It may be that --

(Simultaneous discussion.)

DR. DUMAS: -- as a result of the study it might be available.

MR. HOLTZMAN: I do not think Alex read that right.

(Simultaneous discussion.)

DR. DUMAS: As a result of the study.

MR. HOLTZMAN: Because the proposal is that what you are testing -- your test article might be available. The question is whether the control is intrinsically unavailable.

DR. CASSELL: Yes, it is the control.

(Simultaneous discussion.)

MR. HOLTZMAN: So, therefore, this notion of, well, why not do it in Princeton, the answer is because what I am trying to do is get a treatment regime relevant to the other place. The question at stake -- that is different than I am going to use someone else to test a drug which is irrelevant to them. A case in mind here is the short form treatment, all right, is relevant to the population. The question is my control and whether I should use this as a control in a relevant treatment or not. That is the question that is being proposed by A.

(Simultaneous discussion.)

DR. MACKLIN: Irrelevant but nevertheless something that they would not --

MR. HOLTZMAN: Otherwise -- right.

DR. MACKLIN: -- correct.

MR. HOLTZMAN: And you need to make

distinctions, I think, clearly about the unavailability. I think Eric was pointing out, well, suppose it was not something that was merely palliative but actually cured such that I would -- and I think the case in mind was one where the individuals getting the control are not cured. So I think that is just thinking through a little more of the case that was meant.

PROF. CAPRON: But I thought what you were just raising was actually a different point.

(Simultaneous discussion.)

PROF. CAPRON: Yes, okay.

DR. SHAPIRO: Okay. Tom and then Bernie.

DR. MURRAY: I am inclined to agree with 1A, 1B and 1C. Let me tell you --

(Simultaneous discussion.)

DR. SHAPIRO: What about 1D?

DR. MURRAY: Well, I do not have it written down so I cannot be sure about 1D.

(Simultaneous discussion.)

DR. MURRAY: I know that but listen. Think about a case that would fit under 1A. I think this was the sort of case Harold was beginning to develop. Why would you do this in a country where the standard treatment is not available and will not be available, the established effective treatment, unless you were

either trying to test it so you could market it someplace else where it would be available or if you wanted to establish a new regime for that group of people or some less expensive treatments say that might be made available in that country, that would be the experimental control group. Why are you using a control group? Because there -- you know, that would be an equivalency trial and not a superiority trial. So that is -- so I could see some circumstances on which I think 1A is probably right.

Now 1B looks to me like the 076 perinatal transmission trial. Right? Here you have got a treatment you know works in the U.S. and you want to compare it against a known treatment, which is less expensive. You want to see if it works about as well. People are very upset about that.

1C, there the depends really -- Eric's depends really comes in strong. Well, okay, it has not been fully determined but what is likely. I mean, is there a one chance in 10,000 that it is going to be made available? That is not very good. It looks an awful lot like 1A.

I suppose I am not being very helpful here except to say that this ain't going to be an easy one to choose and I am not sure that any of the current ones

with the possible exception of C properly modified is going to be satisfactory.

DR. CASSELL: I think that is -- I do not want to talk out of turn.

DR. SHAPIRO: Bernie, you are next.

DR. LO: Go ahead, Eric.

DR. CASSELL: I just want to say that I think that is very helpful. I mean, if you come out and say, look, there is no answer of the kind that was -- that started this whole argument in the journal and back and forth where it is so clear, it is not simply we disagree with that editorial, there is no answer that you can make a clear cut statement that applies to all diseases, all impairment, that is very important. Of course, it leads you to the difficulty of trying to enumerate those factors which enter into the decision whether it can be used and so forth and so on.

So I -- there is nothing wrong with coming up and saying there is a certain inevitable uncertainty and that the job of the trial is not to treat the control group or not treat the -- it is to reduce the uncertainty by looking at the factors which make it.

DR. SHAPIRO: Ruth?

DR. MACKLIN: I just want to make a meta-comment now for the enlightenment of the Commissioners.

Eric Cassell's comment just now suggests that there is an understandable ambivalence here and you cannot clearly come down one way or another.

Now that may be what this Commission is going to end up deciding but if you look at 1A this wording, this exact wording, was the statement that this Commission heard in September from Dean Sommer when he gave his -- when some people were away because of the hurricane -- when he gave his presentation. Subsequent to the meeting, the Commission's meeting, he then sent an e-mail message to other deans of schools of public health because he is the head of some, you know, group of deans, the deans of deans, and he posed this question to them. Now it was a small response. There were some 27 some deans and maybe five replied. But every single one agreed with 1A.

So whereas this Commission may take a more nuanced view or say you cannot come down on one side or another, at least those five -- I am not appealing to them as an authority -- I am just saying some people are very certain about that and if one looks then at the interpretation that has been placed on the best proven diagnostic and therapeutic method in Helsinki that, too, speaks or might speak to 1B and say there are some people who are very certain that it is unethical to

withhold it during the trial.

So some people may come down very hard in favor of 1A or 1B and this Commission may for whatever reason decide to take a different view but people do hold a very strong feeling.

DR. CASSELL: I do know that. I know that.

DR. SHAPIRO: Alex?

PROF. CAPRON: Yes. I am not trying to do a 1D thing. I am just trying to get this clarified. Tom's remarks made it sound as though 1A describes a placebo control and 1B describes an equivalency design. I mean, once you supply the control group members with the existing treatment you are per se doing an equivalency design from what we have been told.

DR. LO: No. It depends on what the intervention is.

PROF. CAPRON: What?

DR. LO: It depends on what the other arm is. You may give the control group the so-called standard treatment and give the intervention group that treatment plus a new drug and then it is a superiority trial.

PROF. CAPRON: But clearly if we are talking about something like maternal transmission you cannot give them both. I mean, one is a long course and one is a short course. You cannot give people a short course

and a long course.

DR. LO: Right, but that is an equivalency. But you could give both groups AZT and give the second group a second drug.

PROF. CAPRON: Yes. Yes.

DR. LO: So that that 1A as written --

PROF. CAPRON: But you are still --

(Simultaneous discussion.)

PROF. CAPRON: -- doing an equivalency.

DR. MURRAY: It is not going to fit the suppositions here, which is that this thing would not be available. The main treatment would not be available.

PROF. CAPRON: No, it would. It would fit. But I am saying there you have an equivalency. The equivalency is looking between AZT and AZT plus X, Y, Z.

DR. LO: Well, that is not -- that is not considered an equivalency trial. That is considered a superiority trial.

PROF. CAPRON: A superiority trial. All right.

DR. LO: So it is --

PROF. CAPRON: Superiority trial. All right. Fine. Equivalency --

(Simultaneous discussion.)

PROF. CAPRON: -- or superiority, it is -- I

am just trying to get the terms -- are describing comparison of two active agents. Okay. Neither group is going to get a placebo.

DR. LO: Right. Although you could do a superiority trial with placebo.

PROF. CAPRON: So the answer on 1A that came out of the comments that Steve made before is that a reason for rejecting for 1A is that although the established treatment will never become available in a country, if the experimental treatment works, it will become available? And if it is proven to be at -- it is proven to be better than nothing that is an advance for the country so that is a reason for rejecting 1A.

Then we look at 1B, which is stated as a negative. It is unethical to withhold from members of a control group the established effective even if that treatment is not and will not be available in the country.

What I want to know is where do we look for the statement of what is ethical because these two do not -- these two do not exhaust the universe. We -- do we need a statement? Is it appropriate at this point or do you think it just comes up later to have a statement that says it is ethical?

DR. MIIKE: Alex, the answer is 4B.

MR. HOLTZMAN: 4B or 3B?

DR. MIIKE: 4B.

MR. HOLTZMAN: 4B.

DR. DUMAS: Four.

DR. MIIKE: That is why I said we needed to discuss four first because four is in total opposition to 1A.

PROF. CAPRON: No. Excuse me, Larry, I disagree.

Four is -- deals with an objection to a decision to supply that standard treatment. Four says doing so might look good but it would turn out to be an undue influence, undue inducement. So I disagree. I do not think that is --

DR. MIIKE: The offer is worse than actually giving it or not giving it?

PROF. CAPRON: That is what that argument is. That is what four deals with, Larry. Let's not get back into it.

DR. MIIKE: Well, I disagree. What I am saying is that I do not see how you can say you agree with 1A and you agree with 1B -- I mean, with 4B.

PROF. CAPRON: I am not --

DR. MIIKE: Tom is. I mean, that is what the discussion here is.

PROF. CAPRON: I am not Tom and I have the floor right now. I am saying --

(Simultaneous discussion.)

DR. MIIKE: Let's not get into that about floors, Alex. You are the last person to get into that about floors.

DR. SHAPIRO: All right. That is -- we do not need to discuss that.

PROF. CAPRON: Well, the point I am making is that we do not have the flip side of either of these statements, do we? We do not have a statement that says that it is ethical as an alternative here for us to choose from. It is ethical to withhold from members of the control group the established effective treatment because that -- or when that treatment is not and will not be available in the country where the research is conducted.

DR. MACKLIN: I think this is merely a grammatical point and let me try to explain. I mean a syntactical point actually. It is easier to specify clearly what is unethical than the kinds of things that are ethically acceptable. I mean, it is a -- let me take it back because I see by Alex's face I will have to defend that claim.

Either one of these or both could be

transformed into a statement it is ethically acceptable to either one of these and I do not know that that would help you.

The reason we chose it this way, and this is just a historical reason, was 1A was Dean Sommers' statement to this Commission, which he then went and talked to those other deans about and that is the way he formulated it. We could now or tomorrow morning, Alice and I could, formulate both A and B as ethically acceptable. It is ethically acceptable to deny members of a control group the established treatment, et cetera, or it is ethically acceptable to provide them with it. I mean, you can just transform this from a negative to a positive and I am not sure it would be any clearer but it would say what is ethical about what you are providing or withholding.

PROF. CAPRON: Ruth, I think this is -- perhaps syntactical is the word. I would have thought it is a matter of logic. The fact that one rejects 1A and says I do not agree that it is unethical to provide the members of the control group with the established whatever does not imply that I believe it is ethical to withhold it or that I believe it is unethical to withhold it because the reason for rejecting 1A is that the experimental arm if it proves successful would offer

to the people in the country a benefit which they would not otherwise be able to obtain.

Now then you get into a separate argument which says, well, if you could find that out doing the research in a country where the standard of treatment is now available and you could do it with people who would either voluntarily waive their access to the standard of treatment or would get the standard of treatment and you would have to do a superiority or an equivalency trial instead for them, would that be better ethically? It is a -- that is a whole separate argument?

But it does not seem to me it has any logical implications -- and I realize I am speaking to a professor of philosophy so I should be cautious about this -- about the answer to the question of whether the statement is ethical to withhold from the members of a control group the established treatment when that is not available and will not be available in the country where the research is conducted. Whether that proposition is true or false, it does not follow logically it seems to me from your view on 1A. Does it?

And you are asserting 1A is the proposition that was operative here because it was what Dean Sommers provided to us. I just suggest here as a matter of logic that rejecting one does not imply the embrace of

the other because the reason for rejecting it is -- does that sound right?

DR. DUMAS: I think we are on the wrong track.

(Simultaneous discussion.)

DR. MURRAY: Can I say one thing because suppositions have been impugned to me. I was simply sharing my confusion rather than endorsing any particular position suggesting that one could come up with plausible cases that would make virtually any of these, both good or bad, and so perhaps we could move beyond that and --

DR. SHAPIRO: I tried myself to think about it that way, Tom, when I went through this and tried to think of it. The one I could not get around was 1B. I found it hard. I am not going to ask for examples now.

It is just my own view that I could not think of an example probably due to my own lack of imagination that if I thought myself as adopting 1B and I could not think of counter examples but I do not want to argue that point now. It is the one I found here where I could not construct words and the others I could always find examples that would lead me to want to make it more --

DR. MURRAY: I think I could give you examples.

DR. SHAPIRO: That is -- you are probably right.

Jim?

And then we are going to go on to --

DR. CHILDRESS: I share the puzzlement that a lot of people do and I think that Ruth is right that we need to have at least positions laid out in terms of whatever report we develop will have to address these kinds of arguments that appear in the literature and appear in our discussion.

But I guess in a way one reason I have trouble coming to some resolution on this is that I am always troubled any time I see the statement "it is unethical" and I know this in a way repeats Eric's point about contending but it seems to me that I can think a lot better if I am thinking in terms of generally or presumptively or something like that.

And then the question really becomes, well, what are we doing as our starting point. And so we get sort of what is really critical for us in this first set of issues about sort of where we want to begin.

And if we think about some kind of a beginning point and not think about it as an absolute that would

lead us to “it is unethical” and this may be another way, too, of also trying to get at Alex's concern, then I might be a little more clear headed about where I would want to be. I do not have a solution to this but it does seem to me that I did not really get tied up at the point of “it is unethical” given the kinds of counter examples that can be given.

DR. SHAPIRO: Okay.

Rhetaugh, Bernie, and then we are moving on.

DR. DUMAS: I think we are getting hung up on words. It seems to me that the major objective here is to lay out some broad guidelines that we can agree upon in principle and we can just as well leave the word "ethics" out of the sentence. You know, we could say -- we could say -- the guidelines could be that in cases where a treatment is being provided, the control group should be given the opportunity or whatever. And I think that if we would think about it a little broader and not hang on the particular words we could move it.

So it does not matter to me whether the sentence says "unethical" or "ethical." The sense of it is the thing that is important. If you have an experimental in the control group, are you advised that the control group members should have the opportunity to have the most effective treatment that is available?

DR. SHAPIRO: Bernie?

DR. LO: I agree with the line of discussion that says it depends, and we should try and specify what it depends on but I also think it is helpful to say it is unethical under certain circumstances. So that 1A I certainly cannot agree with as written in all situations, but there certainly is a set of situations where if the intervention group would also be unavailable that is generally considered exploitation.

I think if we can specify some of these very general statements more precisely to come to not a kind of contrived example but an example that is actually fairly common and fairly likely, then I think it would be a service to say we should not be doing that kind of research even though it will not, you know, stand as a general maximum in all cases.

But I think 1A, if we can specify it more, gets at the country that is never going to benefit from the intervention either and you are really going to take it back to the host country and you are exploiting people. If we can work that out, that may be useful even if we ultimately end up agreeing with 1B as a general presumption.

DR. SHAPIRO: Why don't we reflect for a few moments on the propositions under two and see what

observations and/or reactions people have.

DR. MIIKE: Can I ask for a clarification actually of Ruth and Alice? What you are asking then is that even if one can agree with several, you might -- what Tom was saying -- you would prefer us to tell which one you would put on the top?

DR. MACKLIN: Not necessarily. I mean, what we hope to take out away from this discussion is whether any of these propositions as formulated is not only acceptable but whether there is some consensus or unanimity.

DR. MIIKE: But your parenthesis says choose one of --

DR. MACKLIN: Well, that was to get people thinking about it. If we find that people are unable to choose one then we go back to the drawing board and we either (a) write them in more nuanced fashion or (b) provide some of the elaboration or make, as Bernie is suggesting, I think give the clear case of what we would all agree is unethical and it may not be one of these but then we get into the "in principle" language or the “some circumstances" language or the "exceptions" language.

I mean, this is going to form the basis for what will be a chapter and it is going to rely on -- at

this point it is going to rely on the kinds of discussions we heard this morning.

DR. MIIKE: Can I ask you -- do you contemplate seeing like -- if you get down to the bare bones this is the conclusion that we would, in general, reach. However, given circumstances -- but then you start to qualify and say but another choice might be more appropriate if you think of the situation, et cetera, or are you going to try to lay out rather several options among which -- where we do not signal which one we prefer?

Do you see what I am trying to get at?

I thought where you were trying to drive us was picking one and then, of course, circumstances would make other choices desirable in a particular case.

DR. MACKLIN: Maybe the better way to think about it is to reject one. I mean, I heard a lot of objections to 1A, for example, even though I did not -- there were no resounding endorsements of any of the others and people tried to come up with still others. But 1A I did not hear anyone saying, "Yes, this is what I believe. It is unethical to provide members of a control group..." Although what I hear Bernie saying is we could formulate some statement if Jim would accept it that starts out "it is unethical to..." and what would

follow that initial phrase would be the classic exploitation, namely studying something where the treatment will never be available, the control arm will never be available, you are going to take the results back to the industrialized country, period.

DR. MIIKE: But you see what I am worried about is that if we are not clear about where our bottom line is then we come across as really not giving clear directions about what we think are the true ethical foundations for what we are offering. Then we are going to say, well, it all depends on the particular experiment or the particular circumstance and there is no guidance.

DR. MACKLIN: Yes. Well, I --

DR. CASSELL: But, Larry, what Ruth just said would be a bottom line. An exploitation example is the bottom line. You may not exploit subjects for your own use and no benefit -- essentially no benefit to them. It is simple. That is the bottom line.

DR. MIIKE: But that is different from choICH we are given.

DR. MACKLIN: You see, I think there is an intermediate. I think there is an intermediate step and that is probably the next iteration where we will need some examples. We need categories, not just single

examples. When we say it all depends, we want criteria, not just examples but what we will need is criteria that I think Alex tried to press Eric on of on what does it depend.

So we can have a guideline and say exceptions to this might exist if they fit the following criteria and then we might have some examples under those criteria. So that would be a way to structure it that says you have a presumption. I mean, no guideline is going to give you an absolute, but if you can have a presumption and then say what are the conditions or the criteria that are -- that would rebut the presumption or that you would carve out exceptions. And that is, I think, the work that will follow.

DR. SHAPIRO: Alex?

PROF. CAPRON: Yes. I wanted to suggest to Ruth that you try working out one of these kinds of -- Ruth?

DR. MACKLIN: Yes, I am listening.

PROF. CAPRON: -- one of these kinds of flow charts that we have used at other times because that can help to embed some of the "it depends on."

I mean, if you look at one versus two, there are several variables that you built into the different ones. Under one you begin to build -- like 1C -- you

begin to build in the question of is it known or is it unknown and has not been determined whether or not the treatment will be available.

Under two you begin to get into the factor that we were asking about in 1A, which is: all right, the established treatment is not going to be available, but now the question is will the new product be available, and then the question is available to whom.

You have also built in as a predicate here that people will need continued access to that product, that this is an ongoing chronic treatment. And so in your flow chart you might have a different branching of two prime where you are talking about something which is a vaccine or something, which is, if it works, a one time shot and then people are saved from the illness.

Another variable, which may make this too complicated and we may want to sort of say, well, this is the way it looks when we are talking about a disease which is fatal, and this is what we are talking about a serious but nonfatal condition, both because of the extent to which getting treatment is a felt necessity for the people involved and obviously because of what it would mean to withdraw a treatment that you have given them during the research trial. And when you come to the end, you walk away and suddenly the person is right

back on death's door and dies knowing that this thing had kept them alive for the six months of the trial. That it made a dramatic difference.

Will that one answer -- no, I mean, Rhetaugh is right, one answer would be every day of life -- I mean, the classic statement of the Jewish view on these matters is every day is equivalent to all days, every person is equivalent to all persons.

You save one person's life you have done as great a good as you can do. You have given one person a day of life they would not have you have done -- and so you -- it is not a view that does not have strong ethical roots to say those people all had six more months of life and a good life than they would not have had otherwise.

So -- but that would -- if we -- you could then look down this chart and say, well, when you get to this branch if it goes in this direction, no, this is not an acceptable design. I am not going to get into the trap that Rhetaugh pointed out of saying it is ethical/unethical. This is not an acceptable design. This design is okay so far. Now we have to ask a new question about it if you see what I am saying.

And then you sort of say, you know, where does the water flow through and where does it come to a dam

where the IRB ought to say, no. That design is not going to work with a disease of this sort in a country of that situation.

The thing that you do not plug in here yet that we have talked about that Harold raised, is could the same study be done some place else? And part of the answer to that has been purely technical. No, to do this vaccine trial on HIV you have to have a particular place. You cannot study a vaccine in San Francisco for the HIV that occurs in Thailand.

Another part of the argument is practical. Well, once people have access to this other treatment they are not going to forego it to be in a placebo trial and an equivalency or superiority trial is not useful here. It just is not. It is not the question you want to ask and answer.

A third version is an ethical argument. It is -- it would be wrong to ask someone who has access to a curative treatment to give that up to be in a placebo trial even if at the end of the placebo trial if they are still alive you will give them the treatment or you might give them the new treatment if it is better. That would simply be an unethical position to put anyone in even if someone would volunteer to do that.

And these sets of questions are not here yet

but they are important questions for the Zimbabwe compared to Princeton argument. If there are certain things that you could do in either case on the technical level, that is to say the populations are expected to respond in the same fashion to the intervention, but one has available an existing intervention and the other does not.

DR. SHAPIRO: I think --

DR. CASSELL: Just to illuminate what -- just one little thing you said.

DR. SHAPIRO: Go ahead.

DR. CASSELL: You could do the trial in a foreign country of a vaccine for HIV, the same HIV, if there are not enough cases here so that you could get a definitive answer about a vaccine. The case rate is dropping. You may not be able to find out whether the vaccine works in an American population.

PROF. CAPRON: I would say that is a technical -- another version of a technical question.

DR. SHAPIRO: First, I am going to give you a mini-piece, and I hope it is not misinformation, and I stress the mini. As I read over these propositions in all these areas I asked myself which ones do I most readily agree with. That is the answer. That is the way I read it.

And I found out -- this is the mini-piece of information -- that it was 1B, 2D, 3B and 4B. You can just --

(Laughter.)

DR. SHAPIRO: -- stash that away in some --

DR. MURRAY: What was the second?

PROF. CAPRON: 2D.

DR. DUMAS: 1B, 2D.

DR. SHAPIRO: 2D.

PROF. CAPRON: Baker, David, Baker, Baker.

DR. SHAPIRO: Right. But that is a mini-piece of information and I do not want to take it too seriously and I do not really discuss it but that was just my reaction to the most -- the statements I could most easily agree with was my criteria, not whether -- which ones were right and which ones were wrong.

But anyway more importantly than that, is there -- I have been trying to formulate a problem in my mind all day, and I think it relates to what we are discussing now, and I think of it as the macro justice problem versus the micro justice problem. And I am trying to get a handle on just how to describe this.

That is there are issues of justice between countries. Okay. And then there is issues of justice with respect to how you treat a group of people who are

actually participating in your trial and it strikes me that those are really -- can be quite different.

Now I interpreted the presumptions at the beginning, perhaps inappropriately, that when you looked at presumption B, to say that at least for that country they solved the macro justice problem from their perspective. That is how I interpreted 1B. That if we wanted to worry about it, we could, but they in their wisdom felt satisfied.

Was that the right way to -- okay. Because when I went through this, what led me to it and why I think it was just a mini-piece of information is I ignored the macro justice problem after that because I had presumed it was solved by the presumption.

DR. MACKLIN: Well, in part, Harold, but let me just say this is not the end of this.

DR. SHAPIRO: Yes.

DR. MACKLIN: Because these propositions really are intended to focus on the research designed questions that we are dealing with now. We have yet another chapter and another whole set of propositions that are going to deal more specifically with the macro just ICH issues, namely what are the obligations of sponsoring the industrialized country to the host country in which the research is being carried out.

Now the host country agreeing here simply says they are at the table on the question of the research design.

DR. SHAPIRO: Right.

OT DR. MACKLIN: It does not yet say what the obligations of justice are more broadly.

DR. SHAPIRO: I understand. No, I understand that.

DR. MACKLIN: Okay.

DR. SHAPIRO: Thank you.

DR. MACKLIN: I do need to, though, say one quick thing about doing the trial "elsewhere" because there was a presumption in what Alex was elaborating and I think going back to what Harold said that it is always desirable first to do a trial that may be beneficial both in a developing country and to the industrialized country. It is always desirable to do it first in the industrialized -- in the sponsoring country.

That very proposition is currently being challenged as paternalistic. People from the developing countries are saying, look, this might have been true in the past when you had exploitation but now with capacity building and ethics and with ethical review committees within our own countries, with scientists who are now well-trained, we do not want to tell you, you can only

do things in your country and delay the time at which it might be available to our population. If we do the study here in Africa it is going to be available sooner to us.

So I am not going to accept at least at the moment, because we have yet to discuss that question, whether developing countries now still have to be looked at as "vulnerable" communities that stand in need of the protection, so first you do it in Princeton and then you do it in Zimbabwe. But that is a separate issue, but I think I do not want to muddy this one with that because we really have to address that separately.

DR. SHAPIRO: Arturo?

DR. BRITO: This kind of goes along with what you were saying, Harold. I am not sure -- there is one thing that makes me uncomfortable overall about these propositions, among other things -- among many things that make me uncomfortable about them but one thing in particular.

Is there -- given what we have heard over the last few months and just from my own experience and what I know about research within this country and I assume happens in other countries, is there a different level in here somewhere where we jump from availability of treatment in a country to that available to the

subjects?

Should we not have some sort of category about subpopulations within those countries? Because whenever we are talking about these unethical or ethical uses of certain treatments, what about in a situation where you have a developing country where the higher social class, what have you, has treatments available to them but yet other subpopulations who are more likely to be used in research purposes do not. Does this come to play anywhere here or am I just --

DR. MACKLIN: You know, in order -- can I answer that?

DR. SHAPIRO: Go ahead.

DR. MACKLIN: In order to make this fairly simple we did not list a whole lot of assumptions at the beginning. The presumption here, I think, we can add -- I mean, what is intended here is these are resource poor countries in which the majority, the vast majority of the population does not have access to anything that would be available in industrialized countries, although the very small wealthy elite at the top of that country can always buy it and get it, and that is true for triple therapy in almost every country in the world.

DR. BRITO: The reason I bring that up is because I think I have mentioned this in the past is my

worry that the people in host countries that often make decisions for that country are at -- are often at that level, that high level. So then, you know, I am not sure --

DR. DUMAS: Here, too.

DR. BRITO: I mean, I --

DR. DUMAS: In this country, too.

DR. BRITO: In this country, too.

DR. DUMAS: Yes.

DR. BRITO: In this country, too. Therefore, the -- so when we refer like, for instance, in 3B, I know we have not gotten to it yet, but routinely available in the host country. Should that not be something as simple as but may not be available -- routinely available to the subpopulation or what have you or the people that are involved in that.

PROF. CAPRON: To the potential --

DR. BRITO: It is just something to think about when we are writing the -- when we are rewording this. You know, I just --

DR. SHAPIRO: Okay. There is lots of useful advice coming up here but I do want to return to see if anyone has any particular observations on the propositions, whether you like them or do not, under two.

DR. CASSELL: Under two.

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

DR. MURRAY: I was interested to hear Harold describe his at least initial endorsement of 2D. I would have preferred 2A myself. 2A is it is unethical to conduct a study, et cetera --

DR. SHAPIRO: Yes.

DR. MURRAY: -- with the low probability that any successful products would be available to the population as a whole.

Now 2A and B are a set and 2C and D are a set. 2A and B are really your relationship with -- in broad terms with that other nation. 2C and D are your researchers and sponsors relationships with the subjects. They are focused at rather different levels. And, yes, I suppose one could say of 2D that we are not exploiting, you know, if other conditions are fulfilled and we are not exploiting the subjects in quite the same way if we, in fact, give them -- continue to provide the effective trial (sic) to them afterwards.

Then the question is why conduct the study in that nation in the first place if, in fact, there is no prospect that this product will be available to

everybody else.

So I am not entirely unsympathetic to B but I guess I --

DR. SHAPIRO: Well, as I said, I was just very naive like everyone else here and I just -- it said choose one so I chose one. It does not mean I disagree with 2A.

DR. CASSELL: That is an economist, right?

(Simultaneous discussion.)

DR. SHAPIRO: No, that is just sort of a naive way to look at it.

Excuse me, I had a list here.

Eric, you are next.

And, Bernie, you are after.

DR. CASSELL: Well, I would like to say that I think it is ethically acceptable to conduct a study that is 2D in which the successful will be made available to the study subjects but not to the population of that country as a whole. Once again there are caveats. What is the disease we are talking about?

After all, any time you give medical care, any tie, anywhere, it fits that category of individual medical care and, of course, that is always one of its problems. But, in fact, that is what it does, it gives it to some people but not to others even though it may

be available to other people. So I find that ethically acceptable.

The same problem I had with the 2A/B is the question of what is the disease we are talking about. Are we talking about a chronic disease or an acute disease? If it is a chronic disease and you are not going to make it available to them, you dangle it in front of them and then you pull it away. If it is an acute disease you did your thing and you do not make it available and you are back out again.

So it has to do with the nature of the disease.

DR. SHAPIRO: Bernie?

DR. LO: I would just second all the line of thought saying we need to specify a little bit more the considerations and I think I like Alex's idea of sort of seeing if there is sort of a flow diagram you can go through mentally.

I would suggest that 2A and B are different than C and D, and we have to be careful. Are we going down one sequence or is it a parallel track where you answer one sequence thing and go on the second sequence. I would suggest that, as others have said, what you do -- what you owe people who are participants in your study is different from the question of what you owe the

whole population in the country.

So the way they are confused I think may -- the way they are intertwined they confuse more than clarify.

I also think it is really important that these propositions are all interactive with each other. Right?

And so 2D you need to look at, it seems to me, again to go back to question four. I mean, if what you are saying to a person is, look, here is an offer. You have -- you either get the control group, which is good treatment that you will not otherwise get in this country or you will get the control group plus something else that may be even better. In other words, we will treat you like you are in the United States for the purposes of medical care.

Depending again on the nature and the severity of the illness, whether it is chronic or not, and the effectiveness of treatment, that could come very close to being an undue inducement in the sense that I do not really care what the risks are in the intervention arm because I am going to get, you know, at least the control group, which is what the people in America get, and in case the intervention is actually good I am even five steps ahead of the game.

So I think that although it is nice to try and separate these out, eventually you judge a study taking all things into account and then it gets messy.

DR. SHAPIRO: I wanted to raise a question here just because it came to mind a couple of times today but it also came to mind when Bernie mentioned it.

I am not sure that it is always helpful for us to think about the very extreme cases. I just -- that is where it is a life and death case always that we are dealing with. I think an awful lot of these experiments do not go on in that context and that context can distort the lens with which we look at it.

So I think one of the things we should think about, and it goes back to Bernie's other suggestion about examples and so on and so forth, or I guess a lot of people today made suggestions like that, because we do not want to get to argue this only in the life and death cases or what I call these very extreme cases because I think that may not always serve us well.

Bette?

MS. KRAMER: Harold, that was exactly what I was thinking about, too. It seems to me at least it would help me in thinking these things through, if we had a list of the decision points so that, for instance, one decision point would be if the research is -- if

there are successful products resulting from the research, it will have been determined ahead of time that they will be available, they will not be available, you know, or would it have been determined, and what the various possibilities of each decisional point are, and it will be easier for me, I think, to then decide, yes, you know, one from column A and two from column B, and perhaps thereby come up with a set of premises that I can support.

DR. SHAPIRO: Okay.

Alex?

PROF. CAPRON: That is very much what I was hoping we would get in --

MS. KRAMER: Right.

PROF. CAPRON: -- the flowchart. I entirely agree with you because I do not think, for example, the four set out here are -- fit well within the “choose one of these four” for that reason because you flow down them -- the decision points.

You know, Bernie, your example of the thinking that a person can go through, which really is back to point number four of whether or not the control group is getting the standard treatment, and the person's thought process, well, that is so great and if I get the research intervention if I am not on the control arm, I

will be just that much better off.

We have to remember Jesse Gelsinger. I mean, we are going to have to remember people who have chronic diseases who go into an experiment and die quickly in the experiment. And before that there were the liver deaths, and I do not remember which intervention that was about four or five years ago --

(Simultaneous discussion.)

PROF. CAPRON: Yes. -- where, you know, people who had -- they are all dead. So, I mean, getting -- being on the research arm is in the mind of a lot of people having a chance for the new treatment. We have got to remember treatment does not belong in here yet. It is an experimental intervention.

I mean, it was what, I guess, Dr. Chase was saying to us. I think it was he this morning. Let's talk about experimental medicine, not a clinical trial, because clinical trial sounds too much like you are getting the new -- you know, you are cutting edge.

(Simultaneous discussion.)

DR. SHAPIRO: We have a therapeutic solution.

PROF. CAPRON: Yes, exactly. I mean, this is an experiment and experiment -- the reason researchers moved away from the term it has that kind of wild scientist angle to it. I mean, they are just

experimenting here but it is a way of describing the process of which organized research is a part.

DR. LO: Right.

PROF. CAPRON: But it is still under the rubric of an experiment. It is just a reminder to people.

DR. LO: Yes. No, I agree with you. And then the consideration is if you are doing this in a country where, as we have heard from other testimony, that this tremendous tendency to trust that your doctor would not do anything that was not in your personal interest, and so that there is even more of a likelihood that you had this therapeutic illusion, then does it become more unethical to do the study there as opposed to do it in this country where at least the newspapers are playing out the Jesse Gelsinger story and raising the question that research could kill you rather than cure you.

DR. SHAPIRO: Trish?

PROF. BACKLAR: I am still -- I am getting very concerned about this. I feel that we are beginning to forget about real people who may be used for the benefit of others and what our obligations are. And when we go through this list somehow or other we sort of -- I feel as though we are distancing ourselves from -- even though you are saying is it right to do this

without this and so on and so forth, it is -- I want to say again -- too abstract in this sense.

I want to get back to some of the feeling we had when we were discussing research with the vulnerable subjects. I think this is very similar because these people are very vulnerable if they are in such a situation without any medical care and they are as ill as anybody might be anywhere else.

I am not advancing this discussion. I just want to remind us that these are really human beings we are talking about and what our obligations may be as a commission to think about where it is and what it is that we might want to do to make -- to further justice in these issues.

DR. SHAPIRO: Okay. Ruth, and then I want to ask another question.

Ruth?

DR. MACKLIN: Okay. Well, I mean, if we are thinking about human beings, and I just want to say about the use of the word of abstract, principles are always abstract. And then they have to be applied in the concrete to human beings. So surely we need the principles otherwise we do not know what we are doing. It is seat of the pants.

But the aim is to apply these principles to

human beings, and if compassion and concern for suffering human beings is the overriding principle, then it seems to me we choose all the examples in which everybody gets the best even for the short period of time just so long as you are not going to withdraw something that will make them more sick after this.

So thinking about the real human beings and their suffering and their sickness seems to argue for choosing any proposition that gives people a benefit. Remember we are talking both about the control arm that they would not -- other people would not otherwise get because of this standard of care concept.

So I mean the implications of what you say, which I am not -- neither challenging nor questioning nor endorsing -- are that if we are thinking of real human beings and the need to benefit people who are otherwise vulnerable and suffering, we should be trying to benefit them every way.

PROF. BACKLAR: But you see what Bernie said is extremely important and I think we have been discussing that and that these very real human beings may not understand the limits of what it is that is going to be done and they are going to be used in an experiment in which they actually -- their qualify of life may be far less pleasant than if they did not enter

the research protocol.

DR. SHAPIRO: Arturo?

DR. BRITO: Isn't that taken care of in the informed consent process and maybe we should spend more energy in that area?

DR. SHAPIRO: Trish?

PROF. BACKLAR: Go ahead, finish.

DR. BRITO: No, that is it. I mean, I just think that that -- you know, I have been thinking about that. I think one of the --

PROF. BACKLAR: Well, that was one of the issues we were discussing today, trying to find out because in many different places that consent may not be consent from an individual and so on or they may not understand or it may be a country -- as the gentleman who sat in the far chair, whose name began with an "L" [Dr. Lagakos] talked about the psychological -- the differences in understanding consent. I mean, the consent issue is a major part of understanding or not understanding what is going on.

DR. BRITO: Right.

PROF. BACKLAR: I am not disagreeing with you.

DR. BRITO: I am not sure what the answer is to it. I am not sure any of us do.

DR. SHAPIRO: I want to -- before we go on to

more general discussion or feedback on any or all of these, I want to be -- meet my promise to Ruth, namely get us to focus on all -- however, fleetingly -- on all four of these categories.

So I want to focus your attention on category three and see -- and then whatever time you are willing to spend we can circle back and take up some of the more general issues.

Does anyone have any observations, comments, et cetera, on category three in which there are -- we are presented with two alternative propositions or two propositions?

Arturo?

DR. BRITO: Well, I mean, to use Ruth's own words, yes, these are very stark contrasts here and obviously 3B is the one that we -- I think most people would agree with.

Once we get into the language once again, I would just make it -- you know, I am bothered by things like “effective treatment”, you know, as Ruth talked about before. And what “routinely” means and I have already mentioned my concern about “host country” as opposed to “subpopulations”.

But basically one of the things that I think we may make real clear is that effective treatment

involves a treatment that has been proven before where there are no biological or cultural differences or physiological differences.

For instance, we heard the comment today about in countries where there is breast feeding, that might be one of the cultural differences or -- well, actually based on economics, but cultural differences that would change how we view a study, but that is more in the definitive terms of the -- when we start defining the language -- but I am for 3B.

DR. SHAPIRO: Tom?

DR. MURRAY: I seem to be in the role of the contrarian here but there are times when 3A, I think, would be a valid principle. For example, where there is an effective treatment in developed countries but it relies on a particular infrastructure, communication, transportation, refrigeration or some other sort of health system. And where that is clearly an effective established treatment in that developed country. Utterly inapplicable under the circumstances of comparing it to some developing nation that simply lacks the infrastructure that would prevent that treatment from being provided.

And the question would be, can we come up with a good treatment that would actually be effective for

the people in that country?

What would be wrong with it under that set of circumstances where the sort of public health officials say we want to find out if we can come up with a treatment that will work for us?

DR. SHAPIRO: Alex?

PROF. CAPRON: Well, what I would wonder would be how we would feel about the existence of a point, Roman III in here, which would say -- it would have to be in two versions with different consequences -- which would say "and where the study cannot be done in a country in which the effective treatment is routinely available."

Because I mean it seems to me that the way you were putting it you were assuming that that was the case, that if this new valuable advance that does not require refrigeration and so forth is going to be developed it has got to be developed in this country and it is, therefore, legitimate for the public health people in that country to want to have it done there even if they are taking a very protective view of the population at risk versus another country that is otherwise similar but could stretch and provide control subjects with the developed world standard for the period of the study.

It would seem to me that you might answer the question differently with those two suppositions.

DR. SHAPIRO: David?

DR. COX: No one is going to like this. Ruth is not going to like it either. But the -- in looking at these and the trouble that I had trying to deal with these formulations -- I mean, I understand very much why you wanted us to get sort of precise answers to these, but I think in the testimony that we had today it illustrates why we are having difficulty doing that.

The testimony today was not sort of in the context that they are opposed, you know, people fighting about whether you should have placebo trials or not placebo trials, people fighting about whether it should be an equivalent study. These are very complicated scientific issues that depend a lot on the specific study and the design.

What did come out, though, is something which Jim Childress said, which was really striking to me, and that is instead of having people fighting to find out who is going to be the winner, right or wrong, find the commonality between these different forms of -- respecting the relativity but at the same time saying what you need is a group of people of different stakeholders that are going to come together and look in

the specific situation, in the specific relative situation.

I am just concerned that if we are in a place where we start making dicta about whether it is better to have placebo trials or not in a particular situation or even -- I mean, following these -- like one, two or three, that it is going to become an extremely difficult thing to. I mean, we will wedge it in but putting a square peg in a round hole and we are going to end up giving prescriptions that are not going to be very practical.

I mean, I realize it is late in the day to bring this up, Harold, but --

DR. SHAPIRO: No, I think the -- I mean, one of the issues obviously that has come up over and over again is that we have interpreted the language here in different ways and the presumptions in different ways and, therefore, have come either easily or more difficult -- more and more difficult way than certain positions. And it has been added into that here that, indeed, there is a lot of variety out there in the world and even if you understood all the language very carefully there are still issues that would be uncertain in our minds.

DR. COX: And why I waited so long with this

is because I thought maybe it was just my confusion and I was waiting for everyone else to straighten it out for me and it has just gotten worse and worse for me. So this does not mean that we should not follow your guidelines but I just find them difficult.

PROF. CAPRON: Can I jump in here because I am partly responsible, I think, for Ruth having done this. These are heuristics.

DR. MACKLIN: Causal but not morally.

PROF. CAPRON: Not morally.

(Laughter.)

PROF. CAPRON: You acted in free will.

DR. SHAPIRO: No undue inducement.

PROF. CAPRON: No undue inducement.

(Laughter.)

PROF. CAPRON: These were heuristics entirely. They were intended for -- as a means and they may have succeeded and they may simply have revealed the need for greater refinement and attenuation and certain ways of any conclusions.

Not that this was language that was going to be in the report but do we gravitate in one direction or another? What further qualifications do we think are very important? Can we then have another discussion in which we begin to see a way of describing those more

contextually as opposed to having a debate about the 076 versus short term trial -- I mean, you know, short term whatever it is that one wants to call it.

(Simultaneous discussion.)

PROF. CAPRON: Short course trial.

DR. SHAPIRO: Ruth?

DR. MACKLIN: Can I -- I want to just comment. One thing I heard you say, David, which I am not sure it goes against something that Larry wondered about before is almost whether we can say anything with any precision or with any definiteness but just let people go back and decide and sit at a table, et cetera, which is to suggest that there cannot be any guidelines. There can only be procedural solutions.

Now I am not too happy with that myself.

DR. COX: And I did not mean -- I did not mean to imply that so I --

DR. MACKLIN: Okay.

DR. COX: Because -- but there is a fine line between just having people sit at a table and having really proscribed, you know, ten commandments that you have to follow. But I think that there is a space in between there.

DR. MACKLIN: A big space. But can I just --

DR. SHAPIRO: How did you ever come up with

ten?

(Simultaneous discussion.)

DR. MACKLIN: Could I ask a -- we have to work on the next steps really and I would like to propose something and see whether this process would be reasonable because if we do not want to go down this path at all then we have to come up with something entirely different.

We need something like a paragraph or an introduction to this material that sets out a lot of caveats. There is no strict rules. There is no exceptions as rules. There is nothing that is always ethical and always unethical. There is lots of variation out there in the world, et cetera. With all those provisos.

And then even though we have not yet done it at this meeting I saw some gravitation towards some points more than others. So given the caveats the next step might be to come up with something -- a softer version of this with all the all other things being equal, et cetera, and in principle language, and then begin to map out the criteria or the categories. That is if we say it does not all depend but much depends on where we go and then we have to have the criteria for what it depends on. And those are all the things that

we talked about today plus more that I hope you are going to help us with.

Now would that be a reasonable way to go? That is we are not going to stick with these statements as they are but we are going to use these as kind of a framework but changed accordingly as a result of this discussion?

DR. SHAPIRO: Eric, and then Bernie?

DR. CASSELL: Well, I think that is a very good way to go. For one thing just the opening paragraph moves the debate along that you described. It moves the debate away from a sharp “it is right”, “it is wrong”, and loggerheads approach and that in itself -- I mean -- and beginning to spell them out with look at the things that you must look at. After all that -- we are not trying to set a set of free rules but how do you work your way through this thicket and do the right thing and at the same time get the work done?

DR. SHAPIRO: Okay. Bernie, and then David.

DR. MESLIN: Bette.

DR. SHAPIRO: Bette, I am sorry. I did not see you. I will put you on the list. I am sorry.

DR. LO: I also like that sort of procedure. I would suggest in addition we develop some cases to go with each of the statements and the cases it seems to me

can be either the case that sort of raised this or the case -- the strongest case you could make that people can say, yes, this is the case I was thinking about when I say this is unethical or the contradictory case saying, you know, I am reluctant to sign on to this because here is a case where I would disagree with that principle.

I think that would be helpful both to sort of clarify for the commissioners that we are talking about the same thing but also I think it would help you specify what the criteria are that would be relevant to deciding one way or the other.

DR. SHAPIRO: David?

DR. COX: Yes. And I am very happy with your suggestion, Ruth.

I guess the thing that I was least happy with, though, in terms of the specific criteria, to be very careful when we make statements about components that would be part of a study design like, you know, using a placebo or not using a placebo because I think that they are so dependent on the study.

And I like -- at the same time, though, I like Bernie's suggestion because we heard some examples in the testimony of specific examples where the -- I cannot remember exactly who did it but I thought it was really

thoughtful going through and say, "I have a hard time really deciding if it was ethical but in this case it was not really ethical."

So I think that then -- it does not lay it on to a specific, you know, component of a study design but we are talking about that component in the context of a specific case.

DR. MACKLIN: I just wanted to point out that although we are not tied to or commenting on all those existing international guidelines in the ICH and all of that stuff. What we heard earlier today was the ICH follows Helsinki.

Now the present version of Helsinki does have a statement about placebo. The U.S. federal regulations has no such mention of any features of research design but Helsinki does. So I do not know what to say about it. I hear what you are saying but, you know, if possible, we want to be -- continue to harmonize.

DR. COX: Well, my comments are just -- I mean, they are just one person's comments. I mean, this is not my area of expertise.

DR. SHAPIRO: I can understand if you are looking at -- Bette, first. I am sorry because I have been --

MS. KRAMER: Go ahead.

DR. SHAPIRO: No, please, I will wait.

MS. KRAMER: I think the problem I am having is that to do this with the approach that you just outlined, it feels as though you are starting with a conclusion and then looking at the factors that would bear on it. I think it would be easier for me as an individual to come to a conclusion if there was a list of the considerations.

For instance, how do we feel about the role of the host country and what should be the degree of their input. And then list the considerations that would come into play in making a decision about that maybe with some examples or something. I just cite that as an example.

So that we kind of think through -- think through some of the -- again the decisional points that would -- that need to be thought of in order to come to a broad general statement. I think that is where I am getting tripped up at.

DR. SHAPIRO: Go ahead.

DR. MACKLIN: This is relevant to what Bette just said. We are going to get to do that but it does not quite exactly go here and that is because here we really are talking or trying to address the methodological considerations and some of the criticisms

that have been -- and challenges against the design of studies. What you mention is also critically important and it is going to come up in a later chapter, namely what are the -- how to enhance the collaborative research.

So what you said specifically is what is the role of the host country and I guess Bernie is going to ask again, quite rightly, what is the role of consultation in the community and with peoples who are potential research participants, et cetera.

And all that will come in but this -- it cannot exactly -- we cannot do everything at once, I guess, is the question.

DR. SHAPIRO: Alex and Rhetaugh?

PROF. CAPRON: David, I am sympathetic to your concern but I believe I am with Ruth as I understood her on this one and I do not want to, therefore, encourage her to go very far down the road that you suggest. It is certainly true that it would be a mistake for this commission to make arguments about research design on technical grounds. This design is superior to that.

DR. COX: That was my point.

PROF. CAPRON: But we can hardly get away from commenting on, as it were, what the reviewers, whether they are an IRB or CDC or the health ministry of a

country, ought to have in mind about certain aspects of a design that has been proposed to them.

DR. COX: Bingo.

PROF. CAPRON: Okay.

DR. COX: So -- but that is the distinction.

PROF. CAPRON: Yes. As long as we are in agreement because I thought you were almost saying but we should not comment on research design.

(Simultaneous discussion.)

DR. COX: But if we are going to do it we should be right -- I mean, we should not get into the details but basically make our arguments -- have holes in our arguments because of the technicalities of the research design. That is a way that people would pick apart what we say and it puts us at risk of getting --

PROF. CAPRON: Yes. We are not proposing research designs. We are commenting on ones that would be proposed.

DR. DUMAS: But we want to be careful not to conceive of ethical issues as being limited to research design.

PROF. CAPRON: Absolutely.

DR. DUMAS: And there is that danger in the way that we have been discussing it. So I suggest that there are several areas where there are critical ethical

issues and we need to be sure that we kind of isolate and set out those areas and attend to them in addition to the research design and my assumption is that that is what you are going to do.

DR. SHAPIRO: That is right. This section is actually entitled "research design."

DR. DUMAS: Yes. Okay.

DR. SHAPIRO: You are absolutely right, Rhetaugh.

Ruth, I do not know whether you will find this next suggestion helpful or just bizarre, I am not sure --

DR. MACKLIN: Maybe both.

DR. SHAPIRO: Maybe both. But it helped me think out some of this. That is I tried to think out these issues assuming that we were not dealing in the rich versus poor context. I asked myself these exact same questions regarding what would we consider appropriate in the U.S. if it was U.S. sponsored, U.S. participants, whatever the right, going somewhere else but not to a poor country, to a rich country, affluent country.

And that, of course, eliminates a lot of the issues but at least it clarifies which ones are a result of being resourced for, which is the presumption you

have here, and which ones are not -- you know, there are issues here which are not entirely dependent on being rich versus poor. They are just dependent on different issues and different perspectives on what is appropriate.

So I do not know whether in the end that is just helpful for myself or is useful in trying to think through some of these things. So I will just leave it --

DR. MACKLIN: I do have a couple of examples. I do not have them in my head because they are technical examples, but there are a few examples and I will try to bring them to our more knowledgeable medical colleagues in which research that could not have been done in this country because there was already a "standard of care" or “effective established treatment” was conducted in Sweden and I think there was another one in Norway. So there is a perfectly good example because they even have a health care system and those were some of the same questions that arise and so that is helpful. It is not bizarre.

I do need to make sure because at one point Harold is going to say we are finished here and I want as much --

DR. SHAPIRO: Soon.

DR. MACKLIN: Yes, I know. I know. I want as much feedback as possible. The last -- it was actually at the last meeting where I was not present, we had a series of propositions and then Alice and I developed proposed recommendations, which were not in multiple choice form but in the form of recommendations, put them together with what had previously been a background paper and revised it somewhat.

It is in the briefing book. We are not going to discuss that today but we were asking your feedback and so far I think this was sent out. Wasn't it, Eric, on the web?

DR. MESLIN: Yes.

DR. MACKLIN: So at some point we will need your feedback because that will give us the next step in being able to present a part of a chapter.

Would it be useful to do the same thing with the material we have been talking about today, that is taking the next step in some form of what the -- has emerged here from the suggestion I made and the modifications of it to flesh out, not to have just propositions but to have them fleshed out with background material that would include examples, as Bernie has asked for, and some of the other considerations that we can draw on from today's

presentations.

In other words, not start with propositions. Of course, they are going to be softened anyway. Would that be useful or what?

You know, you have got this hydraulic model. I am not a hydraulic engineer and I cannot draw pictures. I can work with words so I need someone who draws pictures or can draw --

DR. SHAPIRO: Eric has got pictures here.

DR. MACKLIN: -- the engineer.

(Simultaneous discussion.)

DR. MIIKE: Ruth, I think it would be useful because really we are discussing these things now, is we are discussing --

(Simultaneous discussion.)

DR. MIIKE: -- discussion all in our own heads and so we are not in common agreement on what we are discussing. If you put it in a form that you take the consent issues -- that still is pretty sparse but then it puts it at least in the context of being able to have a discussion.

DR. DUMAS: Okay. Good.

DR. SHAPIRO: Let me reinforce something that Ruth just said, that is the material that we are referring to, which is under dealing with informed

consent, findings and recommendations or something of that -- like that -- is in the book under 2E and it really would be very helpful if members would via e-mail or ListServ or any other way get any comments you might have either to Eric or Ruth or to each other even preferably so we can see if that is convenient for you and get that done.

Ruth, I as unsure in your last question you asked us whether you were asking not only if we would like it set out that way, which I agree would be a good idea, but whenever that is available we should distribute it as soon as possible, that is we ought not to wait, need not wait, I should say, for the next commission meeting because if we could give you, I think, feedback before then it might be helpful and just helpful in the overall process. It also gives us a chance to look it over more carefully in less of a rush sometimes.

So if that is possible. I do not know if it is possible with your schedule.

DR. MACKLIN: Well, let me just say what we expect. I mean, even in the little caucusing we have done here. The presentations that we had today, the six of them, were so helpful.

DR. SHAPIRO: They were.

DR. MACKLIN: That we would like to be able to incorporate the information that we got from those presentations about research design into one document rather than working with four of them and that will take a little bit of work and I think it is one step before we can begin to weave these items into it. That is we heard some examples today. We heard the different elements of research design.

So we could do a quick and dirty job on this but I think it might be much more useful to draw on the wisdom of the people who spoke to us and get a reasonable compilation or a merger of those documents which you can then use as a basis for putting these in. That means it is not going to go very fast but in the mean time the commissioners could give us the feedback on the informed consent.

DR. SHAPIRO: Sure. Right.

DR. DUMAS: You know, Kay gave us some principles but they are not in her presentation.

DR. SHAPIRO: They are not but I wrote them down.

DR. DUMAS: Huh?

DR. SHAPIRO: I wrote them down.

DR. DUMAS: Oh, good. So it might be very useful to have them.

DR. MACKLIN: We will get them.

DR. CHILDRESS: I agree.

DR. SHAPIRO: Yes. Okay. All right. I think that we have probably carried our discussion on as long as is useful today. Let me thank members of the commission. I do not -- what time are we scheduled, Eric, for beginning tomorrow?

DR. MESLIN: 8:00.

DR. SHAPIRO: 8:00 o'clock tomorrow morning. And I do not know what the earliest departure is. I did not look at the list. I think most of us are here tomorrow morning during most of the morning. So thank you all very much. We appreciate it.

(Whereupon, the proceedings were concluded at 5:12 p.m.)

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