40th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

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P R O C E E D I N G S

OPENING REMARKS

DR. SHAPIRO: All right. Colleagues, I would like to get our meeting underway.

Thank you very much.

Well, let's get today's meeting underway. Let me just briefly review our agenda for the coming day-and-a-half.

Before I do that, let me say how pleased we are to be here in Madison. Alta, I especially want to thank you for helping make arrangements for this. Thank you very much. It is great to be here.

And as Norm Fost just reminded me, we have a lot of Wisconsin alumni on our staff so it is coming home for them and so that is really quite wonderful.

We will be spending all of today on our international research project, various issues which we will be discussing this afternoon, and this morning we have two panels. The first one, which we will hear from in just a moment, deals with IRB perspectives and some of the issues we are concerned with. The second panel will deal with human rights perspectives, that is how bioethics and human rights perspectives might come together to complement each other, and so on, in the areas which we are particularly concerned.

So we will turn -- tomorrow, of course, we will go back to our oversight project and spend tomorrow morning on both the oversight project and, of course, Professor Dickens will be here tomorrow to talk about the challenge of equivalent protections and how you might deal with that between countries.

But before we turn to our panel, let me turn to Eric.

But before I do so, there is one other logistical issue that I want to just inform the commission of. That is, given our schedule of reports and the work we have to get done we are going to have to try our best to actually meet two days at a time. A day-and-a-half just may not be enough to get our work done, so you should really consult your schedules and see if it is at all possible for us to spend an extra half day over the next few meetings in order that we can get it done. If it is not possible for everyone, we will just continue in whatever way because we just have a lot of work to get done between now and in the fall.

Let me turn now to Eric for a few brief remarks before we get started.

DR. MESLIN: Thanks very much. I just wanted to again amplify Harold's comments about commission

meetings. The staff have been working hard to redo some agendas for the June, July and September meetings that would allow for two full days. We know that that may be difficult for some commissioners. We are trying to give advance warning on that now and we will send out sort of revised agendas for people to be a little more aware of what those commitments in time are.

We have also, as I have indicated just in my very brief Executive Director's report that is in your table folders, planned for the possibility, if necessary, of holding a portion of a meeting or an additional portion of a meeting by teleconference so commissioners would not have to travel. This, of course, would be under the auspices of the Federal Advisory Committee Act and the public would be welcome to attend. So we are investigating all of those possibilities.

I would be happy to comment on any of the other items in my report, all of which are relatively benign and uninteresting. I also want to remind you that Ellen Gadbois puts an update, a legislative update, in your briefing books each meeting. If you have any questions about what is happening on the Hill I am sure Ellen would be able to answer any of those for you.

And that is probably all I needed to do, Harold.

DR. SHAPIRO: Thank you.

Any questions for Eric?

Okay. Let me now briefly -- I am sorry, Alta.

PROF. CHARO I am sorry. Just one quick logistical note.

DR. SHAPIRO: Sure.

PROF. CHARO I apologize. Eric is going to be distributing for the commissioners and staff a map to help you maneuver around the area and it has a list of people who signed up for dinner this evening. If you could just take a glance at it and let me know if there are any changes. I need to call in this afternoon to finalize those arrangements. Thank you.

DR. SHAPIRO: Thank you very much.

Let me now turn to Ruth, who wants to bring us up to date on the overview of the work to date on the international project, and then we will turn directly to the panel.

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

OVERVIEW OF WORK TO DATE

DR. MACKLIN: Okay. I can be quite brief because the brief memo does say it all.

We are marching along in trying to succeed in

preparing draft chapters and what we have for discussion this afternoon, the topic that is called "Obligations to Subjects, Communities and Countries in which Research is Conducted," is a much fuller and revised draft of what will be chapter 4, and that is for our discussion this afternoon.

The other item, which is the one area we have not yet discussed, and that is the main focus of this meeting, is on what will emerge as chapter 5 and that is to be entitled "Enhancing International Collaborative Research."

We have referred before to a now infamous document known as Stu Kim's Chart and now you have it. It is here on the table headed -- was it distributed before or just -- okay. It was distributed here.

So on the table is a document entitled "Comparative Analysis of Legal and Ethical Provisions of National and International Documents that Address the Protection of Research Participants." It is a catchy title. And we will be discussing this. Stu will guide us through it and we will be discussing this in some detail. This may be the first effort of its kind in the world and should be very useful, not only for this commission, but for others as well.

So that will form the basis of our two main

discussions in addition to, as Harold already mentioned, the human rights discussion.

What we hope for -- to be able to present at the next meeting, or to have prepared for the next meeting, are almost complete drafts of almost all chapters. Chapter 1 will be a more or less introductory chapter to this report, and by more or less, it will say more than merely introduce, but I do not anticipate that there will be anything so terribly controversial that it will take up a great deal of time in the meetings for discussion.

But what you will see at the next meeting is a draft of the final chapter that is chapter 5, which is the discussion that we are having today leading up to that.

Also, I did want to mention, some of the commissioners had requested returning to the topic of informed consent either at this meeting or perhaps again at a meeting.

And just to explain, we would like in order to have that discussion, we would like to be able to have more of a completed chapter than we -- than you saw last October, I believe it was, and also incorporate into the revision of the chapter some of the comments that were sent by e-mail or that were made at meetings.

So our plan has always been to move forward in the discussion so that we can complete some discussion with the commissioners of the proposed recommendations for the chapters. Then, of course, we should give ample time at the next meeting for discussion of anything left over from earlier meetings but, in particular, the informed consent.

So that is all I have.

DR. SHAPIRO: Thank you very much.

Any questions for Ruth?

Okay. Thank you very much.

Let me turn now directly to the panel and, first, welcome our panelists, Professor Fost and Dr. Nayfield.

I do not know if you have decided amongst you who is going first but, Norm, I have you first. Is that all right? That is at least in alphabetical order if there is no better way to go about this.

I think everybody in the panel knows Dr. Fost and his work very well. It is really a great pleasure to have you here today and I look forward to your remarks.

As you know, this panel is mainly concerned -- principally focused on experiences of IRBs looking at projects that are taking place abroad.

And we will hear directly from our panelists. Norm?

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PANEL I: IRB PERSPECTIVES

NORMAN C. FOST, M.D., M.P.H., PROFESSOR OF PEDIATRICS, DIRECTOR OF THE PROGRAM IN MEDICAL ETHICS, CHAIR OF THE HUMAN SUBJECTS COMMITTEE, UNIVERSITY OF WISCONSIN-MADISON, MADISON, WISCONSIN

DR. FOST: Thank you very much. Thank you for coming to Madison. Thank you for inviting me to share my thoughts with you.

Alice Page suggested that I address two issues. One, the capability of U.S. IRBs to understand local circumstances in developing countries and, second, to talk about mechanisms for making determinations when there are conflicts when the U.S. IRB might have a disagreement or different standards than the local IRB in the other country.

I want to make three main points. First, I think this question about international research cannot be separated from the issue of the erosion of what I take to be the erosion of the IRB system in the U.S. for domestic studies. So I want to make some comments about that because I think it very much affects the capability of IRBs of dealing with international studies.

Second, I will say that I think U.S. IRBs are

capable of a very nuanced understanding of a lot of complex information, both medical, ethical, legal and cultural. And like juries and like commissions, there are excellent resources available on all these issues, and IRBs are capable of dealing with them in an intelligent and thoughtful way.

And, third, I have a little bit less to say about Alice's second question about what to do about how to resolve conflicts. The least I think is that obviously the local control has to be the minimum. That is, one cannot trample over the determinations of a local IRB in another country but it is not so simple as that, and I will make a few comments that you are probably already very familiar with.

First, let me spend most of my time at what I take to be the most important issue here, at least in my perspective, which is the erosion of IRBs as a method of protecting subjects, both nationally, that is in the U.S., and abroad.

It is a common place, of course, that IRBs are over worked and under staffed, or at least have been. There are widespread claims that they are not adequately protecting human subjects.

The shut downs of leading research institutions by OPRR and the press coverage of them,

the inspector general report and now the follow-up report, statements by members of Congress, and statements by members of the commission all support and lend credence to this view.

In my view, the major factor in the over work of IRBs and their inability to deal with research has to do not with anything inherent in their structure or capability but with changes -- dramatic changes in OPRR's interpretation and implementation of the Common Rule. There has been a dramatic shift in the last few years towards a heavy focus on procedural requirements, which in my view are only remotely related to protection of human subjects.

I would appreciate and welcome the chance to talk to the commission at some other point, if that is still on your agenda, in more detail about that issue.

There have, of course, been dramatic and severe penalties for failure to comply with these requirements irrespective of evidence of harm to subjects, irrespective of claims that protocols, which are unethical or problematic in any substantive sense, are going on.

To take our own experience at the University of Wisconsin, our budget in the last two years has

increased 400 percent. We have added a million dollars to the cost of the IRB. A budget of approximately $250,000 is now well over a million dollars. This is almost entirely in response to requirements and expectations of OPRR. If you multiply that times however many IRBs of comparable size around the country, it is a formidable and dramatic change.

In my view these changes, this increase in our work, has done nothing that I can tell to add to protection of human subjects. In fact, the opposite. I believe it has distracted us from protection of human subjects. That is, many activities that we were pursuing we have had to put on hold now for a matter of years.

This has all created a false sense, in my view, of crisis about the IRB system. Headlines of shut downs create the impression that thousands of protocols affecting hundreds of thousands of human subjects are unethical, threaten patient welfare, or are inadequately reviewed.

The occasional serious substantive problems, such as the death of Jesse Gelsinger at Penn and another recent reported death in a gene therapy trial, are not distinguished. There is not a discrimination in the press accounts of those problems from these

thousands of other alleged violations. That is, there is a false impression that there are thousands of Jesse Gelsingers waiting to happen.

So IRBs have been reduced, in my view, to almost clerical roles. That is IRB members, not just their staff, must carry out time consuming clerical functions such as comparing grants to applications, and checking consent forms to see if they comply with approval.

What does this all have to do with international research? If IRBs cannot be trusted to handle the least complicated American studies with some discretion, and that is the impression that has been created, that they cannot be trusted, they cannot be trusted by OPRR, by Congress or by the general public, surely they will be perceived at least as inadequate to the task of much more complicated issues in international studies.

There is the added problem, of course, that this kind of perception by investigators will, as commonly occurs with regulation, drive it under ground or drive it overseas or drive it elsewhere, and we already have some evidence for that. That is I, for the first time in years, had investigators tell me that for nonfederally funded research they are deliberately

avoiding the IRB whenever possible because it has lost their respect. The IRB system is no longer trusted to act reasonably because of rules that are not under our control.

So I believe that NBAC has the opportunity to provide a more balanced perspective of all this but I would respectfully suggest that IRBs will not be able to play a role in regulation of international research or domestic research if this trend continues. This trend in perception and public trust and confidence and investigator trust and confidence in the IRB system.

Point number two: Can IRBs understand complex medical, social and cultural issues in international settings? Yes, I believe there is abundant evidence that they can. There are numerous articles in the literature and the Journal IRB and many other journals of very thoughtful, nuanced reflection by IRBs in many places around the country of the complex issues that arise in international research.

I am not claiming that all IRBs are wonderful and that all do equally good jobs but I just want to say at the least that many IRBs in many settings are quite capable of very high standards of understanding these complex issues.

There are excellent resources available to

them on both the ethical issues, on cultural issues in various countries and, of course, a variety of sets of international guidelines which are inconsistent with each other.

There is no clear consensus even among the most informed and thoughtful individuals on what the guidelines should be on international research and which standards should prevail. The Helsinki Doctrine is almost incoherent on the question of whether all subjects must get the best available care. The CIOMS guidelines are more tolerant of deviations from individual consent than the U.S. Common Rule.

Specific trials like the low-dose AZT study in Africa and elsewhere was likened by the editor of the New England Journal on the one hand to the Tuskegee study and on the other hand supported enthusiastically by the Director of NIH and the Surgeon General and the leaders of many of the countries involved. I mention all this to say that there are disagreements about what the standards should be, disagreements among those who write the leading standards, disagreement among very thoughtful people and, of course, there will be disagreements among and within IRBs.

To take our own experience with the Vietnam study, which is the article which has been distributed

to you, a study of a randomized trial of treatment of breast cancer in Vietnam. This occupied our IRB for a year. It caused intense controversy within the IRB and within the university, and I assume still evokes controversy among those who read it.

But controversy should not be equated with failure to understand local culture and values or to make thoughtful deliberations and conclusions. That is, I believe there will always be disagreements, or at least for the foreseeable future, and disagreements and criticism should not be equated with inadequacy of IRBs to meet this challenge.

At the least, in contentious cases IRBs should be expected to document that they have done such a careful review and that they have reviewed relevant literature, consulted with experts on local customs and to show that they are familiar with not just the national U.S. rules but the international -- various international guidelines.

Referring back to my first point, to take this function away from IRBs or to shift it towards a more centralized system of resolving these disputes has high risks. I have already mentioned what some of those risks are with regard to domestic research that is a distraction from attention to serious ethical

reflection.

A centralized mechanism for resolving these disputes or these questions raises the risk of a greater emphasis on political posturing and lobbying and less reflection on ethical concerns. We have seen this, of course, numerous times in the United States with regard to embryo research, stem cell research and so on. That is I would not have a high degree of confidence that a central system would be more reflective than a local system.

There are the familiar risks of central bureaucracies bringing institutions to a standstill for political or other reasons as has happened in domestic research.

Central review can be beneficial and helpful as a supplement to IRB review and I would support the experience with the RAC, the Recombinant Advisory Committee, as an example of a successful role for a central agency. But my own view is that the RAC is most helpful in providing technical assistance to IRBs, that is the great medical complexities about a gene therapy protocol are difficult for local IRBs to find expertise to just get answers and viewpoints on medical and technical questions.

I would liken this to the Clinical Affairs

Committees of the Cancer Centers around the country. It is now standard for clinical cancer centers to have scientific review committees, often called Clinical Affairs Committees, that review protocols for scientific merit, for design, for issues of competition with other protocols so that the IRB can have the best available scientific opinion.

So the RAC, I think, can and should play a useful role in that and I could imagine a central agency like that providing that kind of assistance.

There is no assurance that a reinvented RAC, if it should be resurrected, will do as well as the original RAC, I should point out. The original RAC went through a halcyon period in which gene therapy was relatively uncommon. There were relatively few protocols. As it becomes much more common the risk of politicization increases.

Finally, with regard to the third point about what to do when U.S. IRB views or guidelines conflict with local IRBs in developing countries, I have much less to say. I think it is difficult, at least it is for me, to reduce this to any algorithm or strong recommendations because there is such widespread disagreement about how to handle these disagreements or handle these issues.

As I have said, the guidelines in this area, the CIOMS guidelines, the Helsinki Doctrine, and the U.S. Common Rule are completely inconsistent with one another and these are all documents written by very thoughtful people who have considered very carefully ethical issues, and yet they cannot agree on the most fundamental questions.

So I think we are doomed to continue sifting and winnowing in this area, and there will continue to be disagreement and no clear principle in my view for resolving these disagreements.

Just to close with just one point, some people have said at least one principle is that the local standards should be the minimum. That is that a U.S. IRB should never be able to overrule, and an investigator should never be able to overrule, a local IRB in a developing country. But that, of course, begs the hard question. If a local IRB says that community consent is adequate, that a village leader can provide consent, it does not follow from that that the U.S. IRB cannot or should not overrule that and say that some higher standard is needed.

My own personal view is that it is not automatic that a higher standard is needed in all cases. I just point that out as an example that I am

sure you have reflected on quite a bit as not being reducible to saying that a U.S. IRB can never overrule a local one. It is a complicated issue. In some cases it might be acceptable and in other cases not.

Finally, let me just say one more time that disagreement on these issues does not mean that the IRB made a wrong or a bad decision. Our Vietnam study still evokes rage among some people. It does not follow from that that it was unethical or that it was wrong or that it shows that the system is corrupt. We did, after all, win a prize for writing in Research Ethics so it got some respect from some individuals.

So ethics, as President Shapiro said many times, is about reflective equilibrium and about trying to at least have access to the best possible facts and all the possible views, and try to come out in a way that at least reflects a good process and careful consideration.

Thank you very much for the opportunity to present my thoughts. I hope I can participate in the discussion.

DR. SHAPIRO: Certainly. I think what we will do is we will -- unless there are questions, purely questions of clarification, we will hold our questions until we have heard from both panelists and we will

have a general discussion.

Are there any questions of clarification for Norm?

Okay. Dr. Nayfield, thank you very much for being here today. We appreciate your presence.

SUSAN G. NAYFIELD, M.S., M.D., M.Sc., CHAIR
SPECIAL STUDIES IRB, NATIONAL CANCER INSTITUTE
ROCKVILLE, MARYLAND

DR. NAYFIELD: Thank you.

My talk is a little different in organization. What I would like to do is to tell you a little bit about our institutional -- the institutional review board that I chair at the National Cancer Institute. This is a unique situation and I think perhaps gives us more freedom in addressing some of these issues.

(Slide.)

I would like to describe how we handle the different types of international collaborations that come before us and then I have two very brief recent case studies that are illustrations of some of the problems we have encountered, first, in a less developed country and, second, in a westernized country.

You have handouts that have reproductions of the slides. Let me begin by explaining the National

Institutes of Health holds a single MPA for all of the institutes under its umbrella. That MPA now covers 14 IRBs. As a rule, each institute, center or division at NIH has its own IRB. The National Cancer Institute has two and I chair one of those.

(Slide.)

The Special Studies IRB was created in 1992 when we became aware that there was need for increased observation and guidance to intramural investigators who were conducting their studies off the NIH campus. And the mandate given to the IRB was to protect human subjects participating in the studies that were done outside the walls of the National Institutes of Health.

The focus of these studies is predominantly epidemiologic, behavioral and genetic. In most of the studies there is little opportunity for direct benefit from participation and many of them pose very interesting and difficult questions about study design and management.

(Slide.)

PROF. CHARO I apologize. that is the Perkin's restaurant next door.

DR. NAYFIELD: They must be having a good time.

Between a third and two-thirds of the active protocols that our IRB reviews involve collaborations outside the United States. These studies are diverse in the geography and the ethnography and they involve unique situations or opportunities for our investigators that they would not have within the United States.

For example, they are conducted in areas that have a high prevalence of specific diseases or in which a specific infection or problem is endemic. They involve unique environmental exposures. Geographic areas that have high concentrations of radon, for example. There are unique occupational exposures in certain countries such as tin mining in China. And there are natural and some unnatural disasters such as the Chernobyl event.

(Slide.)

There are basically four situations in which our IRB deals with international studies and I will spend a little more time on each and come back to each of these.

The first is a study that is in a limited geographic area, which is a collaboration with one or few foreign medical institutions. This is a hypothesis driven study and this is the usual study that -- the

type of study that our investigators pursue. Examples are the development of neurologic diseases and cancers in areas of South and Central America where particular viruses are prevalent. And studies of occupational exposures in tin miners in certain areas of China.

The second situation is which we have very broad geographic areas with many foreign institutions and hospitals of varying sizes and an example of this are some of our registries, our cancer registries or our family registries for genetic cancers. These can involve an entire country and can involve hundreds of hospitals within that country. So it is much more complex than dealing with a single institution and set of investigators.

The third situation is a little unique. It is a multinational collaboration in which large numbers of foreign clinics or individual physicians from different countries contribute to the study population.

And the last situation is when there is a foreign research project usually designed and underway, and perhaps completed, that then invites an NCI scientist to collaborate.

(Slide.)

In the first situation,the more common one with the large studies, we try to avoid conflicts by

planning and leg work before the study is even designed. These studies are set up as partnerships with foreign investigators and this partnership occurs -- is established at the very, very first opportunity before study design begins.

When a mutual planned study design and protocol are developed, the NCI division responsible for this tries to get a project -- to hire a project officer who has lived in the geographic area, in the foreign area, or who is from that country, or who has trained there. Someone who has very strong connections with the area, the scientists and the people. And this person is a bridge between the Cancer Institute and the foreign investigators and populations from whom they accrue.

In terms of the set ups of the study, most of the laboratory tests are performed by the foreign scientists in their laboratories with the assistance of NCI scientists and usually a small percentage of the results are confirmed in the United States. We have found that this is very important in retaining the science in the country that collaborates. We are not just using a country to get genetic specimens or taking away resources that could build the reputations of the scientists in those areas.

The Data Safety and Monitoring Boards includes scientists from the collaborating country as well as non-NCI scientists who have done research in those areas or who have personal ties to those areas.

And in this situation we work with OPRR and the investigators to help establish a single project assurance.

In certain situations, such as dealing with the Ukraine and Belaruss, this has been a very interesting undertaking, and in at least one situation an investigator has gone to the Ukraine and set up an international four-way conference call with investigators in the Ukraine, investigators at NCI, myself and our office of Human Subjects Research representative, and OPRR. That led to very quick discussion and resolution of any remaining questions and really got the project on its feet.

(Slide.)

The second situation is the broad geographic area with many institutions or hospitals. These are usually minimal or low risk studies such as the population based cohorts for epidemiologic studies, cancer prevention and interventions that use nutritional supplements, the development of tissue repositories, for example.

These are done with full collaboration in design, implementation and monitoring, and in some situations they are presented to the countries as an opportunity, a special interest of the National Cancer Institute. So the impetus for doing this does start with us.

There is a mechanism called the International Cooperative Project Assurance that we use in these situations, which basically centralizes the foreign authority and responsibility with an oversight body in that country. For example, the Ministry of Health has to agree to be the -- or a similar body agrees to be the main authority to set up the IRB and to oversee these small hospitals that are contributing patients or cases. This has worked successfully in the few instances that we have been faced with this problem or this situation.

We have had another situation come up on several occasions and that is particularly in genetic epidemiology when there are family studies requiring multiple affected members or rare diseases.

(Slide.)

For example, to study the genetic epidemiology of familial pancreatic cancer. It is very difficult to find families with pancreatic cancer. For some of

these studies that involve susceptibility to viral infections in individuals who receive blood products it is advantageous to have sibling pairs affected with hemophilia and these can be very difficult to accrue.

So a number of our investigators have gone to international accrual. At least for the hemophilia, most of the care that is given is clinic based outpatient medical services, and the physicians who care for these people may not have hospital privileges and they are usually contributing one or two cases at the most.

We have worked closely with OPRR to establish the use of independent investigator agreements in the situations where these physicians are not affiliated with a hospital with an existing IRB, and this seems to have worked very well.

However, in those cases we have brought in a consultant who is experienced in multi-national research to actually help the investigators and the IRB work out the details to make sure that they are sensitive to the cultures and the backgrounds of the participants in all the countries from which we are accruing.

(Slide.)

The fourth situation is -- I do not think is

unique to NCI. It is a situation in which a study is conducted in another country and towards the end of the research project or when the data is being analyzed the researchers realize that they need assistance. They need another special laboratory test for which an NCI scientist has a reagent, or they need assistance with analysis and interpretation and they invite an NCI investigator to participate.

The NIH policy and the Multiple Project Assurance require IRB approval in this situation and it is very difficult for the IRB because it is after the fact and nothing that we can say or do can change the way the study has been conducted or if changes are made in the middle of a study.

So the approach that we have taken in that situation is to review the protocol for the study and to decide whether it meets the standards of research in the United States, and if it does we give permission for the investigator to collaborate. If it does not, then we disapprove the protocol and tell the investigator that he cannot collaborate. This -- in the four years that I have chaired the Special Studies IRB, this has been the only situation in which we have disapproved studies.

(Slide.)

Now moving on, I would like to present two cases to you that show some of the problems that have arisen recently, actually within the past few months, in one study that is ongoing and one study that was a potential collaboration.

In writing these up I have had to simplify, so while the summaries are not incorrect, they are certainly not complete and there are many more details. However, I think that the information here will make a point.

The other thing I would like to say is that these are studies or situations in which there is not really a bad guy. The problems arose not because someone broke protocol or broke regulations. They arose out of sincere efforts to do the research.

The first is a situation that has arisen in China. In 1988, NCI began a study in a province in rural China to determine the prevalence and progression rates for stomach lesions predisposing to cancer. This included stomach infections with a bacteria, helicobacter pylori. Participants from this province, and the participation rate was very high, it was almost 90 percent actually, had endoscopy and blood tests for H. pylori antibodies at baseline, which was 1989, and then again in 1994. And this allowed investigators to

determine the baseline prevalence rate, and to get an idea of whether infections progressed or spontaneously regressed and how quickly any lesions developed into premalignant histologies.

(Slide.)

Based on the finding of this first study, NCI began an intervention clinical trial in the same population. The goal of the study was to explore whether dietary supplements could reduce the prevalence and progression rate of the gastric conditions.

The results from the 1994 studies were used as baseline because many of the participants in that study actually were invited and chose to enter into the intervention study, and then a second round of endoscopies and blood tests for H. pylori were begun in 1996 and extended into 1997.

(Slide.)

As an interim analysis the investigators compared the results of the 1994 and 1996 serologic tests and were surprised to find a 40 percent seroconversion rate.

DR. SHAPIRO: Forty percent what?

DR. NAYFIELD: Seroconversion rate. In other words, 40 percent of the people who had had negative serology at the time they entered the study were

positive for the 1996 and 1997 tests. And this suggested that these participants had actually developed H. pylori infections.

This was a much higher than expected conversion rate particularly from the previous study. The conversion rate was in single digits. And so the investigators considered the following as possible explanations:

(Slide.)

First of all, the prevalence of H. pylori infection in China as a whole could have increased from 1994 to 1997. In other words, a background -- an epidemic in the background of an endemic infection.

A second possibility is that the dietary supplements could have improved immunity in the populations and thus increased the antibody levels by improving general health.

There is something that is very specific about H. pylori that makes this a reasonable hypothesis. When there is a lot of disease the bacterial burden is low and the antibody level tends to be low. And then as the disease gets better, before it gets well, the load of bacteria is increased and the individual can develop antibodies.

So one possibility was that at the beginning

the nutritional status was low of the participants and the infections were severe so there were no antibodies, and then in providing the dietary supplements and so forth, the nutritional status increased and they actually developed antibodies as the infection went through kind of the bell shaped curve or the hump of bacterial load before it was cleared.

A third possibility was that laboratory procedures for testing for antibodies changed during the study so this could be a misleading result.

And the fourth possibility was that the bacteria could have been transmitted by endoscopy if the equipment was improperly cleaned.

The last possibility actually was a very important consideration because we learned that in 1991 the National Health Ministry in China had changed, on a national basis, its policy for cleaning endoscopes. Prior to 1991, they followed internationally accepted standards of soaking the endoscopes in a disinfecting solution for ten minutes before using them in the next patient or the next person to be endoscoped. In 1991, they changed the procedure throughout China to using special wipes that had been treated with disinfectant to wipe the scopes. This was a national policy, and it was invested into the point that the government set up

at least one factory to manufacture these wipes.

At the 1994 site visit, the NCI project coordinator saw that the procedure had been changed. This was a physician who was trained by the scientists in China. They were his mentors. They had been his advisors. And he asked about the changes and was given the scientific basis for them and did not report them to the NCI study team, unfortunately, because he accepted that this was national policy in China and there was scientific evidence to suggest that it would be okay. We learned this a few months ago actually.

The Data Safety and Monitoring Board met and decided the following:

(Slide.)

First of all, they wanted simple studies to be done to determine the cause of the seroconversions. They wanted endoscopes that had been used in patients with infections to be wiped with the wipes and then cultured to see if after the cleaning process the bacteria were still present and, therefore, realistically could have been transferred to the next patient. They also wanted to go back and look at the biopsies from the 1989 study to see if there were severe infections in people who were seronegative.

These were fairly simple studies and they felt

that they could be done within the next six months. However, they were unwilling to wait to treat the participants who had developed antibodies to the bacteria, and decided that these participants who had seroconverted should receive antibiotic therapy without delay.

With input from the Chinese investigators, the Data Safety and Monitoring Board recommended that participants should be informed when they were offered treatment that the cause of the presumed infection was not known.

(Slide.)

The NCI Special Studies IRB met and determined the following:

They agreed that the simple study should be done.

They agreed that all participants should be treated with state-of-the-art antibiotics and as quickly and efficiently as possible.

However, the IRB felt strongly that the participants should be informed that the infection could be related to their participation in the study, since most of the hypotheses suggested that that could be the situation.

(Slide.)

This case brought up a lot of discussion at the IRB as you can imagine and there were some points that the IRB spent a fair amount of time discussing.

The first was the potential conflict of interest for the NCI project officer. Our scientists have made a special effort to find special people who could be project officers for these studies who had ties to the local geographic area, who were scientists, who basically could serve as a bridge for any lack of understanding or appreciation between the American team and the foreign team.

And yet what was not considered is that this could create a conflict of interest for the project officer, as it may have in this case. The people who changed the endoscopy procedures had been his mentors. They had been responsible for his education and for his even coming to the United States. Certainly at least subconsciously this person accepted their recommendations without question and did not report them to the people who had hired him to do a specific job, which was to monitor and facilitate the study.

And, you know, we talk about conflict of interest between the physician as a physician and the physician as a researcher. I think that this is a similar conflict of interest that perhaps we need to

pay more attention to, at least in terms of recognizing that it can exist in this type of situation.

Another point that perplexed the IRB was what to do when there are changes in health care policy in a foreign study site. I mean, this is a national determination for a clinical procedure. This endoscopy was not a research procedure although it was used in a research setting.

And what we have now done with all of our studies in China that do endoscopy is to make sure that the investigators have supplied the appropriate equipment for cleaning the endoscopes, and that they are making certain that in the research situation the internationally accepted standards for cleaning are in place.

I think a third point that is very important here has to do with treating the seroconverters and what they will be told. We have not heard from the scientists in China yet as to whether they will go ahead with this, but what do we do if they say we will not tell these people that their infections could be due to participation in the study? Does the IRB then say, "Well, that is okay. Tell them what you want and go ahead and treat them."? In a sense the IRB members felt that they were being held hostage and this would

be a very difficult type of disagreement with which to deal.

I think that the fourth point here is accommodating differences in standards of health care. For example, one thing that -- one point that came out of our questions and discussions, our investigators were sending disposable endoscopy forceps to China. These are standard -- in standard use in the United States. They are long forceps that go down the endoscope and pinch the little biopsies. And they are made to be used for one patient and then discarded. When, in fact, in China they were being cleaned and reused. And when the investigators have requested that they not be reused for study participants, they were being cleaned and reused for general clinic care.

And I think that this type of thing becomes a problem when there are big discrepancies in standards of care and in availability of equipment and so forth. I think the Third World countries, or less developed countries, are particularly prone to this in terms of taking things from research and using them as best they can to provide better care.

However, this has come up in the United States in terms of HMOs and cost-effectiveness, so it is not unique to our situation in China. And what we are

doing there is we have asked the investigators to contact the companies to see if these actually can be cleaned safely.

DR. SHAPIRO: Could we deal with the second case as quickly as possible because I want to leave time for questions?

DR. NAYFIELD: Yes, sir.

(Slide.)

In 1998, British investigators began planning an international chemoprevention trial. This was to be premenopausal women with genetic mutations predisposing to breast cancer. The participants would be randomized to either observation alone with annual examinations versus a regimen of drugs to suppress the ovaries and then to protect against bone loss and heart disease associated with the ovarian suppression.

(Slide.)

In 1999, the National Cancer Institute's Cancer Genetics Network was invited to participate in the study as an international collaborator. And following long discussions we declined the invitation for the following reasons:

(Slide.)

One was that in the United States women with BRCA mutations are offered tamoxifen for

chemoprevention of breast cancer as standard care. This was established by scientific evidence in the Breast Cancer Prevention Trial and was recommended by the American Society of Clinical Oncology as a standard approach. The proposed trial in England did not allow for this standard of care.

Secondly, in the U.S., observation of these women is more frequent and uses more sophisticated methods than proposed for the British study. Therefore, we felt that we could not randomize women to their observation only arm.

A third issue was that a similar type of intervention had been tried in the United States and those trials are still ongoing. Instead of using a single drug to add back and protect, they use small doses of multiple hormones.

And the problem with that study is that women just do not want to agree to participate. They feel the regimen is too strenuous and the women who do participate find it very difficult to maintain participation, so obviously I think our experience has raised questions about whether we could even recruit to this protocol or would want to. Perhaps a different attitude toward quality of life.

And, finally, the FDA would not allow the use

of a two-drug regimen without evidence of safety of the combination.

(Slide.)

So I think you can glance briefly at some of the points that really were discussed in this situation. One was how the standards of care are set and how they differ between countries and how this can impact collaborative research. Standards of care are frequently set by scientific studies, by recommendations of groups of experts like the professional societies, or because everybody does it. Certainly with tamoxifen the first two come into play with the practices for screening. And following women at very high risk of breast and ovarian cancer, it is more one of everybody does it.

Another is how differences in health care systems enhance or inhibit research collaborations, and I think this is an example of a National Health Service perspective on services versus what happens in this country.

The issues about accruing to this particularly aggressive regimen that patients do not like perhaps brings up issues of how quality of life are regarded and how patient-physician relationships differ.

One of the British scientists in this

basically said to me, "Attitudes are different in England. Patients and participants over here basically do what they are told." Having been a patient during the time that I lived in England, I was not surprised by that comment.

Finally, is how differences in government regulatory systems impact international research efforts. The regulatory bodies in the United Kingdom approved this study. However, in the United States the FDA would not consider it.

DR. SHAPIRO: Thank you very, very much. That is very helpful and the cases are really quite instructive, and I appreciate your effort in pulling those together for us.

I have a number of questions myself but let me first turn to members of the commission and see if there are any questions either for Dr. Nayfield or Dr. Fost.

Questions from commissioners? Larry?

DR. MIIKE: Just for Dr. Fost. On your initial question about the domestic situation. I sort of agree with you on OPRR in the sense that if one looks at their web site and looks at the areas that are of concern to them, there is no prioritizing. It just sort of lists the different areas of the regs and it

says what they run across.

But I think that the main problem is that they have to do a paper review oversight function, and that sounds to me like where your problem is coming from, that they do a paper review and from your experience at the real level you do not really see much of a correlation between that review and what you would consider the problem.

So what is your alternative?

DR. FOST: Well, my friend, Alta Charo, and colleague and I have debated this at great length, and Alta has used the analogy of checklists for airplane pilots who are required to document that they have gone through a checklist. It is a good analogy, I think, and I think the comparison with what is going on in regulation of the IRBs these days would be akin to asking the pilots to check to make sure that the seat trays are all in the upright and locked position.

There is some theoretical connection between the seat trays being in the upright and locked position and safety. I do not know that anyone in the history of aviation has ever been injured or died because that was not the case. So whether it is an important rule or not, I do not know. It could certainly be delegated to flight attendants.

But the current -- so that my problem with the OPRR approach is not that it relies on checklists and on documentation. I think that is one important component of oversight, but I think they are checking now and documenting the wrong things. That is things that have little or no relationship to protection of subjects, and it has forced this enormous escalation in IRB work for things that just are not where they should be spending their time, either staff or IRB members.

So I do not object to checklists, but they should be for the right things and for the things that matter.

Second, I think outcomes do matter, and I think for institutions where there is not a single claim or allegation, either that anybody has been injured or that -- other than anticipated injuries -- or that a protocol has been approved which is -- which should not have been approved in anybody's -- you know, in OPRR's or anybody else's opinion. And neither of those two facts have been suggested in any of the reviews that I have read about.

When neither is the case then the penalty should be proportionate to what the problem is, that is warnings, suggestions, advice. But shut downs -- that is the death penalty -- has led IRBs to do what our's

has had to do, which is to spend literally a million dollars and still with no assurance at all that we can avoid such penalties.

So I do not object to checklists. I think it is a matter of what is being checked for, and whether or not staff are allowed to do it or whether IRB members, you know, senior faculty are being required to do things that can be better done by others.

DR. SHAPIRO: Alta?

PROF. CHARO Again, a question for Dr. Fost but it is based on Dr. Nayfield's very helpful set of examples of problems that can arise.

The first case study, the one in China, exemplified, I think, some of the difficulties that can arise during the course of a study as opposed to the initial points of review.

I know that you are experienced not only with the UW IRB but have talked to a lot of other people at other institutions. What have been your observations about the capabilities of IRBs -- in general, not just at the most active institutions, to actively oversee foreign trials and to, in fact, conduct continuing reviews that will reveal these problems before they arise as opposed to after?

DR. FOST: Well, a couple of things. First, I

think the Data Safety Monitoring Boards are another mechanism for doing that, and happily, in my view, their use is expanding, and I think there are trials in which they should be required, and the trend is in that direction. That is they are in a much better position than an IRB to look at detailed ongoing day-to-day conduct of the trial problems that arise, and so on, in very minute detail in a way that an IRB looking at 1,500 protocols cannot keep track of. So I think DSMBs are a better way to go and, of course, any of their concerns should be related back to the IRB.

Second, it seems to me you are asking a question about investigator's compliance with the expectation, the rule, that problems in the course of a trial be reported back to the IRB, serious, unexpected, adverse effects, changes in the design of the trial or in the conduct of the trial. There may be noncompliance on the part of the investigators with that, in which case they should be hung followed by a fair trial, you know, but the punishment should go to investigators who are not doing that.

I am not skeptical about the ability of the IRB to handle those sorts of problems that -- at least to address them in a thoughtful way if they are brought to their attention. Thoughtful way does not mean that

you and I will agree on the outcome in all cases.

DR. SHAPIRO: Thank you.

Alex?

PROF. CAPRON: Norm, I had a couple of questions based upon your discussion of the international aspects of what you are talking about. I do think it would be useful to have you back when we are talking about the domestic side because your more far reaching concerns about IRBs are obviously at the heart of our evaluation of the kinds of reports that the Office of the Inspector General and so forth have made.

You commented, in light of the erosion of respect for IRBs among investigators, that people with whom you spoke, faculty at Wisconsin, when they were not doing federally funded research, were doing whatever they could to avoid having to go through the IRB. I was not clear what kinds of situations you were thinking of and whether some of them were international research.

DR. FOST: First, I would not want that anecdote to be overrated. I have had occasional -- I have had a few, a handful of investigators tell me that their attitude about IRBs have changed, and I take this -- I think they represent a larger group. I think

noncompliance is not widespread. I think it is anecdotal but I took it just as an example of how IRBs -- if they lose respect of the people who they are supposed to be regulating, they will be less functional.

PROF. CAPRON: Well, I guess part of my question -- if you can respond to it as you answer this -- is under the Wisconsin IRB general assurance, multi-project assurance, if an investigator is compensated partly by the university and partly by private funds, and becomes involved in something which is not going through the university, is that the situation in which you were thinking they were describing? They were saying, well, since this is not a university project I am not involved or --

DR. FOST: No. The anecdotes that I was referring to involved purely domestic studies, indeed through purely local studies, not randomized trials and so on. They were relatively low risk and minimal risk studies. Generally it was substantively an ethical problem, but procedurally I took it to be a serious problem.

Our rules for the issue you raise I think are common, which is any person on our faculty who does research, no matter where it is conducted, under

whatever funding, must be reviewed in the same way.

PROF. CAPRON: The second question had to do with your description of situations in which you would take an interest in the local review process, and you said you get to the point sometimes of saying that process is not adequate. And I think in that context, or otherwise, you commented on the fact that a different IRB might reach a different conclusion about that.

And we recognize that there have been criticisms of the IRB system for the very fact that it reaches different conclusions in different localities. And one of the arguments as to why that should not be regarded as a failure of the system is that an IRB in a particular place, reflecting the mores of that community about a research topic, might say this raises too much risk and another IRB in another community would say otherwise.

When we get to the U.S. sponsored research being conducted abroad, if we take that same attitude, we are, in effect, multiplying that difference, because here, as to the international site where the research is being conducted, what we are, in effect, saying is that Wisconsin thinks that what goes on at that site is not acceptable and Minnesota looking at that same site

says it is. And you do not have -- it seems to me on the face of it, you do not have quite the same sense that -- well, it is reflecting local mores as to what is acceptable in this population that we are familiar with right here at home.

Do you see what I am saying?

DR. FOST: Yes.

PROF. CAPRON: And so the variation -- I wonder if -- if you could help us to understand are there any sets of criteria which could be applied by IRBs wanting to do the right thing in evaluating a host country's ability to provide adequate ethical oversight?

DR. FOST: Well, first, what you describe happens all the time every day in every IRB. That is, in multi-center trials just in the U.S. we disagree. We are told, you know, nine other IRBs have reviewed this project and found no trouble with it. We see big trouble with it or vice versa. We disagree with the FDA in how a project is designed, whether a placebo group is appropriate or not. So you have all the time IRBs with polar opposite conclusions.

And the waive consent rules, which I was involved in developing and involved in several initial trials, that is, these are high risk interventions in

populations in which consent was not feasible. One of the parts of those rules, as you know, was to require community disclosure and something like community consent. And it led some IRBs in some institutions to say, you know, "In the South Bronx this will not fly." And others in Madison, Wisconsin, to say, "I think it will fly here." So you had IRBs saying this is unethical, unacceptable for our population, and another saying that I think this is acceptable in our population.

So you have again differences. I do not think the fact that the two IRBs came out different suggests that one is right or one is wrong. They both were making thoughtful informed decisions.

I am not sure if that is responsive to you.

PROF. CAPRON: Well, actually what you have done is restated my introduction, which was to say there is a model which says that to the extent the IRB -- particularly if it uses a surrogate community consent process -- is quite -- it is quite acceptable that different IRBs are going to reach different conclusions because they are reflecting different local populations, and it is that variation which we use to explain why they would come to different conclusions.

Now let's say two IRBs, one at the -- I said

University of Minnesota and University of Wisconsin -- are looking at a research project of the type that Dr. Nayfield described conducted abroad, and they are deciding whether or not that foreign site has an adequate process, and is prepared to do ethical review, and the standards that have been established for that site are adequate, et cetera, et cetera, and they reach different conclusions.

The fact -- you know, you could say, "Well, they are just reflecting their local differences in an evaluation." But the local differences are not that people are going to disagree looking at the same thing because they go through different processes locally. It is that their local circumstances are different, that the South Bronx and Madison are different enough.

But why should they reach different conclusions about something that is happening in China?

DR. FOST: Well, let me use our Vietnam study as an example. I suspect if Dr. Love's breast cancer trial in Vietnam was put through almost any other IRB in the country or many other IRBs would have rejected it. It was very controversial. It had explosive issues imbedded in it.

One reason they might have rejected it is they

did not know him. They -- from afar, they did not know whether they could trust him and his colleagues in Vietnam to conduct this in a way that they could be comfortable with. Whereas, the Madison IRB know -- it is one of the reasons local control, I think, is very valuable. You can make assessments about the integrity of the investigator, which many people have said is the -- maybe the best possible protection for subjects.

So there is an example in which other IRBs -- this is two different IRBs looking at a Third World site -- might have come to different conclusions. I would not be critical of another IRB for -- I would not say they made a wrong decision in turning it down and I would not think anybody would say we made a wrong decision.

PROF. CAPRON: Well, any other factor besides local -- familiarity with the investigator? I mean, I guess what I am getting to -- really there are two points that I hope that -- I do not want to put you in the hot seat about them, it is not -- I mean, it is not a question of inquiry.

One is are there standards that can be applied? OPRR itself has told us it has no published or otherwise -- no existing criteria for deciding whether or not another site has equivalent procedures,

so they go through this process of negotiating a single project assurance.

There are all sorts of problems with that as a method. I mean, because it is sort of -- it -- rather than saying you are -- we can look at what you are doing and say it is equivalent. Instead, it is the negotiation and you have to meet our standards and, you know, you enter into a formal relationship and we recognize you. It is a different tone.

But beyond that, the fact that there are not criteria for doing it means that each of those negotiations is an ad hoc process. So that is an issue that could equally be applied here.

Are there any standards you would look to? Are there any criteria that different IRBs could apply?

But the second one is something which goes beyond the international and it is the sense that maybe a reason that IRBs differ is just the people on the IRBs have different standards, or different analytic methods, or different tolerance for degrees of risk, or so forth, and they are not reflecting differences in local circumstances.

They are reflecting differences in who happens to be on the IRB so that the same IRB if its membership turned over, over the course of a year, would reach a

different conclusion.

And I do not know that that is troubling but it is a different explanation of why there are differences.

DR. FOST: I agree with you that that happens. I think there is an understandable desire to have some algorithm for resolving each protocol that everyone would come to the same conclusion about it. I do not think that is ever going to happen.

My only point is one way to have consistency is to have a single central authoritative IRB that must approve every international study or every international study in a certain category. I do not see that as producing -- getting around any of the concerns that you are raising. That is having it be political and having it depend on who happens to be on that group at the time and so on.

So I think no matter how you do this, it is going to be, like ethics always is, it is going to be messy and not quite algorithmic. I think the question to ask is whether seriously unethical studies are going on, whether widely shared rules and guidelines are being violated.

I think you should look at Stu Kim's excellent analysis of the various international guidelines.

There are threads that are in all of them that everybody would agree to and any protocol that does not -- you know, there must be some local IRB, something like an IRB. There must be some element of consent. It may be -- I mean, you know what they are as well as I. There are half a dozen or more things that everyone agrees should be part of every international study.

But bottom line, different IRBs, different people, are going to come out different on individual protocols even relying on the same rules.

DR. SHAPIRO: Arturo?

DR. BRITO: Let's switch gears here a little bit and these questions are directed at Dr. Nayfield. Thank you for your presentations, both of you. You are both very helpful.

Specifically for the case in China, I have questions before the problems began to arise that I was struck by a couple of things you said.

You said that participation in the study was 90 percent. I was curious how the participants -- which -- who were the participants in the study? Were they those with symptoms of H. pylori disease? That is number one. And how were they selected? Were they individually consented or was this a community type of consent for them before?

And then when -- once they were selected and the dietary supplements were given, were these given to -- compared to a placebo or were they given to treatments for H. pyloric gastritis or peptic ulcer disease or some cause of H. pylori that those treatments, if I remember correctly, became billable late 1980's and early 1990's.

DR. NAYFIELD: The study for determining the prevalence of disease was conducted in a province and at all villages in the province adults were invited to participate. The selection was really on the basis of age and they were individually consented.

It has been explained to us -- and I think, you know, in response to some of the other questions -- to Dr. Capron's question, the project officer who has ties to that area of the world in which we are doing the study has been very helpful in explaining some of the differences between what the local IRBs require and what we have questions about. And in many cases where we have disagreed, the explanation has made it clear that we can, indeed, approve this.

But the people come into the clinic and they have the form read to them for consent. It is a consent document. So there were basically no exclusions.

The randomized trial was a two by two factorial design because they were testing two different dietary interventions, a vitamin based intervention and a mineral protein based supplement. And so there was, indeed, a control group. Prior -- as part of that study, people who were known to be positive were treated so there were no people who were left in the interventions -- at the beginning of the intervention study. People who had been positive, who had positive serologic tests in 1994 were treated and they were treated with standard therapy.

DR. BRITO: Standard therapy --

DR. NAYFIELD: In the United States.

DR. BRITO: -- in the United States.

DR. NAYFIELD: Right.

DR. BRITO: Okay. And then with the 90 percent participation rate, that -- what was the standard of care there in that province, and I am curious about the therapeutic misconception, and did the people understand this was a study, and were they guaranteed a treatment if they were found to be H. pylori positive or antibody positive?

Do you understand the question? In other words --

DR. NAYFIELD: Right. Right.

DR. BRITO: -- when you are recruiting and you get the consent from the participants in the study, is part of the motivation or was part of the motivation that they would be afforded therapy for treatment of something that otherwise they would not have access to?

DR. NAYFIELD: It has been explained to me that the care for these people is very limited and that one advantage for them participating in research is they get care to which they would otherwise not have access. This is rural China. There are not endoscopists around and only people with the most severe problems get referred and endoscoped. So, yes, in the initial study people who were found to be positive at the beginning were treated at the beginning. The original study was set up in 1988 before our IRB was established so I do not have the records from that original study. It is very interesting that if we had not done the second study, the intervention study in that same population, the problem never would have been picked up.

DR. BRITO: Okay. And one last question not related to the study but just more general. In your population based studies and your family studies and genetic studies, do you take into consideration potential for stigma and/or discrimination based on

results as part -- when you are calculating what risk is in these studies?

DR. NAYFIELD: We do, indeed, and if it involves bringing in an international consultant to help us with that, we do.

I need to point out that I -- our IRB has the luxury of dealing with one -- with this type of study. We do not have to review clinical trials and monitor for adverse events. We have more time and I think more ability to ask questions and get responses than does the typical busy IRB.

DR. BRITO: Thank you.

DR. SHAPIRO: Thank you.

Larry, then Alta and Trish.

DR. MIIKE: Again for Dr. Nayfield. I am interested in the England study. Particularly the reasons for rejecting a two drug regimen.

My understanding is that if you have an approved drug, doctors frequently use it for other indications even though they were never approved by the FDA. So I was a little curious about why the statement here was that the FDA would not have allowed it. It seems to me that -- and my question is sort of multiple. Number one is that is it -- is there routine procedure at the NIH when they do two drug combinations

of drugs that are already approved, whether you routinely go through an FDA process seeking to get permission on ultimate FDA approval so that you would do a Phase II trial before doing a Phase III trial to check the safety.

My second question is that because this was in the United States population, would you have also objected if this -- if NCI was involved in a clinical trial in another country using two drug regimens, would you have rejected it on the same basis?

It seems to me that what you are saying here is that before you would participate with any other country, they would have to conform to the process by which it would gain approval for a drug by the United States FDA. Am I wrong in that?

DR. NAYFIELD: Most of the research that we do that would go -- well, anything that would go to a relabeling of the drug would need to be done under an IND. In other words, if the combination of two drugs were -- the drugs were to be approved and the package insert was to read that this can be used --

DR. MIIKE: No, I understand that but are you saying --

DR. NAYFIELD: -- in preventing breast cancer --

DR. MIIKE: -- then that NIH would not participate in a trial by another country that has comparable standards without saying that they would not participate unless it would meet the U.S. drug approval process and U.S. approval for a new indication for that drug?

That is the implication I get from your statement here that one of the objections was that FDA would not have approved.

DR. NAYFIELD: That is correct. One of the objections was that we could not do this from a regulatory standpoint.

DR. MIIKE: But if you were involved in a trial, with a British sponsored trial where ultimately they may have wanted to seek British approval for that combination, if it did not meet FDA standards you would not have participated?

DR. NAYFIELD: I am perplexed by your question because unless we do --

DR. MIIKE: Because my question --

DR. NAYFIELD: -- meet -- now these are for prevention studies. These are not treatment studies.

DR. MIIKE: But you are using drugs here and --

DR. NAYFIELD: That is correct. And certainly

at least my understanding is that we are precluded unless we have regulatory approval of doing these studies, particularly in our individuals in the prevention setting. Now in the clinical setting it is not a problem for an individual physician to decide to use drugs off label and I think that every practicing physician has done that. And an example here --

DR. MIIKE: Then are you --

DR. NAYFIELD: -- an example here would be if the British had wanted to use Zolodex to suppress the ovaries with tamoxifen. We would have been able to do that because those two drugs have been used together in the treatment setting and there is evidence that they are effective and there is evidence that they are safe.

DR. MIIKE: No, but what I understand is that you -- from what -- what I hear you saying is that NIH would not participate in any trial unless it was in a formal track into the FDA process for approval of the drug.

DR. NAYFIELD: Now what I am saying here is that the Cancer Genetics Network, which is supported by NCI and comprises eight university centers, the scientists did not feel that they could participate in this study without FDA approval. I am not saying that

this is policy. I am saying in this situation this was one of the major concerns.

DR. MIIKE: That is fine but I still do not understand why that decision was made. That is all I am saying.

PROF. CAPRON: Can I ask a clarification? This is about enrolling of U.S. women, is that right?

DR. NAYFIELD: That is correct. This is not about the enrolling of --

DR. MIIKE: I understand that, Alex, but I am talking about two approved drugs.

DR. NAYFIELD: They are approved individually for different purposes.

DR. SHAPIRO: Not in combination.

DR. NAYFIELD: Not in combination.

PROF. CAPRON: This is part of an IND.

DR. NAYFIELD: Yes. I mean, that was our -- I --

DR. MIIKE: I do not think so. But my second part of the question was that -- is that -- if applied to the international situation, would the same requirements hold?

DR. SHAPIRO: Alta, you are next.

PROF. CHARO Well, I will just -- I will make a comment on this but the point was really for

something else.

I think one of the areas we probably need clarification on is whether it is possible to do a trial that uses two approved drugs in the United States with U.S. citizens on the -- and to do that without an IND knowing that failure to get an IND means that the data from that trial cannot be used by the FDA for a subsequent approval process of a relabeling, but nonetheless can one do the trial because you simply want data from the U.S. that might be used by a foreign government where there is no such objection. I think that is where the point of confusion has arisen.

What I actually wanted to speak to, if I may, goes back to Alex's intervention about the variability in IRB reviews of foreign trials. And his question about whether there is any reason that there might be local variation beyond purely, in a sense, random variations in people's personal values.

I would like to suggest, without saying that I am still committed to the idea of local variation holding the day, that I do think there are some factors that may account for this.

If you were to look at New York City, for example, I would suspect that the IRB at King's County hospital, which has a large indigent population, might

react differently to protocols that would study populations of people who are poor and/or illiterate than would the IRB at New York hospital which tends to draw from a very different group of people, highly educated, self-protective, and aware of medical procedures at a more sophisticated level. So that their lack of experience with impoverished populations may lead them to evaluate the reasonableness of informed consent procedures and relationships between doctors and patients somewhat differently.

Similarly, IRBs in Los Angeles may have members on them who are recent immigrants, children of recent immigrants, people who work with immigrant populations at a much higher frequency than an IRB in, for example, Kansas, and thus may have more familiarity with the actual culture in which these trials may be going on.

So these kinds of things may actually cause different IRBs to have different areas of expertise as well as different preferences about how one intervenes in these environments. I am not sure whether that argues in favor of the continued variation in the decision to collaborate or whether it argues in favor of regional or central bodies that are constructed with an eye to diversity so that we can have a common

standard in the United States, but one that also reflects some actual knowledge of conditions abroad.

DR. SHAPIRO: Thank you.

Trish?

PROF. BACKLAR: Thank you. You both were very interesting and informative.

This is a question for Professor Nayfield.

I am interested when you talk about the participants, the suggestion was made that participants should be informed that the infection may have been related to the study. Do you have any information? We are very interested in how subjects who are in these studies react and feel about having been in a study. Do you have any information about how the subjects reacted to this information? I know that you did not have a Weichert scale probably.

DR. NAYFIELD: This -- when I said this was very recent, this was very recent. The Data Safety and Monitoring Board met less than a month ago so this, you know -- this is very recent. So actually the participants in China have not yet been offered treatment and we have not heard back from the Chinese investigators as to whether they are willing to tell the participants that this might have been part of the study.

The scientists, the project director, and several of our consultants have felt that there is a very positive attitude among these people towards the research project, and they are not predicting that the project will fall apart because of this.

PROF. BACKLAR: So are you talking about a positive attitude from the people who agreed to be subjects or a positive attitude from the local health authorities?

DR. NAYFIELD: A positive attitude from both actually, because the type of research here provides resources to the local health authorities that they would not usually have.

PROF. BACKLAR: Would -- are you going to in some way -- you are going to take care of people after the study? Particularly if they are ill now because of the study. Is there --

DR. NAYFIELD: The study with the dietary supplements is going on and continues and the people are -- who seroconverted are receiving therapy as they continue in the study.

This is an interesting situation because the study that is ongoing now is not the study that was the problem.

PROF. BACKLAR: Right.

DR. NAYFIELD: The study that caused the problem, we think, with the endoscopy instruments was closed, and there is nothing to indicate that there is a problem with the nutritional interventions or the current study except that it has to accommodate the treatment, and the statisticians have actually evaluated whether treating these people will in some way alter the ability to tell the effects of the nutritional interventions, and they feel that it will not.

So the study is going on and these people are continuing to get care. The plan is that the people who seroconverted, or who have seroconverted to this point will be offered treatment. Following treatment they will be given a breath test which is the current way to determine an active infection and if the antibody -- three drug antibiotic regimen that is the one used in this country has not cleared them then they will be provided with a second course of antibiotics and the Data Safety, and Monitoring Committee has experts in tropical disease and gastroenterology trying to recommend what the second course of antibiotics should be because this is -- I do not want to say it is controversial, but it is not standard.

PROF. BACKLAR: Right. And this -- you had

extensive prior agreements before these studies were started with the --

DR. NAYFIELD: With the Ministry of Health.

PROF. BACKLAR: In China.

DR. NAYFIELD: Yes. And actually there are other ongoing projects with this particular Ministry of Health. This is not an isolated project. This is a continued research collaboration over years and for a variety of different topics.

PROF. BACKLAR: It would be interesting to see the -- is it possible for us to see these prior agreements?

DR. NAYFIELD: The -- I am not sure what papers I would show you. The contract awards -- these are awarded by contracts -- are certainly available and the single project assurances with OPRR are certainly available.

DR. SHAPIRO: Why don't we pursue that, Trish, to see what it is that we get that might be useful.

Okay.

PROF. BACKLAR: Okay.

DR. SHAPIRO: Ruth, Bette, and then I have some comments, and then I think we will have a break.

Ruth?

DR. MACKLIN: Yes. My question is going to be

for Dr. Nayfield. But first let me point out that Dr. Shapiro should be very happy because since the very beginning of this project he has been seeking examples or even just one example of research that could not be conducted in the United States or a decision was made that it could not enroll people from the United States but could be done or would be done or agreed to be done in another industrialized country, and here we have it. Okay.

DR. SHAPIRO: Thank you.

DR. MACKLIN: So my -- I was delighted when I knew that Susan was going to -- Dr. Nayfield was going to present this case.

So my question is was there any discussion -- I take it, it was the investigators and not your IRB who declined to participate in that -- in the British study because American -- because -- to enroll American women. Is that correct?

DR. NAYFIELD: Right. There are several -- I play several roles at NCI that involve consultation and assistance in issues like this. And this never went to the IRB because the investigators as a whole were uncomfortable enough with it that they decided that they would look for other venues.

DR. MACKLIN: Yes. Well, I mean, my question

is -- and I guess it would have been more telling in a way if it had gone to the IRB but my question is was there any discussion among the investigators about whether or not it was ethically acceptable to do this study in another industrialized country? Not for NCI to participate but for the British group, on the grounds that, for example, the "observation" of the women in the U.S. is more frequent and more sophisticated. The British collaborators could very well have been trained and not only apprised of this, which they may have known anyway, but trained to do those more sophisticated observations in Britain.

So, I mean, the question is in a proposed collaborative study, and we think of this with the so-called capacity building, the obligation for U.S. researchers who are highly trained and scientifically and technologically knowledgeable to help to build capacity in developing countries that have not had that capacity to date and that is part of the general obligation.

But here we have another very well developed country and presumable -- I say presumably, you can correct me if I am wrong, even the tamoxifen might have been offered or might be able to be offered in Britain even though it is not the "standard" care or the

standard of care.

So my question is was there any discussion among the investigators about, hey, we have these collaborators here, we would like to collaborate with them but they are doing a study we could not do here. Is it ethically acceptable for them to do it there?

DR. NAYFIELD: There was discussion of that on a different level, not among American investigators. The American investigators focused on whether or not they could collaborate.

This study was planned to be multi-national. It was spearheaded by investigators in the United Kingdom but it was to include Scandinavian countries and countries in Europe, and in September of last year I attended an international meeting and there were a number of questions that came up.

One, the question that I raised at that time was tamoxifen and there was one other country that said that this had become the standard of care. It was Germany. And they would have some problems dealing with this. The Scandinavian countries, the other European countries, did not feel that this had been an accepted practice in their countries.

There is a reason for this. Internationally there were three trials of tamoxifen for prevention.

The American trial was the only one that showed a benefit. The British trial did not and the Italian trial did not.

The second point that came up for discussion internationally was the second drug, reloxifen. After you suppress the ovaries with Zolodex, is reloxifen the drug that you want to add back. And there was a lot of international discussion about the choice of that second drug to the point that it was decided the international study could not proceed as such but instead each country would do its own pilot and then after the pilots were done they would be considered and a multi-national trial would be designed.

So the Dutch are looking at the combination of Zolodex with another drug called Tibalone, the Germans are looking at a combination of Zolodex with another estrogen receptor modulator. So this is how that sorted out.

A lot of the questioning was between different international countries, which I found interesting and encouraging.

DR. MACKLIN: But, I mean, just to follow up very briefly on your point about the reasons why the Scandinavian countries, for example, did not want to participate, and this was because, as I heard what you

said, conflicting results of different studies. That is if tamoxifen was shown to have some benefit in a U.S. study but other studies were done elsewhere, this is at a level of scientific -- either disagreement or uncertainty.

DR. NAYFIELD: Right.

DR. MACKLIN: That is one does not yet know.

DR. NAYFIELD: I think the issue was the different countries -- you know, we said in this country tamoxifen is a standard of care for very high risk women. It has been established by scientific evidence with our own prevention trial and by the recommendation of a professional knowledgeable body of experts.

And this has not become the standard of care in very many other European countries. It apparently has in Germany but not in the others and the reasons for that are complex.

The science is part of the reason and I think that in some cases the national health system and resources and so forth may be other issues but the point had to do with variations of standards of care in the countries.

DR. MACKLIN: Thank you.

DR. SHAPIRO: One of the interesting things to

speculate regarding your question, Ruth, is whether this conversation that took place would be any different if it was not just rich countries getting together to talk about it and disagree on fine points of science here but whether there are other issues involved. I do not want you to speculate on that now but that would be an interesting exercise to just turn around in our heads.

DR. NAYFIELD: If I could point out that the study was to take place in the context of testing for genetic predispositions for cancer and right now it is only the countries that have resources that can do this.

DR. SHAPIRO: I understand.

DR. NAYFIELD: So in a sense it was -- that issue was limited.

DR. SHAPIRO: Right. Bette?

MS. KRAMER: Thank you very much for your presentation.

One of the possibilities that we had talked about was a central IRB or a central IRB that would consider the international protocols. When you were responding to Arturo's question you made mention of the fact that your IRB was quite different because you had the luxury of both resources and time to go into these

issues in great depth without -- unlike most IRBs. So I wondered if you would like to react to that possibility of a central IRB? And if you thought that that had merit, how would you suggest incorporating or allowing for -- allowing for the possibilities that Alta referred to? Regional considerations that come about from regional diversities and cultural diversities?

DR. NAYFIELD: I think that the division of the IRBs at NCI into the clinical center IRB that deals predominantly with the clinical cancer treatment protocols done on campus and the more epidemiologic and behavioral studies has been a very good one. And I am not sure whether levels of bureaucracy like regional central IRBs are the answer to the situation. I know that there are some universities, and perhaps Dr. Fost can comment on this, that actually do have two IRBs. One for medical treatment studies and one for behavioral studies. I believe Utah, for example, has a medical IRB that has the MPA -- has an MPA number with an XB on it, which means barred from behavioral studies. And that the behavioral study IRB MPA has an XM so they are barred from reviewing medical studies. That is the only situation that I know of in the United States that has taken this model and there are

advantages to it. Certainly my IRB has different expertise than the clinical center IRB.

To some extent, one of the reasons it has the time to ask these questions is that it does not deal with the same intensity of monitoring of adverse events and so forth that the treatment clinical trials with experimental drugs deal with.

So I think that one alternative to consider is the model of splitting the responsibilities of the different institutions.

MS. KRAMER: But keeping it local?

DR. NAYFIELD: But keeping it local for the institution.

I know, for example, with the things that we have to have reviewed by OPRR, the single project assurance, the international cooperative project agreements, even the cooperative project agreements we use for the clinical trials cooperative groups because of the central nature and the nature of OPRR take a very, very long time.

One of the criticisms of the IRB system is that it takes a very, very long time and I think to some extent the international studies would become much more difficult if time constraints were added to the constraints of understanding and negotiating

differences in systems.

Dr. Fost, would you like to comment?

DR. FOST: As I said earlier, I agree completely. I think the worst problem with a central IRB is it greatly increases the likelihood that political considerations rather than ethical reflection will prevail. I think we have seen that several times.

DR. SHAPIRO: I am going to ask a question just before we break. You said, I think, two different dimensions that trust needed to be restored in the IRB system. One was the trust of investigators or belief of investigators in the viability of the system. But the other was the trust -- the public trust, I think, because I see these various controversies have been taken -- played out in the media. It is really the latter that I am interested -- that I want to ask about, namely public trust in the IRBs because I want to put that together with another, I think, very appropriate observation you made. Namely that controversy per se does not say that anything unethical is going on. Indeed, ethical reflection is going to generate controversy with all these various IRBs.

I have been trying to put those two things together in my mind because you think it is difficult

to sustain trust with so much controversy, which is an inevitable result of dealing with these difficult problems. I do not have a solution. I am just wondering how that plays against the need to have trust.

You have suggested one answer, namely outcomes. Is anything bad happening? But do you have any further reflections on that?

DR. FOST: No. I think controversy is healthy. I mean, God knows our country depends on it to have public acceptance, to have open controversy debate. I am not at all fearful of public controversy about any particular trial or protocol.

The part -- what has undermined trust is the false impression that there are thousands upon thousands of studies and hundreds of thousands of research subjects who are not being protected because the tray tables were not in the full upright and locked position.

That is a false mistrust. IRBs only should have trust if they are -- if the trust is warranted and there is no reason to mistrust IRBs because of the sorts of violations that I think have been the cause of the -- so it is controversy over substance, over whether Dr. Nayfield's study should or should not have

been done. I think that is healthy and expected and people will disagree and that is as it should be.

But controversy over things that have, in my view, almost no relationship to protection of subjects is very harmful and destructive and it creates a false sense of mistrust.

DR. SHAPIRO: Any final questions? A short question, Arturo?

DR. BRITO: A short question but I am not sure about the answer.

It is just something --

DR. SHAPIRO: They are responsible for the answer.

(Laughter.)

DR. BRITO: Okay. Dr. Fost, that just prompted something I remembered hearing yesterday. I was at a town meeting down in Orlando and one of the issues brought up is that there seems to be more a focus in the media at least that there is more criticism of academic institution IRBs and yet little criticism of things that go awry in private IRBs or private company IRBs. Do you get that perception or that feeling also? And the fact that OPRR seems to be coming down harder on academic institutions right now, what is your -- just your feeling about that?

DR. FOST: You know, I do not know of any data or any studies on whether commercial IRBs do a -- or private IRBs do a less good or better job than academic ones. There is a wide assumption that because they are commercial that they will not do a good job and that they will have incentives to just sort of -- that is not -- the few that I know something about, that is not true. But I do not know of a systematic study of it nor do I know why OPRR -- the fact that OPRR has not, as far as I know, shut down any private IRBs that -- we cannot conclude from that that they are all doing a great job. So I do not know of any data one way or the other but I have no reason to believe *a priori* that one or the other are better or worse. There are conflicts of interest in academia for sure that might lead IRBs to do a poor job but it is not my view that they are succumbing to that nor do I have any reason to believe that commercial ones are succumbing to that.

DR. SHAPIRO: Thank you.

Alex has an even shorter question.

PROF. CAPRON: Dr. Nayfield, was the China dietary supplement a controlled study?

DR. NAYFIELD: It was a two by two factorial design so that one group got supplement A, one group got supplement B, one group got both, one group got

neither. It is very difficult to do true placebo controls in that situation.

PROF. CAPRON: And all got endoscopies?

DR. NAYFIELD: Yes.

PROF. CAPRON: Thank you.

DR. SHAPIRO: Thank you.

Well, let me thank you both very much for coming today. We really appreciate the time.

Let's take a 15 minute break and reassemble at quarter to.

(Whereupon, at 10:30 a.m., a break was taken.)

DR. SHAPIRO: Thank you very much.

Let's now go to our panel on human rights perspectives. Again we are very grateful to have two wonderful people here to address us. Thank you both very much for coming and spending time with us today. We very much appreciate it.

And there has been increasing amounts of discussion, as many of you know, regarding whether very important movements in the human rights area over the last decades now in one way or another should have a greater level of interaction between the kinds of things -- with the kinds of things that bioethicists have concerned themselves over the same period of time.

And we have had some interesting material that

was distributed to us. I hope you all got a chance to read it but we have been looking forward to hearing from both of you.

Now somehow I noticed that the way you were listed on this program is not alphabetical but we will go by the way you are listed unless there is some reason the two of you prefer to go in some different way. Is it all right to go first of all to you, Ms. Gruskin?

Welcome. It is very wonderful to have you here. Thank you for coming to Madison to be with us today.

PANEL II: HUMAN RIGHTS PERSPECTIVES

SOFIA GRUSKIN, J.D., M.I.A., DIRECTOR, INTERNATIONAL HEALTH AND HUMAN RIGHTS PROGRAM, HARVARD UNIVERSITY SCHOOL OF PUBLIC HEALTH, BOSTON, MASSACHUSETTS

PROF. GRUSKIN: Thank you. It is a pleasure to be here and I want to begin, first of all, by thanking Dr. Macklin, Dr. Page, and the commission for inviting me to be here.

I am actually delighted to have this opportunity to try to bring together a human rights perspective on the ethical issues in international research.

What I thought I would do is start by saying something about how I plan to use the time that has been allotted to me just so it is clear where I am going in my presentation.

I wanted to begin by briefly clarifying why it is that human rights can at this point in time be understood to be relevant to the work that you are currently engaged in and then lay out some of the key points about human rights in the hopes that it would be useful to you before closing with some of the general comments on the proposed chapters and recommendations that were distributed to us.

And the thrust of my presentation will really be on the key points in human rights but I do promise to focus my remarks on the issues which I believe will be most useful to your discussions of international research.

I want to begin though by saying that human rights as we are able to work with them now were really born out of a global consensus building exercise. They were not in the first instance based on scientific evidence or bornE out of research. They were inspirational, which means that while human rights can provide a framework of analysis and a method of work that is useful to thinking about international

research, it does not mean that bringing human rights into the discussion that human rights should be asked to or assumed to solve any and all problems.

And the reason I am saying this up front is that I was at a meeting at WHO last week and the question was put to me if we bring human rights into our processes, can human rights make these decisions for me. And we were talking about resource allocation and about priority setting, not about international research. But the question of the value added of human rights really seemed to have a corollary with what we are doing today so I just wanted to flag that up front.

And just to say the answer was no there and the answer is no here.

And human rights concepts and methodologies on their own are not sufficient to do this but what human rights can do is to provide a framework and instruments that are sympathetic to and supportive of the ethical approach that we are discussing here but human rights may also be useful to organize thinking and action around the design of the methods and tools of international research and the ways that the results of this research can be applied to policy and program decisions. And human rights can do this in the language of the legal and political responsibility and

accountability of states under international law.

Now in the past decade or so there has been increasing rhetorical and political commitment to human rights in the context of health and, therefore, in the context of international health research. This is true at the level of the U.N. system, of NGO's, and of governments. And since we are here in the United States, I thought that what I would like to do is to begin by placing our discussion of human rights in the context of the United States' international legal obligations and to say first that at this stage of the game the United States has ratified and is bound under international law for its obligations under several relevant human rights treaties. The Covenant on Civil and Political Rights, the Convention on the Elimination of All Forms of Racial Discrimination, and the Convention Against Torture.

Now it was President Bush who made sure that the United States would be bound under these treaties as one of the last things that he did before leaving office in 1993. The full text of two of these treaties, those most relevant to our subject matter today, were put in the materials that were distributed to you.

As well as for the sake of completeness and

for full and fair disclosure, the reservations, declarations and understandings that the United States took as well with respect to these treaties are also in your materials.

And we will come back to some of the content of these rights later in the presentation but I wanted to draw your attention to their existence in this context to flag out a procedural point that may be relevant to our later discussion.

Every several years, two years after ratification and every five years thereafter, every country that has ratified a human rights treaty, including the United States, has to present a report on how they are and are not in compliance with their treaty obligations to the treating monitoring body responsible for overseeing governmental compliance with that particular treaty. This includes laws, policies, programs and practice, as well as any obstacles that they are encountering and progressive steps that they are taking.

And at that time what happens is that a dialogue ensues between the treaty body and the government in question and the treaty body ends the dialogue by making concluding comments and observations which are made part of the public record. These

comments and observations are revisited each time that the government is up for reporting and so, for example, even as we are speaking today, this week representatives of the U.S. Government are in Geneva reporting under the Convention Against Torture. So it is relevant even this week.

Now the final piece of background information in the United States and our compliance with international human rights standards that I wanted to draw your attention to is the Executive Order that was passed by President Clinton in December of 1998, which is also included in your materials. But it is particularly relevant to thinking about the U.S.'s engagement in international research and I just wanted to highlight a couple of key passages.

First, that the U.S. has committed to, and I quote, "fully respect and implement its obligations under the international human rights treaties to which it is a party, including in our relationships with all other countries." And U.S. federal agencies and departments, including those with health related responsibilities, have been instructed to "maintain a current awareness of United States international human rights obligations that are relevant to their functions, and to perform these functions so as to

respect and implement these obligations fully.

So it is a rather key step and in the last seven years or so the United States has been paying increasing attention to its international legal obligations in terms of human rights. That is the United States.

What I also wanted to do is just to flag out very quickly something about nongovernmental organizations in the U.N. system, and to say that in the last several years -- something that I think everybody here is well aware of -- that NGOs and a range of activists who are concerned with health issues have found human rights to be an increasingly powerful language for them to use in pointing out injustices, in making claims against governments and the work that they do, and that the parts of the U.N. system that are dealing with health have found human rights to be increasingly useful to the work that they are doing in relationship to giving them structured access to a method of analysis, which provides concepts, as well as methods of obligation, responsibility and accountability for their work.

Well, why I am raising that here is that currently there is a number of actors using the language of human rights in relationship to health and

what is clear is that while human rights is an increasingly common language for doing health related work, for this to actually be useful we have to be clear that we are all using the words in the same ways.

The blessing or the curse of the language of human rights is that it is language that everyone feels that they can own and that everyone feels that they can use, and that happens, I would say, to a much greater extent than say with epidemiology or statistics, which I think has generally added to the confusion about how rights or what rights are actually relevant when we are talking about international health research. Which means from my perspective that I always want to begin by being clear about how people are using the words.

Even if you start with the idea that you are using human rights as they relate to the responsibility and accountability of governments under defined internationally agreed upon international human rights law and not to talk about something you want to claim as a right which has not yet been internationally recognized as such or to talk about the specific actions of individual physicians or researchers or research groups, or in any other way.

The way in which you use the language of human rights and even the documents themselves can still be

very different even if you are talking about the same rights. You might use the same right very differently if you want to use it as rhetoric to claim something, if you want to use it for advocacy than if you want to use it to analyze what a government is doing or is not doing, and you would use it differently again if you want to use as part of a framework to design or implement a policy or a program.

So that being said, the way that I would like to use rights in this presentation is actually more conservative and more narrow than I might personally like to do so but what it does is it allows me to use them in such a way that I am confident that there is international consensus and legal accountability for what I am putting out and hopefully that can give us a solid discussion and solid grounding for being able to talk about the way that that relates to international health research.

So what I would like to do now is to move into some of the several key points about human rights that are relevant to thinking about the work that we are engaged in here and some only need to be mentioned but a few require a little bit of elaboration.

The first thing I would like to set out is that human rights are a set of obligations, of

international legal standards that governments have agreed that they have in order to promote and protect the rights of individuals. This includes what they can do, what they cannot do and what they should do. And they, therefore, set out the obligations of people who are working on behalf of the state or with the support of the state, including those working in health.

One more thing is that at this point in time every country in the world is party to at least one human rights treaty that includes attention to rights that are relevant to health and to health related research so that even if the details themselves are controversial this is something actually very solid to work with no matter what country one is dealing with. It also means that it is possible to use the consensus that exists around the rights framework to find common ground with very diverse partners.

The human rights treaties deal with civil and political rights and/or they deal with economic, social and cultural rights. Some of the treaties are more focused on specific populations like the Convention on the Rights of the Child, and others more on specific issues like the Convention Against Torture but all fall within this basic framework.

As I believe everyone here is aware, the

United States has only ratified human rights treaties to protect civil and political rights, not economic, social and cultural rights. So in the context of international research this means the U.S.'s international legal responsibility for rights like information and privacy but not for others that would also be relevant to this discussion such as the right to health or the right to the benefits of scientific progress and its applications.

Having said that, I want nonetheless to allude to economic, social and cultural rights in this discussion when they are relevant for a couple of reasons.

First, because they are legally binding on many, if not all, of the countries that the United States is dealing with in the context of international research and because the principles that are embodied in these rights may still be useful concepts to incorporate into this work, whether or not it is because there is an international legal obligation to do so.

So what I want to do now is to move into talking some about government obligations under the treaties and here I would like to say that the concepts require a bit more elaboration and I would like to

start by saying that governments are responsible not only for not directly violating rights but also for ensuring the conditions which enable individuals to realize their rights as fully as possible. Under international human rights standards this is considered and obligation to respect, protect and fulfill rights, and governments are legally responsible for complying with this range of obligations for every right in every human rights document that they have ratified.

So let me use the right to privacy in very broad terms to illustrate this respect, protect and fulfill concept and starting with respect.

"Respecting the right" means that a state cannot violate the right directly. So if a government would -- a government, for example, could be found to be in violation of its responsibility to respect the right to privacy when in the context of research it has immediate access to personally sensitive or private medical information about a person and it makes that information available to the media or to that person's neighbors or to that person's employer.

To protect rights means a government is responsible for preventing violations of rights by nonstate actors and offering some sort of redress that people know about and that they can access if some sort

of violation does occur.

So a government could be found to be in violation of its obligation to protect the right to privacy if personal information about research subjects was made available by private researchers for purposes other than that for which consent was given and no form of redress was available that research subjects knew about and that they could access.

As for "fulfill", fulfilling rights means that a state has to take all appropriate measures, including but not limited to putting into place laws and policies, administrative and judicial structures and budgetary resources towards realization of rights. So this means that a state could be found to be in violation of the right to privacy if it failed to incrementally put into place the modes and the mechanisms necessary to insure the privacy rights of people who are research subjects within its borders, which leads to the next point that I would like to make which is the concept of "progressive realization."

Now in all countries resources and other constraints can make it impossible for a government to fulfill all rights immediately and completely. The human rights machinery recognizes this and acknowledges that in practical terms a commitment to the right to

privacy in the context of international research is going to require more than just passing a law or putting a policy into place. It is going to require financial resources, trained personnel, facilities, and more than anything else a sustainable infrastructure. Therefore, realization of rights is generally understood to be a matter of progressive realization, of making steady progress towards a goal.

Now starting with Article Two of the Covenant on Economic, Social and Cultural Rights, this idea is explicitly written into the human rights documents and it is now increasingly being understood to be relevant not only to economic, social and cultural rights but also to civil and political rights. It is part of what a state has to show when it presents its report to a treaty monitoring body, is that it is taking steps to progressively achieve the rights contained in the treaty.

Now this principle of progressive realization is of critical importance obviously for resource poor countries that are responsible for striving towards human rights goals to the maximum extent possible but it is also relevant to wealthier countries in that their human rights obligations include not only respecting, protecting and fulfilling human rights

within their own borders but also progressively through their engagement in international assistance and cooperation.

So it can be understood to be part of what they need to do in terms of development and bilateral assistance and by extrapolation. And here I am going beyond what has been internationally agreed upon. I would say in terms of their responsibilities in terms of international research.

So the next point that I want to just flag out here is that the human rights framework recognizes that it can be considered legitimate to restrict rights for the sake of public health. Interfering with freedom of movement when instituting quarantine or isolation for a serious communicable disease, for example Ebola fever or typhoid or untreated tuberculosis, are examples of restrictions on rights which could be necessary for the public good and could, therefore, be considered legitimate under international human rights law.

On the other hand, something which has been of obvious concern throughout the HIV epidemics are arbitrary measures that are taken by public health authorities which restrict rights and which fail to consider other valid alternatives. Now these obviously would not be considered legitimate.

Can I ask you to put the overhead on?

(Slide.)

The only overhead. I wanted to put this up there and say that even though interference with most rights in many of the situations relevant to health research can be legitimately justified as necessary, this can only be done as a last resort and if those criteria that are listed on the overhead have been met. I am not going to go into the details about what is up there but this approach, which is often called the "Syracuse principles" because they were conceptualized at a meeting in Syracuse, Italy, for no other reason than that, although they are still rudimentary, are helpful for identifying situations that are abusive, whether intentionally such as -- now to use some of the examples that were given in the informed consent section of the draft document we were handed. If, for example, the central government of a country mandates the participation of individuals in research or unintentionally such as when in deference to perceptions about local custom, a husband or a father's consent is considered sufficient to enroll a woman in a trial as a research participant.

Now the last general point I -- and that is it for the overheads so feel free to take it off.

The last general point that I wanted to make about human rights is to draw attention to the range of internationally accepted rights under the human rights treaties that are relevant. When one thinks of the relationship of rights to health research, it is rarely the case that only one right in isolation will be relevant. And just to name a few where there are obvious connections and first to name some of the economic and social rights, the right to enjoy the benefits of scientific progress and its applications, the right to health, to education, to housing, to safe working conditions. And then the more civil and political for which the U.S. has international legal responsibility, information, privacy and association, the right not to be subjected without free consent to medical or scientific experimentation, and the rights to participation, to equality and to nondiscrimination. While all of these are obviously key I particularly want to draw attention to the last three, participation, equality and nondiscrimination because they bring together many of the points that I would like to comment on. First of all, in the excellent draft document that we received but also because it relates some to what was being discussed this morning.

Recognition of the rights to participation,

equality and nondiscrimination leads to questions concerning the processes that go into the determination of the acceptability of particular research projects or the adequacy of review procedures, and to questions about how the panels that make these decisions are constituted. Who is on them? And who is making the decisions that determine what research should be carried out where and in what ways, and in what ways are the decisions themselves being made. Participation, equality and nondiscrimination lead to questions about who represents who, who decides, and who do these decisions impact, and in what ways.

The last thing I would like to say on this is that applying human rights principles to international research decisions will not necessarily change the outcomes but it may well change the processes. Now this analysis raises a related issue and it is worth acknowledging that if the guidelines and the other documents that were given to us as part of the comparative background for the draft document that we are reviewing here that Uganda and Thailand are the only countries represented who are primarily host countries. Even the focus of the India document is primarily on the research that they will be conducting. Well, the Uganda and Thai documents also deal with

research that they will be conducting and the fact that those two documents do not necessarily represent the views of the impacted communities themselves. It is nonetheless my opinion that it is worth giving more weight to the concerns raised in these documents. From my perspective, I understand those concerns to be issues of participation, equality and nondiscrimination in all stages of international research. Issues that are dealt with more in these documents than in any of the other background documents under review.

Let me move no w/in closing to a few general comments that are prompted by the draft document and in that context I would like to try to flag out some of the strengths and weaknesses of applying the human rights framework itself to support the work that you are engaged in.

First of all, human rights puts the onus on looking at the actions of governments. In this case the actions of the United States in both conducting and sponsoring research as well as the actions of the host country government, which leads to a general proposal from my perspective about the chapters that we are considering today. And to say that throughout the document it would be useful to be sure that the specific actors in question are explicitly named and

disentangled each time that they are raised. From a human rights perspective this is relevant because the obligations are different depending on which actors are being considered and what their responsibilities are. This is where the respect, protect and fulfill concept particularly comes into play and it means, for example, paying attention each time to the differences between the U.S.'s responsibility when it conducts research itself, which is more about respect, when it sponsors research, which is more about protect, and the differences that this might mean in what would be required, for example, in ensuring that the choice of study participants is not arbitrary or discriminatory.

Along these same lines more attention should be given each time it is mentioned to distinguishing what is meant by host country. Whether it is the government, the research participants, the community or the population as a whole. I would ask that this be made more explicit each time throughout the document.

And it also means, just to speak from one specific example in chapter 4, for the comparison between WHO, which is an intergovernmental association -- organization, the International AIDS Vaccine Initiative, which is a nonprofit organization, and VAXGEN, which is a private company, to be more useful,

the differences in the responsibilities and obligations of these different types of actors would need to be more explicit.

Now another reason I raised that particular example is that it also points out one of the major weaknesses of the human rights system, which is that by its very nature it is a state centered system with its focus on the action of governments and, therefore, these other types of actors who are increasingly major players in this field are only taken into account in relationship to the responsibility and accountability of governments. Nonetheless, it is still more than what currently exists so I want to put it out there but I do need to say that.

Now using the human rights framework can also help to insure that there is not just the imposition of one set of standards on others but that agreements about research can occur around a common framework, which imposes obligations on all of the governments concerned.

Currently the treaty monitoring bodies do not systematically consider international research when they look to the extent to which governments are respecting, protecting and fulfilling their international human rights obligations but it would be

interesting to think over the next few years about bringing these processes together so that the treaty monitoring bodies could actually be useful in helping to insure the ethical conduct of research.

The utility of the rights framework is that it forces any discussion of a particular research project to go beyond its isolated context and to be considered in terms of a larger obligation of the concerned governments towards the health of populations. This means the discussions about individual research projects at the stage of design, implementation and evaluation would have to take place in the context of the health needs of the chosen population but also in the larger context of infrastructure, safety nets, capacity building and all of the issues that are raised in the proposed document. But within the framework of progressive realization and to put it into rights terms, in relation to the obligations of the relevant governments to respect, protect and fulfill rights, in their considerations of who gets ill and what they do about it.

In closing, I would like to propose that human rights may offer an approach which can help in trying to harmonize the different ethical standards that exist between the U.S., the countries it collaborates with,

and those with whom its only relevant contact is that they host its research. Now in a number of places throughout the document I believe that human rights can help to strengthen what is already there. In other places it may provide an additional organizing tool to help concretize international standards through its focus particularly on the responsibility and accountability of governments.

Thank you for this opportunity.

DR. SHAPIRO: Thank you. Thank you very much for those very helpful remarks. Indeed, if you do have some prepared remarks that you would be prepared to share with us, we would be glad to distribute it to the commission. It would certainly be helpful to us but thank you. Thank you very much.

Unless there are any purely clarifying questions now I really want to go on to the next panelists.

Clarifying question?

PROF. CHARO Yes. Just to clarify if I may.

Ms. Gruskin, you said toward the end of your presentation that in the context of disentangling the actors here that the standards -- if I understood you correctly, the standards or the concerns might be different depending on whether the U.S. Government is

conducting or sponsoring research. If it conducts, the issue is respect, and if it sponsors, the issue is protect. Are you suggesting that there are different substantive standards that apply and, if so, what is -- I did not understand what you meant by respect versus protect in that context.

PROF. GRUSKIN: Very briefly, and we can come back to it in the discussion period, but since respect is about preventing direct violations, whereas protect is about preventing violations of rights by nonstate actors and then offering some sort of redress that people know about and that they can access. So those are different kinds of pieces to be considering when thinking about the U.S.'s engagement.

PROF. CHARO Thank you.

DR. SHAPIRO: Any other clarifying questions?

Thank you very much.

George, thank you very much for being here this morning and thank you also for distributing the paper, which we all received. We look forward to your remarks.

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PROF. ANDREOPOULOS: Thank you very much. Let me begin by expressing my thanks to the commission for its invitation to address this meeting and I understand that my task is, among other things, to comment on the draft chapters in the proposed recommendations from a human rights perspective.

I would like to begin -- I have a very brief timeframe here so I would like to begin with making some very general remarks about human rights. Already Dr. Gruskin alluded to some of the things.

What I would like to add is that we should not forget that one of the reasons that human rights discourse has become so relevant nowadays is because, for better or for worse, is the only discourse that is considered as universal -- constituted as a near universally accepted framework for moral discussion. And how do we know that?

We know that because of the explosion of international human rights instruments since 1945 and the signatures of states on these instruments which indicate that they agree with at least the spirit of the document, if not always with the letter of the document because some of these countries, including the United States, have introduced some reservations. In

particular, in the International Covenant on Civil and Political Rights that at least according to myself go against the object and spirit of the treaty. But at least they are a frame of reference for discussion.

The second thing is that human rights discourse has been accused as an aspirational discourse. I am not going to make any defense about it. In fact, I am delighted that it is an aspirational discourse because it tries to transform situations. We do not talk about human rights when something is pleasant. Human rights is an antistatus quo language. When we come -- when we make reference to human rights, we do it because there is something wrong that we need to change.

Now sometimes this transformative vision, which is in the essence of human rights discourse can go overboard and become irrelevant because nobody adheres to it and in that case, of course, it needs to be criticized. But let us not forget that you cannot really change something unless you are prepared to go beyond the existing parameter.

The third thing that I want to mention in this context is that human rights are in a sense demands for some type of social action that enhances the individual or the group capacity to achieve certain things. So we

are talking about capacity enhancement. Capacity enhancement rights that enable an individual or group to achieve certain fundamental social objectives. It is a mobilizational tool, the human rights discourse.

They are premised on two fundamental principles. The principle -- the inherent dignity of every human being and, of course, a commitment to nondiscrimination.

Now after having set the stage here, let me say that -- and Dr. Gruskin again alluded to that, that since 1945 the human rights discourse has been dominated by the legal paradigm, which kind of poses an antagonistic relation between the individual and the state.

The state is considered as the perpetrator of the human rights violations and the task of the international human rights community is to constrain state behavior by setting standards which are codified in human rights instruments again which state behavior can be monitored and sanctioned.

Having said that, however, and it is a legitimate focus, leaves a whole area, which only recently the human rights constituency has begun to explore and this is the area of nonstate actors and their responsibilities under international human rights

instruments.

Of course, we have some declaration, some resolutions that we refer to but this is kind of a big gap that only recently the human rights community has been seriously paying attention to and, of course, this relates to a couple of the examples that I will draw from the draft chapters that were given to highlight this.

And the first example that I want to bring is the discussion in the draft chapter on informed consent, which of course, as you all know here, is a very fundamental tenet of research ethics and it, of course, would be ethical principle of respect for persons, which obviously leads us to the notion of respect for autonomy.

Now a key notion in respect for autonomy is the notion of self-determination, which is a very basic human right, which is ensconced actually as Article 1 in both the International Covenant on Civil and Political Rights and the International Covenant on Economic, Social and Cultural Rights. Basically self-determination articulates a participatory notion to rights, protection and promotion.

A key ingredient to a participatory notion is the right to education, or as it has been famously put

in the text of the Helsinki Declaration, the Helsinki final act, is the individual's ability to right (sic) and act upon his rights and duties in the field. It is a very important right at the center of enhancing the individual's capacity to transform a situation.

And I would like when there is a discussion in the revised draft on informed consent to have some reference both to the right to self-determination and the relevant international human rights instruments and the right to education as it is ensconced in Article 26 of the Universal Declaration of Human Rights and reiterated in Article 13 of the International Covenant on Economic, Social and Cultural Rights.

Now these things -- these observations on the self-determination capacity enhancement for individual action, the right to education, and my previous comment about the big gap. And one of the weaknesses actually of the human rights discourse on the role of nonstate actors and the need to pay greater attention to them as violators of human rights come into discussion on, for example, findings and recommendations 3a, 3b and 3c of the informed consent document.

For example, when there is a discussion on the need for a woman if it is to participate as a research subject to get her husband’s permission. Then

obviously this is more extended in 3b about the involvement of family members and 3c actually the permission of the community leader or the relevant village council.

Now what is relevant here from a human rights perspective are several things. First that there is no way that we can really address the need to respect the rights of individuals that participate in a research project and respect their self-determination and the ability to decide for themselves if we do not really consider seriously the role of the right to education.

Empowering individuals in these constituencies to know more and be able to act upon their rights.

The instrument is sensitive, of course, to cultural particularities. It adopts what we would call in the human rights discourse a weak universal exposition. That is it reiterates that under no circumstances if you bring a wider constituency in, in the informed consent process that this -- under no conditions can it replace the requirement of individual informed consent, and in that case I would say it is consistent with the spirit of universal -- a weak universalist notion because you want also to incorporate the cultural particularities.

But -- and this is a very important thing to

stress, that when we discuss this issue the critical question here is where does the locus of decisional authority lie. And to remember that it is not only states that are abusers of human rights but also communities.

Communities, whether they are the village elders or the village council, and so on and so forth. Because even in these constituencies and even to a -- even also in the smaller unit like the family we have uneven distribution of power and there is always a subject who is lower -- an individual who is lower in the pecking order of a family.

In this case the woman can always be subjected to abusive conduct by the husband, by the extended family, and even if you want to move to a wider circle, by the village community. So the right to education to empower these people -- without, of course, doing away with a need to bring in the cultural perspective, to consult also the wider constituency. But we should be striving towards the eventual empowerment of individuals to make critical decisions that affect their lives.

And, of course, human rights organizations having focused on most of their active life in confronting the abuses of the states only now are

turning their attention to the need to deal actually with abusive conduct conducted by nonstate actors. If we engage the human rights community and the bioethical community in discourse on the responsibilities of nonstate actors, not only we will benefit from this kind of interaction but I hope also the bioethical community. I think it is a struggle so to speak that we need to fight together.

The second comment that I want to make on a different document, it relates actually to Chapter 4, which refers to obligations to subjects, communities, countries in which research is conducted. Of course, I would like to focus my remarks on the proposal of prior agreements, which I must admit I consider personally one of the most forward looking but also most exciting recommendations that I saw in this -- in the draft documents that you sent me.

Of course, for those of you who may not be familiar, this will refer to the arrangements that are made before research begins that laid out a realistic plan for making the proposed research project available to the host country.

Now what are some of the relevant notions that human rights instruments can bring into a discussion prior agreements and prior agreements basically refer,

as I understand them, to the need to make accessible to wider communities the benefits of research?

Immediately it comes to mind the relevant provisions in Article 27 of the Universal Declaration of Human Rights and Article 15 of the International Covenant on Economic, Social and Cultural Rights of the need to share in the scientific advancement and its benefits. This is the language of the UDHR. Or in Article 15 of the International Covenant on Economic, Social and Cultural Rights to enjoy the benefits of scientific progress in its application.

I would be happy during discussion time if anybody is interested to go a little bit further into the legislative history of these two provisions and why do we have different phrasing in these two instruments.

Now what is fascinating, however, and this is the only comment I will make on legislative history, is that when the Article 27 was discussed there was a concern for a moment some people proposed to strike out the provision for the benefits and there was concern that in that case the document will become too elitist because it will address only the needs of the providers of scientific knowledge and not the consumer of scientific knowledge.

At that time everybody who was participating

in that committee felt strongly with one or two objections that it is very important if we are to be consistent with the spirit of the Universal Declaration of Human Rights to make scientific advancements widely accessible.

Now since the International Covenant on Economic, Social and Cultural Rights has been -- was adopted there have been certain normative guidelines that have tried to refine and help us understand better what are the obligations that states have under the International Covenant of Economic, Social and Cultural Rights.

Dr. Gruskin already alluded to a distinction between the right to respect, to protect and to fulfill, which was an elaboration that was put forward in the Maastricht guidelines but there is a previous document that I would like to bring to your attention.

These are the Limburg principles that were articulated in 1986 and it was -- they were articulated in a meeting which included many representatives from state, international organizations, NGOs, research universities and so on and so forth.

And I would like to discuss a particular -- the interpretation that the Limburg principles gave on

Article 2 of the International Covenant on Economic, Social and Cultural Rights and see how that will affect an interpretation of Article 15 on the reference to sharing the scientific -- you know, the enjoyment of the scientific advancement and its benefits.

Article 2 says that each party to the present covenants are to take steps individually and through international assistance and cooperation, especially economic and technical, to the maximum of its available resources with a view to achieving progressively the full realization of the rights recognized.

Of course, here -- and some people have pointed out -- is too much of an aspirational language. It lets states off the hook because progressively you realize you can do basically whatever you want and interpret it in whichever way you want.

Well, the Limburg principles -- and it is interesting that when they interpreted this provision they used the language "shall" as opposed to "should" indicating that this is the status of international law at the stage that they are doing the interpretation.

They said that the progressive achievement actually should be disentangled from the notion of increasing resources. Not that this is irrelevant but we should also bring it to the question of the most --

the best available use of already existing resources. Immediately putting a government on the spot that they cannot resource scarcity as an excuse not to try to satisfy certain fundamental economic, social and cultural rights.

And, of course, in the context of sharing in the -- I mean, in the context of the enjoyment of the benefits of science, this would mean that resource scarcity is not an excuse for a government not to try to do something to ensure its population the benefits of scientific advancement.

Another -- on another key term, when it refers -- the Article 2 to the maximum of its available resources, the Limburg principle says available resources, not only those that are produced domestically but also those that would get through international assistance.

Bringing into the picture the responsibility of the international community to try to do something about it. Intergovernmental organization, governments, or probably also now with the new developments about the increasing accountability of nonstate actors, nonstate sponsoring agencies will come under this rubric.

Of course, individual and through

international assistance and cooperation, it basically -- the Limburg principle says here that there is some kind of an increasing responsibility of actors, international actors to help countries, especially less developed countries to promote their economic, social and cultural rights.

Now this -- so this in combination with an article -- this interpretation of Article 2 on the base of the reading of the Limburg principles in conjunction with Article 15, I would say that generates certain obligations for state actors, non-state sponsoring agencies, and the indigenous -- the host country government to try to do something along the lines of the spirit of Article 15 of the International Covenant on Economic, Social and Cultural Rights.

And I think that it would be useful to have some kind of a reference in the text in the section on prior agreements to some of these instruments and the normative guidelines, the Limburg principles, and the master principles that Dr. Gruskin mentioned.

I would like to spend my remaining time commenting on some of the criticisms that have been raised against the idea of this type of agreement and bring a parallel that is happening in the human rights field, which I think is very exciting and your

commission should seriously consider it.

I think that the document does a very good job rebutting some of the criticism that may be raised of why prior agreements are not necessary or they may not -- may be counterproductive.

One of them, of course, they are not legally binding and, of course, those of us with a legal background should be reminded that law is not created distantly but in many cases what you do is try to engage your partners or your potential opponents in some kind of a collaborative practice that if it is sustained over a long period of time it can coalesce into a type of practice that exhibits a sense of legal obligation and then you can talk about legally binding instruments. The question is how do you start the discussion?

There is an interesting parallel here with what is happening in the human rights community with the attempts of certain groups, forward looking groups, to pressure corporations, multi-national corporations into agreeing into some types of codes of conduct. In particular, concerning the condition of their plants usually in developing countries, whether they adhere to certain labor standards and so on and so forth.

This criticism also has been criticized by the

human rights community itself. One of the criticisms that is usually raised echoes the criticism that is cited in the document that they are not legally binding, that basically the danger that we may run in to get it -- if we get into this type of agreement is that we will offer our moral imprimatur to types of arrangements that are not going to be legally binding and corporations will feel easy to run away from, to break. And what we are going to be left -- we are left in a situation of the anthropologist going native, going and studying the tribe so to speak, and sounding like the tribe.

Mainly those human rights monitors that will be in these corporations, they will have rendered their imprimatur. The corporation will have broken eventually its commitment under the human rights principles. And the only thing we are going to end up with justifying corporate culture and the lack of accountability because of the lack of the binding nature of this instrument. Well, I think that -- of these agreements.

I think that this is a very mistaken argument for the very simple reason that most of the criticism, it seems to me, is waged not against the ideals in agreement but what the agreement will contain.

The challenge there is not to shut off the option of reaching into an agreement and bringing these divergent constituencies into the picture for a greater accountability on human rights but to insure that there is enough incentive for them to do so but at the same time an effective monitoring mechanism.

Of course, in some cases it may not be successful and we may end up breaking certain agreements or arrangements but this is not an argument against exploring that option in the first place.

So I want to urge that the commission very seriously consider the notion of prior agreements in this context which parallels a similar move that is happening in the human rights community to increase the corporate accountability especially primarily on labor standards but also health standards.

I think that it is a direction that is very promising because it also can bring communities in the context actually of prior agreements in the spirit of Chapter 4, communities of researchers, human rights activists and other organizations and groups that are concerned with human welfare to increase the pressure on nonstate actors and make them realize that they do hold certain responsibilities vis-a-vis the communities in which they do work even if this cannot be put in

legally binding terms.

So if something like that would go forward, we will have in my mind two advantages. As far as government and sponsoring agents that are nonstate actors, we will hopefully give them incentives to rethink seriously their obligations under certain international human rights instruments or certain declarations like the Declaration in 1974, the General Assembly Declaration.

Sorry, 1975, on the Use of Scientific and Technological Progress in the Interest of Peace and the Benefit of Mankind, which among other things, says that "all states shall take measure to extend the benefits of science and technology to all strata of the population and protect them both socially and materially from possible harmful effect of the misuse of scientific and technological developments.

This in conjunction with the recent declaration that was approved by the General Assembly in 1998 on the right and responsibility of individuals, groups and organizations of society to promote and protect universally recognized human rights and fundamental freedoms constitutes an entry point, nothing more than an entry for a meaningful discussion to bring these constituencies on board.

As far as the human rights constituency, I think if initiatives that that were to go forward, we will first of all begin to redress the serious imbalance of not taking as seriously human rights violations committed by nonstate actors and we will make actually the human rights constituency live up to its promise to be a more effective spokesman for its transformative vision.

Thank you very much.

DR. SHAPIRO: Thank you very much and thank you very much for those very interesting and I think very provocative remarks.

Let me now turn to questions from the commission for either of our guests here today.

Larry?

DR. MIIKE: Well, listening to both of you, first Dr. Gruskin and then Dr. Andreopoulos, I am not sure that -- and correct me if I am wrong. I am not sure if I feel comfortable with taking an overt human rights perspective on this study of international research collaboration.

The reason I say that is to me the human rights agenda is necessarily highly politicized. You have moral decisions about what is right and wrong and then you have the legal interpretation of that by

government action and even yourself, Dr. Andreopoulos, you said that it is often a question of culpability.

PROF. ANDREOPOULOS: Pardon me?

DR. MIIKE: Culpability. And I do not see in the research -- international research are a systematic culpability by foreign governments or foreign researchers to the extent that is normally associated with human rights violations. I see it more a question of ignorance, a difference of style, different cultural mores.

For example, your example of the individual versus community decision making. I did not get to the same place. And I think just as you said that in the private side if you lead by action and example, and it is sort of the moral force of the argument makes the private sector have to move forward in that way, and it is hard to reach those kinds of actions by some governmental action. They would not get to the same place.

So I would like both of your reactions about whether a very overt human rights argument in this area is really -- would really meet our ends and whether that is a little bit of an over kill in the area that I am talking about, which is the international research efforts with the United States sponsors.

PROF. GRUSKIN: I will go first.

DR. MIIKE: Sure.

PROF. GRUSKIN: Just to remain in our order. To start with, I mean I think it depends on what you are using human rights for and the first comment I would make is that when I started out my remarks I was clear about the fact that human rights are used by different actors for different purposes. And I think that if you use human rights as advocacy to claim something, in that case I agree with you completely. It is not useful.

It depends. If you are using human rights as a system of analysis and there was a framework for the way that you shape the work that you are doing then it is something else. And in that context I would say I personally -- and I do not know if we agree here -- do not feel the need for you to actually use the words.

I do feel the need for you to think about the concepts and their application.

PROF. ANDREOPOULOS: Let me add to this that you talked in terms of culpability and I think in a sense your answer falls -- the assumption behind your question falls into the trap that a lot of the human rights work has fallen before of trying to think always in terms of legal obligations and violations.

In my remarks especially on the need for these prior agreements, if you notice, I did not speak in terms of legally -- of legal obligations that state or nonstate sponsoring agencies would incur. First of all, that will not be possible as far as the U.S. Government is concerned because the U.S. Government has not ratified the International Covenant on Economic, Social and Cultural Rights. So they will say we do not incur any responsibilities under Article 15. Of course, then we can get into some kind of interesting legal debate. Fair enough.

But what about Article 2 of the International Covenant on Economic, Social and Cultural Rights that you have some responsibility to help? Is this part of customary international law by now or not? And in that case do you incur any responsibilities?

But I do not like to get into a legal argument here. I think what is important to bear in mind is that we are using the language and the concept as an entry point for mobilizational purposes. This is -- at least this is the thrust of my argument here and I think one of the problems why sometimes the human rights movement has not been as effective as it could have been is because it has always been thinking, if I may use the expression, the procrustean bed of legal

accountability and this antagonizes governments, this antagonizes corporations, and makes them feel sometimes like criminals.

I have been in meetings with corporation officials in which we tried to discuss about labor standards, and I had some of my colleagues that basically they were treating them like they were committing ecocide in the societies in which they were doing, you know. Ecological genocide.

Now from both a strategic point of view and given also the weakness of our legal instrument at this point I think that the strength of the human rights language in this case is to sensitize communities. In this case, of course, research communities, the corporate community and so on and so forth, to come together to agree on a code of conduct and responsibility.

In that sense I see the human rights language being a useful catalyst in the process. Not in the sense of putting them in the dark or putting them in the procrustean bed and either chopping their head or their feet if it does not fit.

Okay.

DR. MIIKE: Then we agree.

PROF. ANDREOPOULOS: Okay. All right.

(Laughter.)

DR. SHAPIRO: Alex, then Alta.

PROF. CAPRON: I guess I would like to get both of your responses to the following: It seemed to me that Professor Andreopoulos' presentation in talking about the transformative discourse was in some contrast to Professor Gruskin who was emphasizing more those rights which arise to a level of governmental enforceable.

And you both have looked at our Chapter 4 and you particularly, Professor Andreopoulos, addressed that praising the discussion of prior agreements.

I wondered whether you have thought that most of the discussion of the obligations that are discussed there to the community or to the country in which research is conducted are best seen in the more discursive way, the way of setting aspirations that you described, Professor Andreopoulos, or the way that you described, Professor Gruskin, in terms of protecting and respecting or perhaps fulfilling the human rights obligations.

And if it is the former of the aspirational, would there be value in the commission endorsing something not because we can show that it is ethically or in human rights terms obligatory but that it is a

standard which if people would adhere to it would advance the ethics of what is going on.

PROF. ANDREOPOULOS: You want to go first since this is the order?

PROF. GRUSKIN: This is the order. We will continue it in our order.

PROF. CAPRON: Sure, that is fine.

PROF. GRUSKIN: I need to begin with a comment about that, which is to say that when I began my remarks one of the other things -- the caveats that I made was that I was not speaking as an advocate and that I was doing my best to -- I was using the language of human rights in a more conservative and more constrained way than I might personally want to.

PROF. CAPRON: Yes.

PROF. GRUSKIN: Okay. My feeling -- my personal feeling is that the importance of making human rights usable is that they need to be more practical tools for people to use beyond simply the purpose of advocacy. In that context I would say that I feel that it is more useful from my perspective to think in the context of your Chapter 4 to be thinking concretely about the obligations themselves and what they are about because of who this document is intended for and what its intended purpose is, which is not to say that

I do not think that I should be pounding at your door to make sure that, in fact, the things that I want in there are in there and that there is a perfect understanding about the way that these things need to work together.

But I do feel clearly that if we are to use human rights in a way that they are understood by institutions that are not sympathetic to them to put it in terminology. It is most important to recognize what we concretely have to work with and to use those things because that is the wedge that can make things better.

PROF. ANDREOPOULOS: Well, I have a slightly different angle here. By the way, are you trying to drive a wedge in the human rights constituency here?

(Laughter.)

PROF. ANDREOPOULOS: Anyhow, so there is nothing wrong with that by the way. We would tend to be very vocal in our arguments. Basically I think it is not an either/or situation here because what we are confronted with -- we are confronted with different actors. On the one hand, in these agreements we are going to have state actors. They do incur certain responsibilities under international human rights instruments.

Now again we can engage into a long and

tortuous argument. Well, what exactly does it mean to enjoy the benefits of science using my available resources if you try to engage into some kind of an interpretive discussion of the meaning of Article 2 in combination of Article 15, and we can discuss that forever.

But we also have in the picture nonstate actors. Okay. We do have pharmaceutical corporations that sponsor research. This is a different set of issues. So the reason -- one of the reasons that I on purpose avoid using too much of the language of obligation is because in the context of the agreements you have to find the common denominator to build a credible discourse and in this context I see much more the moral, the aspirational aspect of the human rights discourse coming into the picture but, of course, when we address separate sets of actors in this agreement if we -- we have to remind states that they incur a certain different level of responsibility under already existing international human rights instruments than nonstate sponsoring agencies.

DR. SHAPIRO: Thank you.

Alta?

PROF. CHARO Perhaps because I am here at the University of Wisconsin, which with several other

universities has been ground zero on sweatshop labor issues --

PROF. ANDREOPOULOS: We do very well in New York by the way on that, too. Yes.

PROF. CHARO I find myself listening with great interest to the moments at which there are references to the human rights debates around labor practices when the United States Government or U.S. companies, in fact, operate abroad. There are some obvious similarities in the arguments.

We find in both areas international research and labor arguments about whether or not the imposition of standards that are equivalent to U.S. standards would, in effect, protect people to death by removing opportunities that are locally advantageous against background conditions that are frankly appalling.

We also find discussions about ongoing obligations in the labor area, obligations to facilitate unionization, for example, to create long-term solutions and here are obligations to provide access to the results of research in some fashion or another.

Because I like to think that there is a zeitgeist that directs the approach to problems, it makes me wonder if you might have some observations

about other areas of similarity and difference between these two discussions that might help us to choose a basic direction to take in the kinds of recommendations that we are making.

I am not saying that they have to be consistent with what is going on in labor but it helps me when I am undecided to then look at other areas and my reactions in those areas to see if I am at least being roughly consistent in what I am trying to accomplish with regard to U.S. actions abroad.

PROF. ANDREOPOULOS: Actually I think there are some similarities but also some differences and I was talking yesterday with Dr. Macklin whether there will be an opportunity for those of us who have participated in this meeting to subsequently -- if, of course, there is an interest on the part of the commission to elaborate on some of these issues in writing and provide the more elaborate actually written comments and I would be delighted, in fact, if I am given the green light to do that. This is actually one of the areas that I would like to elaborate further.

PROF. CHARO I cannot imagine she did anything but jump up and down with joy.

(Laughter.)

DR. SHAPIRO: We would welcome any further

comments or observations that either of you have. Indeed, it would be a dividend for us. So if -- we do not want to impose unnecessarily on your time but that would be most welcome.

PROF. GRUSKIN: I just have one brief comment on that, which is it is interesting. The ILO is about to do something which is considered incredibly radical in the context of international organizations, which is about to make a pronouncement that it is going to withdraw all relationships with Myanmar (?).

DR. SHAPIRO: With?

PROF. GRUSKIN: With Myanmar.

(Simultaneous discussion.)

PROF. GRUSKIN: With Burma. And it will now -- for the first time, as a U.N. organization basically say that because of the labor conditions specifically that are happening within that country it will no longer function there. One of the questions that it raises particularly -- I mean, in the context of where it came up for me was in the context of the work that WHO does.

Does it mean in that context -- does it mean that we then decide particularly in doing health work that we do not deal with countries that are extreme human rights violators. And I am careful in terms of

health because I think that the issues are different and we need to think seriously in terms of the impact on the health of the population and the differences that I see in the context of the work of ILO versus the WHO, in this context in the case of looking at labor issues and looking at health issues more broadly is something that we really need to disentangle much more clearly, I think, than I feel that I can just make a pronouncement, which I feel I also want to be very careful as opposed to making a general pronouncement about these are how these two things relate.

I think we would have to look very specifically in very concrete places to have that discussion.

DR. SHAPIRO: Just to take that case that you talked about which I had not known about at all, the ILO case you just brought up, and thinking back about one of the principles apparently that is involved here, namely progressive implementation towards an aspiration.

Do you know at all if the ILO in whatever way it was thinking about thought about that particular issue or not? I am just interested in the case.

PROF. GRUSKIN: Yes. But I am not speaking officially here at all.

DR. SHAPIRO: I understand.

PROF. GRUSKIN: But, yes, in fact, the objection on the part of the ILO representative who was speaking was the fact that they had been trying formal and informal negotiations with the government over such a long period of time that it was clear that there was a complete stonewall and then at that point what they needed to think about was something as close to sanctions as one could imagine.

DR. SHAPIRO: Let me ask a question about the issue of progressive implementation, which I think from what I understand from what you have said today and what we have read is an important aspect of this.

Is there discussion in the human rights community regarding whether the path to implementation is understood or agreed upon, that is do we know or do people think they know --

PROF. GRUSKIN: It is progressive.

DR. SHAPIRO: -- how to get from one place to another and I do not want to overuse this sweat shop issue so I guess I will not. I just will not take an example from there.

But that strikes me as an interesting issue and I am just interested to know if there is literature and people who have thought about this which we could

access and look at.

PROF. GRUSKIN: Sure, briefly. In terms of the movement, again it comes back to something that you all were talking about this morning, which is the situation being so locally specific, which is that a key issue to constantly remember.

However, there are international standards and there are things that can be looked at in terms of what is progressive realization and what is being done, and many of the things are the things that Dr. Andreopoulos just was referring to in terms of the kinds of issues that one looks to, to see if things are moving forward, and again there are monitoring mechanisms that focus very closely on that and that our thinking now in terms of structures.

And just one last piece on that, which is the fact that again the criteria are different depending on which rights we are talking about. And again it gets into the fact that when we are talking about international research we are talking about a ranges of rights.

So again I feel like I want to -- I am hedging because I would like to be able to give something more concrete as the example.

PROF. ANDREOPOULOS: Well, very quickly, two

points on the issue of the progressive realization. Interestingly enough, only now we begin to think in terms of when actually the rights under International Covenant on Economic, Social and Cultural Rights are being violated but we are not exactly -- how we go there, how we get there, and what do I mean by that.

Recently there have been some attempts to say, well, how, for example, would you violate your right to education. You look at countries that are similar in most socioeconomic indicators and you check, for example, their illiteracy rate. If in one country the literacy rate is 50 percent while the other country with similar socioeconomic indicators is 20 percent, then the country that has a 50 percent illiteracy rate is clearly violating, you know, the standards, especially its commitment under the right to education.

The question, however, which you ask, which is more difficult, is how do we get from reducing the 50 percent illiteracy rate, for example, to a 20 percent illiteracy rate. That -- obviously there are -- there is no consensus in the international human rights except, of course, some broad references to the need for -- in the case of illiteracy broadly based educational strategies and so on and so forth.

But there is not actually a blueprint if that

is what was the tenor of your, you know, question, no.

DR. SHAPIRO: Thank you.

Trish and then Ruth.

PROF. BACKLAR: I want to thank you both. It was an extremely important contribution to our discussion.

I have a question for you, Professor Andreopoulos, and that is you made mention about practice over time that appears to be legally binding and I wonder if you could give us some examples of that that might be useful in terms of what we are trying to prepare here.

PROF. ANDREOPOULOS: Yes. Let me tell you just one example and this has to do basically with torture and, of course, the whole international community engages into -- with all this big soul searching of the aftermath of the Second World War -- actually as you all know, in a sense both medical ethics and human rights share some kind of a common province and this was the Nuremberg experience, Second World War and so on and so forth. And, of course, the realization that torture was something that it is appalling and needed to be condemned but we -- it took us a lot of time to come up with a convention against torture and for many, many governments to sign and

ratify it.

But in the meantime while this process was going on, you would see less and less governments being willing to -- not to say that they were not engaging in torture but to publicly admit that they were doing it, and this is the ultimate test.

Because it was so universally condemned despite the fact that -- of course, we did have some reference against torture and cruel and unusual punishment in other human rights instruments but we did not have a convention against torture until much later.

But a momentum was building through discussion through the Second World War experience, through embarrassment of governments, that we came to the realization -- and I would argue -- some people may disagree with me -- even before the Torture Convention came into effect that torture was something that governments may engage in and they still engage in. You only have to look at the annual reports on human rights practices by the State Department or by other human rights organizations but no government will publicly admit doing it.

This is the type actually of consensus that builds around that then makes in some case a legal

instrument that comes later. Basically a ratification of an already existing mentality.

PROF. GRUSKIN: May I respond more briefly as well?

DR. SHAPIRO: Yes.

PROF. BACKLAR: Oh, yes, please.

PROF. GRUSKIN: Because I have a more modest example but I felt like I -- since we are doing the back and forth, it is --

PROF. BACKLAR: Yes.

PROF. GRUSKIN: -- which is that in the context of HIV/AIDS and to say that in the international human rights documents as they are drafted, there is no specific mention of HIV whatsoever. And we have been engaged over the last decade in the work that I do normally in terms of changing that.

And so what has happened is there is a -- it is a process in terms of trying to move things forward where you end up with, first of all, a U.N. system recognizing the relationship between HIV and human rights in a variety of different ways, both in terms of people's vulnerability to becoming infected as well as what happens once people are infected.

Then you move a process where you get

governments to start working with the process of human rights as it relates to their obligations in terms of HIV and then you begin to work -- and this is the process we are engaged in now -- with the treaty monitoring bodies, which is why I was talking about why it is that we might think about moving the treaty bodies to be useful to your process. Because we are engaged now with a process with them where what they are now demanding over the next two to three years will be demanding legal accountability for governments under the human rights treaties for their obligations in relationship to HIV.

So what it does is it moves HIV and the discussion about HIV happening strictly as a health issue into one that is also a human rights issue and moves the sense of legal obligation forward and, hopefully, therefore, can do something better for people that are affected.

PROF. BACKLAR: May I have a follow-up?

DR. SHAPIRO: Yes.

PROF. BACKLAR: One of the reasons I asked you this question is because I am concerned as I look through our chapter on prior agreements that they have no teeth. And that is, of course, I am interested in any ideas that you can give us that would bring about

some way that we would get some bite to this.

Perhaps you could follow up with some more specific suggestions in light of that. Is that -- am I asking too much? Maybe not right now.

PROF. ANDREOPOULOS: Yes. I would just say I hope -- you know, if I am asked I will be happy to submit some further remarks but may I say something again -- and I may -- you know, without appearing I am shooting myself in the foot because as you can see from my card here, J.D., I also have a law degree so I should not be speaking very negatively about the legal paradigm.

But having said that, I think that if I may say so at this stage I do not think it is useful to think in terms of instruments with a bite, with a legal bite. We should be thinking in terms of instruments that create incentives. Incentive created instruments to get all the actors concerned to agree on a mutually beneficial type of behavior.

Of course, you have to do give and take, give and take. Fair enough. We may have to compromise some of our principles to get there but we do that all the time when somebody is engaged in advocacy work.

I think it will be -- I think it will not be very useful, if I may say, at this stage to think in

terms of legally binding. That is if the commission feels that the reason that they should reject the proposal of prior agreement is because they may not have legal teeth, I think this will be a very wrong approach to adopt because what we need -- we need to get a momentum going on certain agreements and if the momentum builds up.

Then eventually we may say, well, listen, we look around, and this started from one type of agreement. Then two, three, four, five. Now we have twenty, thirty. Well, should we be thinking in terms of some kind of an international instrument putting it all together and giving it the legal bite that you are talking about? I think this is the strategy that we should be pursuing.

DR. SHAPIRO: Thank you.

Ruth, you will be the last question.

DR. MACKLIN: Well, it is appropriate because I guess it goes back to the practicality of our report.

When we invited the human rights experts I do not think we were under the illusion that you were going to solve and resolve the problem. What we did hope for is exactly what you gave us, some good argument, some links with the instruments, and some

strategies.

Now I guess what worries me most and so I would like to hear from both of you but I am going to start with Sofia because she was the one who raised this concern -- How did you put it so felicitously? There are actors who are not sympathetic to human rights language and concepts. Okay.

We do not want the document that we prepare to be rejected out of hand or to be dismissed simply on the grounds that, huh, look it, they are talking about these human rights instruments and we know what we think of those. I mean, partly but not entirely for the reasons Larry mentioned about the politicization but for those who are not entirely sympathetic.

You did say, though, Sofia, that you thought we could use -- not use the language specifically of human rights but use the concepts that are in them.

Well, in a sense that is what brings bioethics and human rights together. That is the concepts that are really common to both but human rights language does have the additional benefit or bonus of having these international instruments and knowing that a lot of the world has signed on to them even if our own government in its recalcitrant way has declined to sign on to those that are the most critical here.

So what then do you see as the best approach for this document? I mean, we would like to be able to use the human rights, which is precisely why we invited you to incorporate that into this, into a way of thinking about this so it will not seem like, you know, a bunch of bioethicists sitting around and contemplating our philosophical navels.

But at the same time given the difficulty of the language and the resistance and those who are not entirely sympathetic, how best should we proceed?

PROF. GRUSKIN: Can I ask a question first? When you talked about those not sympathetic, are you speaking within the U.S. or outside?

DR. MACKLIN: You used the expression not sympathetic.

PROF. GRUSKIN: No. But when you said -- but in that context, in terms of your question.

DR. MACKLIN: In the U.S. I mean, this is a report.

PROF. GRUSKIN: Okay.

DR. MACKLIN: This is the National Bioethics Advisory Commission. It gets submitted to the President of the United States. Clearly among the most interested actors -- and I want to thank you for saying again that, you know, we should name all these actors

and be more explicit. I mean, if there is anything I detest, it is the use of the passive voice because it never mentions an actor.

So this gets, you know, submitted to the Executive Branch and, of course, those who are looking very carefully and very closely at it are people from the NIH, the CDC, the main national agencies and organizations that sponsor and conduct research.

So against that framework.

PROF. GRUSKIN: Okay. If I may --

PROF. ANDREOPOULOS: Sure.

PROF. GRUSKIN: -- just in that -- one of the reasons I began my presentation by talking about Clinton's Executive Order specifically and the actual legal commitments that the U.S. Government made under President Bush was very much in order to put out quite clearly the fact that there are structured reasons why it is that reference is all right in that sense in the context of the U.S. And the fact that it gets away from the question of partisan. And partisan gets away from a whole lot of different things. It allows something concrete.

That being said, which is why the problem with that, of course, is that what it does is it focuses on -- focuses the discussion on the rights that are in the

treaties that the U.S. has ratified. So what it does is it limits the discussion, which is why I say the concepts, not only the documents.

And I -- so where I say the concepts is, for example, the questions of -- I do think that the respect to protect concept is useful in terms of thinking about obligations.

I do think that progressive realization is useful in terms of thinking about concepts. Thinking about the question about chapter 4, I think those pieces -- disentangling the different actors and looking at the various relationships is useful, whether or not you say this is human rights or not.

I will stop there. Go ahead.

PROF. ANDREOPOULOS: Okay. The only thing I would like to add to what Sofia said is that -- and it goes back to a discussion we had with some human rights colleagues from different parts of the world on the notion of building some kind of a cross cultural communication on human rights issues, and sometimes I feel that the debate on building a cross cultural communication should not be focused only when we talk with people outside this country but also when we talk with people inside the country.

And we all came to the conclusion -- I do not

know whether you would agree with this or not -- that human rights may not be something that is universally -- okay, the documents there are -- but it may not be universally accepted in the sense of it raises immediately some red flags and some antagonistic attitudes. But almost every culture, every constituency has a notion on human dignity.

And one of the things -- if you want to bring something in more aspirational language -- and I am saying this is in addition to the comment that Sofia made, is that to play more around the notion of human dignity as opposed to human rights. Because this -- the -- I mean, the term "human rights" immediately poses some kind of an antagonistic relation while human dignity can -- it draws more easily consensual approaches in order to promote human welfare.

And I believe that if you look at least in some of the other cultures that I have looked at -- and this is, of course, an old debate in the human rights constituency, which every culture has a notion of human rights, and there are big debates. But I think there is almost near universal consensus that every culture, every constituency has a notion on human dignity.

And I would say that you should use that concept.

Of course, there are other things I could say but just as an initial short reaction to your question.

DR. SHAPIRO: Well, thank you very much. I really very much appreciate your presence here today and the contributions you have made.

I would encourage you, my colleagues have already encouraged you, if we can get any more of your time to -- it would be terrific. We will really learn a lot and we will take it very seriously. So if you have got time and other things you would like to share with us that would be very much to our advantage and I hope you will find some time to do so.

We will have to take our break now for lunch. We were due to start back at 1:00 o'clock. I do not think that is going to be realistic but let's try to make 1:15 simply because that is -- I do not know if we will have anyone for public comment but that is the time we have advertised and I do not want to be too late for that.

So let's adjourn now and reassemble at 1:15.

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

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

DR. SHAPIRO: Thank you. I would like to call this afternoon's meeting to order.

We have two people who have signed up for public comments and I have already spoken to both but I want to also publicly apologize for the fact that we have kept you waiting beyond the 1:00 o'clock time that we had designated for this. So please accept our apologies for any inconvenience that this may have caused either of you.

We have two people signed up. There may be others who wish to speak to the Commission but let me call first on those who have signed up in advance.

The first is Mr. Steve Barney.

Mr. Barney?

It is probably most convenient if you just come up and sit at the table here and use a microphone. Any one of those chairs, I think, would be fine.

PUBLIC COMMENT

MR. BARNEY: I would prefer to go second. I am kind of just --

DR. SHAPIRO: All right. Mr. Rinehart, do you mind going first?

This is Mr. Terry Rinehart from Indianapolis.

Thank you very much for being here today.

MR. RINEHART: My presentation this afternoon is entitled "Technology Developments and the need to review research projects with the potential of abuse in human subjects research."

Mr. Chairman, Commission members, I appreciate the opportunity to once again provide public comment on strengthening Federal laws and regulations on human subjects research.

At the December 2nd, 1999, meeting of this Commission, I presented information on research that the Department of Defense is conducting with microwaves and the existence of non-consensual research. My purpose today is two-fold:

One: To reiterate that non-consensual research projects continue to exist in various forms at various locations throughout the Department of Defense and other agencies.

And also to inform the Commission that at least two federal agencies, specifically the Department of Defense and Department of Justice, have technologies available which makes it difficult to obtain a resolution to non-consensual research situations.

The Department of Defense is a large agency and a non-consensual research project could occur at military installations in various locations. Even as

close as Maryland, or Ohio, or Texas, and the Pentagon may not even be aware of these project exist. The DoD then would state publicly or even possibly to this Commission that non-consensual research is not conducted by the agency. It may be believable but not necessarily true. Unless victims are willing or have the opportunity or able to speak out that non-consensual research does occur, and then that the DoD is questioned as to what is actually occurring and why, I believe that non-consensual research would continue.

The Advisory Committee on Human Radiation Experiments limited the definition of radiation to ionizing forms. However, there are also non-ionizing forms of radiation which are known to cause cancer and can be just as deadly as ionizing radiation, depending upon how the non-ionizing radiation is applied. Exposure criteria for non-ionizing forms of radiation exist to protect individuals from the known effects of non-ionizing radiation on the human body.

The Advisory Committee made a number of recommendations to strengthen human subjects protection as a result of the gross misconduct discovered in their investigation. The efforts of the Advisory Committee and this Commission to review and strengthen human subjects protection regulations is appreciated and

necessary to prevent situations which occurred in the past from being repeated.

The challenge faced by the bioethics community is to maintain and increase the knowledge of research areas where potential human subject abuse may occur. The DoD has been involved in the development of non-lethal weapons for a number of years. As the world has become reliant upon electronic technology, the military has developed technologies to monitor and disrupt electrical and communication systems.

Medical research in the 1990's has focused on increasing our understanding of the brain and the central nervous system, which is the human electrical system.

From information obtained throughout the world, technologies that employ non-ionizing radiation have been developed to disrupt and interfere with the normal functioning of the central nervous system. Some of this technology does not require contact with the human subject and most of the general public is not aware of nor do they have access to the necessary shielding if they were exposed to this type of radiation. This technology has also been transferred to the law enforcement community through a Memorandum of Understanding between DoD and DoJ.

Technology used to monitor and interrupt electronics can also be used to interfere with an individual's effort to resolve a situation involving an agency, which may be non-consensually or illegally using technology. It certainly violates the intent of the laws to protect human subjects involved in research.

The Department of Defense has also stated microwave technology can be used to confuse or disorient a subject, which would be applicable to psychological methods of deception to obtain superiority. This, too, violates the intent of human subjects protection laws and creates a situation where the research involves more than minimal risk. These technologies also will protect the agency rather than the individual who may be involved in the research.

My purpose today has been to inform this Commission of the technologies which have or are being developed and that technologies exist which protect the agency rather than the individual involved in the research effort. I again encourage the National Bioethics Advisory Commission to ensure that all Federal agencies comply with laws and regulations related to human subjects research and strengthen protection for human subjects.

I also recognize that this is a specific area and this Commission tends to deal with broader general issues but I do appreciate the opportunity to address the Commission.

Thank you.

DR. SHAPIRO: Thank you very much. Let me see before you leave if there is any questions or clarification any member of the commission would like on this issue.

Thank you very much for being here once again and for taking the time to come and be with us this afternoon.

Thank you.

Mr. Barney?

MR. BARNEY: Dear members of the National Bioethics Advisory Commission:

I am going to introduce a new term into the deliberations of the Commission. A term which has not, as far as I have been able to determine, been raised until this moment. As you reflect on the ethical issues of human research, please keep in mind the fact that your decisions will impact potential subjects of nonhuman animal research. The new term is "animal rights."

It is wrong to view human and nonhuman animal

research, human rights and animal rights, as if they are two unrelated subjects.

The result of placing restrictions on human research sometimes results in a shift of the burden of the research from human subjects to nonhuman subjects of research. This sometimes means that fully sentient and cognizant nonhuman animals, from rats to chimpanzees, are forced to suffer in experiments which could, potentially, be done with permanently nonsentient and unconscious members of the human species.

Examples of permanently nonsentient and unconscious human beings, humans who are alive only in a biological sense, not in what is sometimes called a biographical sense by philosophers such as Princeton University's bioethicist Peter Singer, include anencephalic infants and permanently and irreversibly comatose patients who are warehoused in Madison, and all over the country.

Along with philosophers like Peter Singer, I believe experiments on such human subjects is morally acceptable. Experiments on nonsentient humans could take some of the burden off of nonhuman subjects. Who knows how many rats, dogs, pigs, monkeys, chimpanzees, et cetera, could be spared by such a practice.

I, along with Peter Singer and many other people in this day and age, object to unjustifiable prejudice and discrimination against animals and it is time to extend the same equal consideration to nonhuman interests, as we extend to the interest of human beings.

Again, it is illusory to view human research as if it is totally unrelated to animal research. The placement of restrictions on human research often shifts the burden from human to nonhuman subjects of research. A current example of this is the shifting of the burden from human embryos, another example of nonsentient members of the human species, to pigs and baboons. I am talking about human embryonic stem cell research and xenotransplantation, that is animal -- nonhuman animal to human organ transplantation. Even though there seems to be scientific consensus that embryonic stem cell research promises a solution to the organ shortage, for example, which is medically superior to xenotransplantation, the burden is shifting onto the relatively unprotected laboratory animals of this world.

Thank you.

DR. SHAPIRO: Thank you very much.

Are there any questions from members of the

commission?

Yes, Alta?

PROF. CHARO Mr. Barney, since you focused so much on sentients as the key characteristic of interest, can you identify for us any animal species that you feel lack sufficient sentients to make them appropriate for use in medical research?

MR. BARNEY: Well, I think everybody accepts -- you know, there is scientific consensus that all farm animals, for example, are sentient. But there is a gray area, you know, in which there is controversy. I do not know about mollusks and, you know, lobsters. I am not certain about lobsters and such. But that same controversy -- well, I guess that is -- I cannot give, you know, a really perfect answer to that. All I can say is that I do acknowledge that there is a gray area where it is not certain.

PROF. CHARO Thank you.

DR. SHAPIRO: Thank you. Any other questions?

Thank you very much for taking time to be here today. We very much appreciate your comments.

All right. We now return to our regular agenda and we are going to -- I am going to turn to Ruth in a moment. I believe we are going to begin by looking at some of the material that will eventually be

part of chapter 5, "Enhancing international --" but it is from our overall international project.

And then after spending some time in that we will go to the material that is really part of chapter 4.

Ruth?

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

DISCUSSION WITH COMMISSIONERS

DR. MACKLIN: Let's first collect the materials we will need to correct. We are actually in one moment going to turn to Stu Kim who is going to begin with a presentation but let's alert the Commissioners to all the documents that are relevant to this presentation.

There will be excerpts. Stu will be presenting some excerpts and brief discussion from the larger chart so you do not need to attend to the larger chart right now.

There are handouts on the table that are the handouts of the overheads that we are going to see in a moment and what Stu -- he will describe for himself what he will be doing but the idea here is that so we do not have to walk through the entire chart to pick out some of the key differences that exist in the various international and national documents so we can

then address the question what do we want to recommend when these kinds of differences exist.

So this is actually the introduction to our discussion, a broader discussion, of enhancing international collaborative research. Following which, after we hear from Stu and have any questions that he will be able to answer, we will then turn to the broader question of what the options are or should be when there are gaps, differences or inconsistencies in the U.S. Federal Regulations, the international documents, guidelines and other regulations, and national documents.

So we can hear first from Stu then.

MR. KIM: Good afternoon.

As Dr. Macklin said, the focus of this afternoon's discussion is on enhancing international collaborative research. In your briefing books at tab 2d, Commissioners have been provided with a list of questions that address differences between the United States regulations and documents from other countries and international organizations addressing human subjects protection.

To assist Commissioners in developing their recommendations we have provided two handouts that were distributed this morning. The first is what is now

known as Stu Kim's chart. This very long, thick document.

The comparative analysis includes 20 documents which were chosen for three reasons. First, these documents are not equivalent in terms of focus. Some are legal documents. Others are ethical guidelines. And many of them were created for a variety of purposes but we felt they represented a breadth of perspectives, both nationally and internationally.

Secondly, many of these documents included in the analysis are already being cited in research ethics.

Thirdly, we attempted to recognize the work of both developed and developing countries across several continents to include a wide range.

At this time I want to acknowledge the assistance of outside colleagues who were gracious in providing English translations to some of these documents as well as the legal specialists at the Library of Congress who have been very diligent in my requests for obtaining some of these documents.

The chart itself is organized into six parts, which some would parallel the chapters in the report. The first four pages of the chart provide an introduction and a further explanation of the column

headings that you will see. The column headings reflect the diversity of provisions contained within the documents.

Of course, due to the comprehensiveness of the analysis, the second handout summarizes differences in these provisions contained within the 20 documents. I have chosen to use the questions that were included in your briefing book as guidance but I have modified the order of them to further our discussion.

It is this document right here. The title of document is "Enhancing International Collaborative Research." And there is a small chart on the first page.

DR. SHAPIRO: Does everyone have this? Thank you.

MR. KIM: The first question that was posed is what are the substantive ethical principles or standards articulated in the United States regulations that are absent from other documents. And after going over the chart several times there really were not any principles that were lacking in the United States regulations -- that were in the United States regulations that were absent from the other documents. And I think part of the reason was the United States regulations are among the oldest and many other

countries have followed the United States model in terms of adopting language or approaches to some of these principles.

DR. SHAPIRO: I am sorry to interrupt you. The question on the sheet says what procedural requirements.

MR. KIM: That is the second question.

DR. SHAPIRO: Sorry.

MR. KIM: This actually -- the second question is actually a subquestion in your original briefing book material but we decided to include it with number one and that is what procedural requirements articulated in the United States regulations are absent from the other documents.

The one example I included was the question of continuing IRB review, which will be on the first overhead.

(Slide.)

And with the exception of the documents that are listed in this small table, all the other documents do not have language explicitly addressing continuing IRB review and the ones here are the Food and Drug Administration, the Common Rule, and the USAID, UNAIDS and Canada. And I have just highlighted the language that I wanted you to pay attention to.

And in conversations with Dr. Macklin and Alice Page, the idea of contniuing IRB is a procedural requirement as opposed to a substantive ethical principle but we felt that it moved it up to the level of greater importance, which is why it is included here.

(Slide.)

The third question is what substantive ethical principles or standards articulated in other documents are absent from the United States Federal Regulations. And we came up with some other examples.

The first is the point of written informed consent not always being required. I did make a note in your handout and I also want to clarify that a waiver is granted for research if it is requested and the research itself is involved -- is considered minimal risk. A waiver usually is not granted if research itself is considered minimal risk. There has to be a request and discussion with the IRB.

These documents that I have highlighted for you here have language that permit alternatives to the notion of written informed consent and the one I want to point your attention to is Canada, which actually includes language culturally unacceptable or where there are good reasons for not recording consent in

writing, which we found interesting.

The next example is actually -- is providing adequate access to health care.

(Slide.)

And the four examples that are in the next overhead actually divide out into two groups. The ICH and the Ugandan guidelines talk about adequate access to health care during and after the clinical trial. The Council of Europe and the CIOMS-WHO guidelines refer to health care after the trial is completed, and language is highlighted there for you to consider.

PROF. CAPRON: Stu, can I just ask a question very briefly?

MR. KIM: Sure.

PROF. CAPRON: Would it be possible to list the first thing under three as actually something -- a procedural requirement in the United States which is absent in other countries? I mean, it seems odd to describe -- if what you are focusing on is written informed consent, that seems a procedural thing, and it seems odd to say that it is present in other documents and not in the U.S. when it is -- what is described here as the absence of a requirement. You see the way you have put it just seems to me --

MR. KIM: I understand your point.

PROF. CAPRON: -- to flip things over.

MR. KIM: The IRB has the authority to waive any or all of the requirements for informed consent but there is nothing explicit that says we will accept something other than a written informed consent for this particular category. So I understand your point. It is well taken.

The other point is there also had to be some choices made in terms of the presentation of this and I excluded the U.S. language here for some purposes of simplicity as well.

But your point is taken. It is a procedural requirement but it does also, I think, rise to a certain level of principle similar to the continuing IRB review.

PROF. CAPRON: Well, but you have continuing IRB review under the procedural side. That is exactly my point. Don't you?

MR. KIM: For number two, yes, but I think it sort of falls in between the --

PROF. CAPRON: Well, I am not going to -- there is no reason -- I made the point. I just ask you to reconsider and think of putting that particular written thing under number two.

MR. KIM: Oh. Under number two. Okay.

PROF. CAPRON: What I am saying is it seems to me (a) it is procedural and (b) the presumption sort of goes the other way.

DR. MACKLIN: Could I just interject? We will fix it. Okay. I mean, I think we have got a lot of important things here and I am not saying it is not important to get it right but we will fix it.

DR. MIIKE: Can I just make a comment on this? I guess from my standpoint the question is which is more rigorous? The always required informed consent in writing or to give leeway. I think that is part of what Alex is asking, you know, because we are looking at what is absent and the implication of what is absent is that there might be a weakness.

PROF. CAPRON: It just has to be addressed. That is all. I am not putting a moral weight on it.

DR. SHAPIRO: Keep going, Stu.

MR. KIM: All right. Then the fourth question which we added are what -- this is categories in your handout.

(Slide.)

What other ethical issues articulated in other documents are absent from the United State Federal Regulations and again there will be one example I can think of that there is at least a mention which I will

highlight to you.

The first example that I have is the level of treatment. That is what we have referred to in the category heading. The Declaration of Helsinki has used the terminology "best proven diagnostic and therapeutic method" and other documents have adopted that language as well.

I want to point out two things. One is the CIOMS/WHO guidelines and the Canadian guidelines talk about the use of placebo controls in an ethical justification as to when it can be used in a clinical trial.

The other is the United Kingdom, which talks about the availability and feasible health care in the particular developing country as it relates to the best proven diagnostic and therapeutic method. I wanted just to call your attention to those.

DR. SHAPIRO: Stu, just a second. Alta has a question.

MR. KIM: Yes.

PROF. CHARO Excuse me. Before you move on, I just wanted to ask a clarifying question about the provisions concerning the duty owed to research participants during and after the trial because you have text here that describes the Council of Europe,

ICH, CIOMS and Uganda, provisions that suggest an enhanced obligation to provide care during and after trials than is present in the U.S. Common Rule.

Do you or does -- do we as a Commission yet have the ability to identify those situations, if any, where these rules have actually been applied and to see whether or not, in fact, this kind of extended care has been offered to people and how well that has worked?

I mean, is there an ability yet to link these provisions to some empirical information about how well they have actually functioned in practice?

DR. MACKLIN: Can I answer that?

MR. KIM: Yes.

DR. MACKLIN: As you know, and I guess it is a short-coming about the time and the resources for this Commission, in putting together the chart we were looking at documents.

PROF. CHARO This I understand. I did not expect --

DR. MACKLIN: And there was really no attempt -- that is it would be quite an undertaking if you think about it to inquire into the application -- implementation of these principles. So the answer to -- the simple answer to your question is, no, there was no attempt to look at that. These are items that

appear in the guidelines or regulations.

PROF. CHARO I have no criticism of the fact that we do not have it yet because just getting this is kind of amazing because it really clarifies for us what the alternatives are. If it is at all possible when some of these alternatives come up for discussion of recommendations we might make, any information we have about how they have operated on the ground that is available would be very helpful.

MR. KIM: The next example is providing research results to participants.

(Slide.)

And there were six documents that had language discussing the sharing of research results to participants. The two I want to focus your attention on are the United Kingdom and India in which they use language talking about the sharing of information during and after the clinical trial. And that language is highlighted in the overhead.

(Slide.)

Next is the treatment and compensation for injured research participants. The United States regulations do have a statement that prohibits the inclusion of exculpatory language in the informed consent.

These documents that you will see in the overhead have slightly more explicit language. The first set, the first three, the UNAIDS, India and Australia, actually say that compensation needs to be spelled out beforehand and made clear to the research subjects.

The second set, the CIOMS, WHO, Uganda and Netherlands guidelines, talk about responsibility for compensation and no specific language I want you to pay attention to but it is there.

(Slide.)

Next are the successful products made reasonably available and there are actually -- in your handout there are two sets. I am going to skip over the first two, Canada and the United Kingdom. These documents essentially say that there should be a discussion of successful products being made available after the clinical trial is over.

The ones I wanted to focus on are the four documents that are on the overhead and they actually talk about an understanding that products will be made reasonably available and the fact that these need to be spelled out in the beginning before the clinical trial is actually started.

There is also some discussion in there about

making the successful products available not only to the participants in the study but also to the inhabitants in the local community.

(Slide.)

The next is the discussion on equivalent protections or harmonization of standards. Now i should say that the United States, the FDA -- the United States regulations, including the FDA, the Common Rule and the USAID do have statements in their regulations that talk about equivalent protections. So I have left them out here. I have only included the ICH, CIOMS, Uganda and India guidelines here.

The most interesting is the India guidelines which refer to written descriptions of the specific procedural implementation that needs to be made of this equivalent protection discussion.

DR. MIIKE: This refers to regulations that are absent in the U.S.

MR. KIM: Right.

DR. MIIKE: But you just prefaced your comments by saying they are in the regs.

MR. KIM: And I did do that. The reason I think that we put this in this category -- well, there was actually some difficulty because there were some statements just made by the various documents and we

were looking for something to go a little beyond. This may be a little misplaced in terms of the organization.

MS. PAGE: Excuse me.

DR. MACKLIN: A clarification.

MS. PAGE: Alex, this was not supposed to be included under number four. This was supposed to be listed as a separate point of discussion because it is one of the issues that is going to be discussed after Stu's presentation. It is not supposed to be included under that particular question.

I am sorry. Larry. I am sorry.

DR. MIIKE: This is point six.

MS. PAGE: Yes. It is supposed to be a separate point of discussion.

(Slide.)

MR. KIM: And then lastly is the notion of research and review of research conducted in other countries. And there are again two sets that I have divided and identified under this section.

(Slide.)

The first is on the overhead. Looking at the CIOMS, WHO guidelines, UNAIDS and the United Kingdom. They actually have language that talks about community standards or the local custom to be included in the

analysis of reviewing the research.

The Canadian, Indian and Australian guidelines, which I have not put on an overhead, talk more in general about the review requirements, about research that are done in other countries, and that is included in your handout.

(Slide.)

In this overhead it shows that but it just discusses review requirements.

DR. SHAPIRO: Thank you. That is really extremely helpful.

Any questions for Stu?

Diane?

DR. SCOTT-JONES: I have a question about part four and also about the first one. For part four the topic is providing research results to participants and I am wondering whether your sense is that these documents are referring to providing results about the participant's own condition or providing general statements about the findings such as this treatment is better than no treatment or this treatment A is better than treatment B, or is it providing information about the individual's own condition?

MR. KIM: That is a very good question. The documents use a variety of different language and there

may be different meanings contained in them. My sense is that -- for example, India, and I think CIOMS, they wanted to have some transparency. They wanted the participants in the clinical trial to be part of the research study. And as a result they were hoping that there would be an exchange of information.

The idea of a particular patient's own condition -- at least the way that the chart is organized -- I think might fall under duty of care for physicians to interact with the participants during the study.

DR. SCOTT-JONES: Okay. It is not all that clear. I have a second question. It is -- I am sorry.

DR. SHAPIRO: Go ahead.

DR. MACKLIN: It is not clear in the wording but I can say with some confidence what the intent is. The results of research mean the findings -- the conclusions of the study that would be published, for example, about the efficacy of a treatment or compared to a standard treatment. It is a general statement and so even though it is worded ambiguously in the CIOMS, for example, when it says it will be told of findings that pertain to their health.

What it means generally is if they are cancer patients or if they are HIV patients and now a new

treatment comes out and they have this disease, they will be told about this finding so that the people who are the participants will be told what the results of the study are but it does not -- it is never intended to mean individuals will be broken out because very often the researchers do not even have that information in that form when they write up the results.

DR. SCOTT-JONES: Okay. My second question is about continuing review by the IRB. This is on the first page under number two. The phrase "continuing IRB" has some ambiguity.

At our previous meeting we had a discussion by an anthropologist who talked about the lack of continuing IRB review. That is once the IRB makes a judgment about a project, the IRB does not typically in any way track the research project to make sure what is going on.

I believe the sense of these is that there may be a recurring IRB review say at a year interval. This is not meant to imply that the IRB in these instances does any continuing tracking of the -- or monitoring of the review project, is it?

MR. KIM: Another difficult question. The -- I think implicitly in some -- in all these documents that there may be continuing IRB review but the

language is lacking. And these are the only four documents in the scope of the chart that use the term "continuing IRB" or "continuing ethics review."

DR. SCOTT-JONES: But it just means recurring. Say at a years interval it is reviewed again as is the case say at my institution at my IRB but the issue of continuing to monitor and track and to determine that the principal investigator is, in fact, doing what he or she said, that is not implied at all. I mean, is it implied here?

MR. KIM: No, I do not think so.

DR. MACKLIN: Monitoring is even -- is actually a much newer concept and it is something quite different. This is exactly what you have described. Namely re-review and re-approval at specified intervals such as the IRB may determine at the time of its first doing it. So it is simply continuing. It does not mean monitoring. It means re-review or re-approval.

DR. SHAPIRO: Thank you.

Alex

PROF. CAPRON: Let me just take up, if I could, on that point. In light of data submitted by the principal investigator, we are not denying that, isn't it? In other words, continuing reviewing is not monitoring in that the committee is not taking on the

function of going out and observing or gathering data but its re-review is supposed to be in light of the experience gathered, which may alter its determination of the balance of risk and benefits, and the information in the consent form, et cetera.

Is that correct?

DR. MACKLIN: Yes.

MR. KIM: Absolutely correct.

PROF. CAPRON: I thought you were taking a step further back --

DR. MACKLIN: No, no.

PROF. CAPRON: -- they simply have to say, yes, we still have an ongoing protocol and we have not stopped it.

Two small points for clarification. Could you address on page five your thinking about the compensation issue and how you divided these? I gather that you saw these as falling into two categories. Is that right?

MR. KIM: Yes. One of the difficulties in compiling the chart is we had established the different columns for the different parts of the chart and then to fit provisions from these documents proved to be -- sometimes be a difficult task because the focus was different. So there were some language that seemed

similar that for me sort of grouped together.

PROF. CAPRON: Right.

MR. KIM: Others that did not necessarily fit very well. So for this, the UNAIDS, the India and the Australian guidelines, they actually speak of having a mechanism in place for some type of compensation if a research subject is injured. I thought that was different from the responsibility of what -- of the investigator or the sponsor if a research subject is injured during a study.

PROF. CAPRON: Well, that is interesting because I think you need to -- I guess I would have a sense that you need to tease that out a little.

Looking at them it seemed to me that the UNAIDS statement, and maybe it is just the way you have it edited here with the ellipsis.

I read it as simply being a disclosure specification and I saw that as falling on one side of the line closer to the U.S. policy, in fact, and the difference between say Australia and the Netherlands or something seemed to me rather small. The difference between saying that arrangements exist to ensure compensation versus the injured party has the same right against the governmental service as he would have against an insurer, meaning an insurer who is

responsible for his health care costs. It seems to me a nondifference. So I just again -- this is a matter of asking you to go back but could you address the first one.

You know so much about this, Ruth, that you could address it. Am I misreading that? Is that anything really more than a notification requirement?

DR. MACKLIN: That is what it looks like here. What we do not have and I apologize because I do not have the document with me, I did not bring here to Madison, is each guidance point has a commentary under it in much the same way that CIOMS does. And I do not now recall the exact language in that.

It could be -- very well be that the guidance point itself was taken out but that the real reference may be in the paragraph that follows it. Just as, for example, the making products reasonably available language occurs in a CIOMS commentary but not in one of the actual CIOMS guidelines.

So we will check this and see. I think you are right. In reading this it looks like it is simply a requirement for disclosure but it could be that in the larger paragraph it looks more like the CIOMS and my guess -- my recollection but I do not want to say it with certainty -- is that it is more like the CIOMS --

the way the CIOMS reads.

PROF. CAPRON: And the other small comment was just you might want to check the Points to Consider developed by the RA, which would be in the nature of a footnote here. I have a vague recollection that they require disclosure to the subjects of research in gene transfer. Information about the results. So it would be an example of an American human subjects regulation that falls in that category.

Have you tried -- and I know it is so different that as to most categories it would just be inapplicable, but have you tried looking at any of the human rights documents that were cited to us this morning? Particularly those that are approved by the United States and ratified and see if they fit.

MR. KIM: At this time, no. We have not looked at those yet.

PROF. CAPRON: Because perhaps as to some -- you have some categories on your bigger chart about privacy, I believe, don't you? And some other things.

MR. KIM: That is correct.

PROF. CAPRON: There might be a few things there where again you could fit them in even if they were not on all fours with most of the points.

DR. SHAPIRO: Thank you.

Any other questions for Stu?

Larry?

DR. MIIKE: On page five I would prefer that this listing be separated into treatment as one and compensation in a broader sense as the other because to me it raises quite different policy issues about obligation to treat an injury versus financial compensation for that injury or death or disability.

PROF. CAPRON: Larry, that is -- which -- I am looking at these quickly. Do any of them divide that way? They all use the word "compensation."

DR. MIIKE: No. But if you look at --

PROF. CAPRON: Or --

DR. MIIKE: -- look at the Netherlands. If you look at the Netherlands, I could read that to mean it is a health insurance issue. Regardless of whether they --

PROF. CAPRON: I see it. Yes.

DR. MIIKE: Yes. And regardless of whether they do not, I think in terms of a choice it is breakable into is there an obligation to treat for disability or death. Well, death is a different issue. But -- because there obviously you are always talking about monetary compensation. But it seems to me that from a policy perspective and just sort of the

substantive remedies it is different to talk about money versus treatment.

PROF. CAPRON: Right. It is just that none of these are very explicit.

DR. MIIKE: Right.

MR. KIM: I should also say that the headings -- there are other documents that I think address what you just said but that were not included here.

The broad heading of treatment and compensation for injured research participants, I think, there are some documents that talk about treatment of the research participants but they were omitted here just in terms of comparison.

DR. MIIKE: Okay. So again this is really one about compensation.

MR. KIM: Correct.

DR. MIIKE: Okay.

MR. KIM: I just gave the broad heading so that you would be able to find it on the chart without too much difficulty.

DR. SHAPIRO: Let's take a few more questions and then I really want to move on.

Will?

MR. OLDAKER: Yes. I basically read this also as compensation and almost -- at least if you look at

India and think about their legal theology, there is almost a strict liability. They are saying that an organization has to agree to make payments for any injury or impairment and then it would only be a matter of determining. The only thing that would be justifiable would be what the amount was. And that would be far different than our legal system here where you would actually have to prove -- you know, have to go though a lot more injury.

So I may be misreading this because it is out of context but that is one way to look at it.

PROF. CAPRON: The Indian language is using the CIOMS document --

MR. OLDAKER: Okay.

PROF. CAPRON: -- language in the first sentence, and I do not know what the second sentence adds except it makes the sponsor agree to that.

MR. OLDAKER: Right.

PROF. CAPRON: As a predicate. It is a nonfault. It certainly is.

MR. OLDAKER: Correct.

PROF. CAPRON: Both of those are nonfault statements but I do not think that they are arise -- it does not arise peculiarly out of an Indian context if it is using this international CIOMS language.

MR. OLDAKER: Correct.

DR. SHAPIRO: Diane, then Alta.

DR. SCOTT-JONES: You may have already told us this but how many documents were reviewed in the preparation of this information?

MR. KIM: We have 20 at this point right now and we are going to be adding the Chinese regulations in the next version.

DR. SCOTT-JONES: Okay. And how many of the 20 documents were from African countries?

PROF. CAPRON: Uganda.

MR. KIM: I think it is just Uganda.

DR. SCOTT-JONES: Oh. I am sorry. I have it. Sorry. Thanks. Just Uganda. Okay.

DR. SHAPIRO: Alta?

PROF. CHARO First, once again I have got to tell you that this is immensely helpful.

The thing that would make it even more helpful, at least for me, is perhaps when we are doing special pull out charts and such to help us decide which recommendations we want to adopt for ourselves, to identify in a paren what you have later on in the more detailed chart, which is whether or not this particular provision has the force of law and is enforceable in that country or if it is simply an

aspirational statement because that helps to evaluate whether or not to adopt that language in our context where almost everything we do adopt is going to wind up having a regulatory status that gives it force of law.

DR. SHAPIRO: Thank you. Okay.

Ruth, why don't we take the next step.

DR. MACKLIN: Move on. Okay. The next step, in preparation for the next step --

DR. SHAPIRO: Thank you, Stu.

DR. MACKLIN: Thanks very much, Stu. We are going to be needing this even in moments to come. This is background for the discussion.

But let's take one short step backward before we move forward and we will call your attention to a case study. It is rather -- it is a page and a quarter but I am just going to hit the highlights. It is in the briefing book behind -- help me where it was.

MS. PAGE: I am trying to find it.

DR. MACKLIN: It is in the -- just before -- that is it. The case study. It is called "Ethical Reviews for International Human Subject Research: Case Study from the Department of International Health, School of Hygiene and Public Health," and it is principal investigator.

Let me explain briefly. Do we know where it

is?

PROF. CAPRON: It is tab 2d.

DR. MIIKE: It is after the OPRR responses.

DR. MACKLIN: Okay. Right. 2d, the lengthy response from OPRR and it is a one page sheet. It comes after that. Maybe we just need more tabs when these are -- it is immediately after that and before the document that says "Nepal Netra Jyoti Sangh."

(Simultaneous discussion.)

DR. MACKLIN: Yes, that is the one. That is the one.

Now I want to tell you briefly why that is here. It is only an illustration but it is, I think, an important illustration and there are two important points that come out.

Quite by accident this is before you. you may recall at the very first meeting that we had on this project Don Burke, a researcher at Johns Hopkins, made a presentation on different models of collaboration and cooperation north and south.

Don Burke is a colleague of -- I guess they call him Jim Tielsch at Johns Hopkins.

In an exchange between them in which Professor Tielsch was complaining about this situation and wrote to his colleague in great frustration, Don Burke, and

said, "Look, here is what I am up against yet again. What can we do about this? Is there anything we can do about it?"

Burke wrote back and copied me on this particular -- and other Johns Hopkins' colleagues, including Nancy Kass, who is one of the consultants on this project, and Dr. Burke wrote back and said, "You may not know -- you may or may not know that the National Bioethics Advisory Commission has a project dealing with this and related issues." He said, "To my knowledge, the Commission has not yet dealt or has not dealt with this particular problem."

I then interjected having been copied on the message and said, "Well, you know what? At the very next meeting NBAC is going to be looking at this problem." And I asked whether or not it would be possible to get this information for this purpose and I said to Dr. Tielsch, "If you wish, you can take out the name of the country, take out the names of anything you want, you know, but we would like to have the illustration."

He was so happy for the opportunity to do it he wrote this up and presented it.

So here are the highlights and then I will say what I think are two important points. Let's look

under issue. I mean, this is a study that Johns Hopkins is doing in collaboration with Nepal. He has been working in Nepal for the last 12 to 14 years, he and his colleagues at Hopkins. So this is not -- he is not parachuting into Nepal for the first time.

Over the past 12 to 14 years his studies have been funded by USAID.

Now he has got -- and he describes here briefly what the review process has been. And the people with whom he discusses and negotiates and who ultimately approve this are the -- this is the document you say -- the Nepal Netra Jyoti Sangh. That is the collaborating institution. And the Nepal National Health Research Council. That is the group referred to here as NHRC. They review research and approve them for compliance with ethical principles.

Now the issue then arose because NIH is the funding source for this latest trial, not USAID, he ran into some problems. He was required by the OPRR requirements to send the document -- to ascertain the exact composition of the local IRB, the procedures of its meeting, its decision making process, its record keeping and reporting responsibilities to the U.S. Government.

He says here in this memo that he was a bit

reluctant to approach the National Health Research Council in Nepal with this requirement but he did so. Apparently, as he says, as an expected, the NHRC rejected the document, refused to sign it, and the senior members expressed extreme irritation that the U.S. Government would meddle in the internal affairs of a government agency in Nepal that was complying with the principles of the Declaration of Helsinki in their role as an IRB.

The investigator then turned to OPRR and asked if they would consider amending the language, that is the languages in providing a single project assurance. That is what he was seeking. And that is now pending. In other words, he is waiting -- awaiting the decision to see whether OPRR will amend their requirements. Failing which, he could not do this research under NIH sponsorship with the Nepal collaborator, who he has otherwise been collaborating with, with no difficulty, for all these years.

Now his last statement -- let's just look at the last paragraph. "Whether or not OPRR shows flexibility in the language of this particular SPA, single project assurance, a key question is whether the SPA process is needed at all in a case like this. In what way does another set of documentation related to

specifying the review process for an IRB provide additional protection for human subjects over and above that already documented by the Johns Hopkins University IRB, which has an MPA, a multiple project assurance."

In a sense he is raising some of the questions Norman Fost raised earlier in his presentation.

"This is not to suggest that a local IRB is unnecessary. In fact, we agree that it is appropriate and required." At the end he says, "We will have spent --" he says, "The subjects in this study will not have been protected any further than was the case before such a document was even considered. We will have spent significant amounts of time, energy and good will on a process that merely documented again what was already in place." And he says a few more things there at the end.

So this is really meant to illustrate an episode but it is a real episode and it is a current episode, and that is why it is brought to you. But the additional and possibly even curious aspect of it is that another Unite States agency, USAID, had been approving, sponsoring and -- as the sponsor of research for 12 to 14 years without this particular requirement or this onerous requirement and not having produced any difficulty.

So the questions before us -- this fits into our larger context and we are going to -- after this discussion -- just go to the next step here, which is to say here is an illustration of what the current mechanisms and requirements can lead to.

DR. SHAPIRO: Trish?

PROF. BACKLAR: Can I ask you one question? I am a little perplexed that you have also given us this informed consent document, which I presume is for this study. At the end of it there is an attachment B, an informed consent document. And it is odd because in the informed consent document it does not reflect, in fact -- it does not mention this randomization or that there is placebo. It is as though everybody is going to get -- there is some sort of discrepancy unless I have missed something.

I wondered if this was of any importance. I mean, it is of some importance but it is -- have you noticed that?

DR. MACKLIN: Well, we -- I, myself, did not examine that for this purpose. Okay. I mean, in order --

PROF. BACKLAR: I realize you are looking for something else but it is of some concern.

DR. MACKLIN: Well, we will have to visit it

and revisit it. Okay.

PROF. BACKLAR: Okay.

DR. MACKLIN: I mean, I --

PROF. BACKLAR: Okay.

DR. MACKLIN: -- the purpose of bringing this to you was for the comparison of the thing.

If we -- and we might consider doing so -- started looking at a lot of informed consent documents, we may find a lot of problems. Okay.

This is here essentially because it was provided by Dr. Tielsch as the documentation and the background for this.

If we want to revisit it in connection with the informed consent -- I mean, I think that is a perfectly reasonable thing to do but I think that it would digress a little from what we are doing now if we had to come back to it. I think in order to look at any consent form we probably need a full research protocol, too, to do the proper job with it.

DR. SHAPIRO: Alta?

PROF. CHARO Well, actually, Trish, if you look at the second paragraph, it does tell them that the tonic will either have zinc or no zinc, and that it will be determined by the flip of a coin. So there is something in there on that point.

But let me just ask if this is an appropriate moment then to link this case study to what you present as option one on what we ought to do about the question of equivalent practices.

DR. MACKLIN: Well, we are going to go to that next. Yes, we are going to that next. Now we only want any questions or comments on this episode and we are going right into --

PROF. CHARO Well, it relates exactly -- I do not know how to separate them.

DR. MACKLIN: Okay.

PROF. CHARO The question is because you present to us the USAID language that your researcher refers to as having guided the first two studies before he met up with the NIH, the question I have is how is USAID deciding whether or not something, in fact, is equivalent. I mean, I can imagine that they might say, well, there are three basic goals. Self-determination, which requires full information and voluntary signed consent, risk minimization and an assurance that benefits outweigh the residual risk. And there might be something -- whatever it is -- but there is no hint here --

DR. MACKLIN: The hint is under option two. If you turn over the page --

PROF. CHARO Right, that is what I am looking at.

DR. MACKLIN: Yes. You see option two. That actually is expanded. I mean, since these materials were prepared we have more information about USAID, and I believe there were four procedures. I mean, Alice is the expert on this and could expand -- well, she was the one who had the conversation with Jim Shelton and all of this took place within the last two days, I think, or last three days. So there is actually an expanded picture of what the USAID model is.

PROF. CHARO So this -- I actually -- I read them separately. I might have just misread your paper. I am sorry. Where you talk about substantive application of the there pillars, that is actually an explication of the USAID. I am sorry. I thought that was separate and that the only thing from USAID was the mere statement of equivalency. Okay. Sorry.

MS. PAGE: No, this is all in their regs.

PROF. CHARO That is their effort to explain what it would mean. Sorry.

DR. SHAPIRO: Alex?

PROF. CAPRON: Well, in some ways I was coming to the same type of issue by looking at Stu Kim's chart. The larger chart. Is it paginated, Stu?

MR. KIM: Yes.

PROF. CAPRON: The pages are stapled under. Page 51.

But perhaps Alice will be answering this in a moment. I just wanted to know what USAID says it is doing and I guess what it is doing is issuing a statement of equivalency as opposed to the SPA. Is that known?

MS. PAGE: Well, it has -- USAID has four ways that they do this. There is either an MPA that they have directly with the agency or if a united --

PROF. CAPRON: A foreign agency.

MS. PAGE: Hmm?

PROF. CAPRON: The foreign agency when you say the agency?

MS. PAGE: Yes. Directly with the --

PROF. CAPRON: The foreign institution.

MS. PAGE: -- the institution, the foreign institution.

PROF. CAPRON: Okay.

MS. PAGE: Or if there is research that is being supported by a U.N. agency and they -- like the WHO or UNAIDs -- and they make a determination that there is equivalent protections. USAID will accept that as a determination of equivalent protections.

Jim Shelton told me that that is the most frequent way that they make their equivalent protections determination is by relaying on a U.N. agency determination.

PROF. CAPRON: And in conceptualizing that, would that amount to a statement that having looked at the U.N.'s standards, they have determined that they are equivalent? So if the U.N. says X institution in another country is in compliance then that is -- it is indirect equivalency as it were?

MS. PAGE: Exactly.

PROF. CAPRON: Is that a fair description?

MS. PAGE: Right.

PROF. CAPRON: Okay.

MS. PAGE: Then they have the example that was used by Professor Tielsch in the previous case study and then USAID has developed their own equivalent protections test, which is listed here under option 2, subpart B, where they have the substantive application of the three pillars of human subjects protection.

PROF. CHARO Wait, Alice. I thought that was what they were doing in the Tielsch example. So what did they do in the Tielsch example that is not that?

MS. PAGE: No. The difference there is that Hopkins has an MPA with USAID. And so if Hopkins

reviews the procedure in the -- that is going to be used in the host country and the host country also goes through that procedure as well then USAID will accept that as equivalent protection. They do not make an independent determination. They rely on Hopkins or the institution.

PROF. CHARO And Hopkins is using what criteria?

MS. PAGE: Their own but they have got an MPA already with USAID.

PROF. CAPRON: This is where all --

PROF. CHARO This is beginning to get very circular.

MS. PAGE: I know.

PROF. CAPRON: Not just that it is circular but it comes down to this -- what seems to me remains the basic question. Let's not say Hopkins. Let's say Rotten university, I mean, just to take the extreme, has an MPA. And what it does internally at that institution is okay but they use rotten standards when they are looking internationally because they are eager to get international work and they will approve anything. How does USAID or NIH or anybody else know what the standards are that are applied other than that this institution says we are applying the standards?

I mean, this is beyond the question of whether Hopkins says, "Well, we would never touch that institution because they do not have good standards," and Rotten University says, "Oh, we are happy to do business with them," and we get "two different results" varying by local circumstances.

MS. PAGE: Because Rotten University has the MPA with USAID, USAID is relying on that. I mean, that is what is happening.

PROF. CAPRON: But what do we know from these MPA's? I mean, to what extent --

DR. MACKLIN: Well, what you are asking --

PROF. CAPRON: If Hopkins, which has an MPA, does not have criteria then in looking at their MPA how can UNAID know what -- not UNAID, USAID, excuse me -- know the quality of the standards and judgments that they are going to reach?

DR. MACKLIN: Presumably -- look, what we do not have in place here is what criteria USAID has in place for issuing the MPA in the first place. Presumably, they do not hand them out like lollipops. I mean, that is in order for an institution to qualify for an MPA that is a much more -- that is a rigorous general process by which -- in virtue of which, USAID then determines. We do not have that --

PROF. CAPRON: But as I understand it, part of that rigorous process does not include the institution having articulated criteria by which they are going to judge the other institution, which will vary. I mean, the whole point of this is if the other institution had adopted 45 CFR as its template, there would not be a question. It would not be equivalent. It would be -- they, themselves, could get an SPA just like that. And the point -- or an MPA just like that.

The point is that institution operates under the Declaration of Helsinki or operates under something else and has their own procedures and the issue is are they giving adequate protections for a U.S. agency to be involved in their research.

If Hopkins says, "Well, here are the criteria by which we decide that, and that is part of our MPA," that is an answer I understand.

But I thought the answer I got from Alice was Hopkins tells us they do not have such criteria. They make judgments based upon their own judgment as to whether or not this institution is in compliance.

MS. PAGE: That is not --

PROF. CAPRON: Oh, that is not your answer?

MS. PAGE: That is not my understanding.

PROF. CAPRON: Oh. Okay. So the answer is we

do not at this point know.

MS. PAGE: We do not have that information.

PROF. CAPRON: We need to learn from USAID when they are giving an MPA and, in effect, delegating to somebody else this process, how do they assure themselves that that body will be Johns Hopkins and not Rotten University. Is that a fair, if somewhat inflammatory, way of putting it?

DR. MACKLIN: Could we go back, though, to the Tielsch explanation?

PROF. CAPRON: Sure.

DR. MACKLIN: Because I thought that was what he was saying was the problem here, duplicating a set of documentation that they already have.

"In what way does another set of documentation..." on the bottom of the first page "...related to specifying the review process for an IRB provide additional protections for human subjects over and above that already documented by the JHUIRB, which has an MPA."

Now presumably what I infer from this is that having the -- Johns Hopkins having that MPA is already required to make this documentation to provide --

PROF. CAPRON: No, I do not read that at all. All I read it -- is what OPRR, through this SPA, at

least as originally written when it was in its most offensive form, and maybe still now when they have tried to make it look nicer, is OPRR requires a certain format of the IRB. We know that there is language about how an IRB is made up, how it keeps its records, how it meets, and so forth, and that it reports to the United States Government, in effect, on that, and that it conducts, you know, this kind of review and that.

And these people, understandably in Nepal, are saying, "We are a government agency of our own. What are you doing making us --" that is where the offense comes in. "All you are doing is making us go through a documentation process."

The other part of this sentence says, "Over and above that already documented by the Johns Hopkins, which has a multiple assurance." It means one of two things or maybe both things to me. One, Johns Hopkins is already very rigorous in looking at what happens there. That is to say they want to see what they think is a good consent form. They want to know people are in a position to say yes or no. They look at the risk benefit. They are, in effect, doing the IRB work themselves.

And (b) they have a lot of experience with this review body in Nepal and they are comfortable that

they are a good and conscientious group.

The latter may be the most refined judgment you can get but how if I were sitting at USAID would I know without again just sort of relying, I know the people at Hopkins, they are good people, they are not Rotten University, they are Hopkins -- do you see what I am saying? And that I can rely on their being -- having good judgment and using -- but they cannot tell me that this is their checklist, these are their criteria. This is how they decide whether something is or is not equivalent. They have no established standards for that.

I am relying on their judgment.

DR. SCOTT-JONES: May I interject something?

PROF. CAPRON: Well, let me just say as a bottom line to all of this, I am coming increasingly to the conclusion that probably a lot of what works about IRBs in this whole process is exactly that.

And we may in the end be banging our heads against a wall or being overly rigorous if we think we can be a lot more refined but I would at least like to know if that is where we come out internationally or domestically, that that is what we are saying. That, you know, basically American people -- you ought to be comfortable with this because a lot of good and

conscientious people are engaged in the best human effort. But it is so individualized and it is so detailed that we cannot begin to specify it and there are going to be a lot of mistakes, and people are going to differ. Reasonable people will differ and some things will be approved at X that could never be approved at Y.

Not because one is in the Bronx and one is in -- because they have different populations but just because people are going to reach different judgments, and there is nothing to be done about it. It is just a matter of discretion.

And what we really get out of this process is something better than if there were no process at all but that is about as far as we can go.

Anyway, so I -- in raising this I am not trying to say we are going to -- if I do not get a good answer this I want to hang them on it. I would just like to know whether we are talking about that kind of a system or a system in which -- as you are saying might be the case -- USAID has a set of things that they expect to see in an MPA where the IRB at that institution will be its surrogate, its deputy sheriff, deciding that the foreign process meets standards that USAID is never going to touch itself. They are just

going to say you are doing it, you have an MPA, that is all we need.

DR. SHAPIRO: Okay. Diane?

DR. SCOTT-JONES: I can pass on most of what I had to comment on but I will just say that I am a bit concerned about the statement at the end of this example. I guess what is the PI's bottom line, and that is that he believes that there is no point in attending to what he does with the participants in his research and that we should be concerned about the broader social inequities.

That seems to me to be misplaced there because, of course, when his project is reviewed the issue of concern is not social inequities but is that particular project. So it seems to me simply trying to direct attention away from this project and on to bigger issues that no one is going to address. It seems a bit troubling.

PROF. CAPRON: Rhetorical.

DR. SHAPIRO: Larry?

DR. MIIKE: This last discussion answered one of my questions, which was who is actually making the determination and it was Hopkins. It was not USAID. Right? In terms of the adequacy of -- at the -- well --

DR. MACKLIN: You know, there is a lot of gaps here.

DR. MIIKE: No, no, but --

DR. MACKLIN: I do not think -- Alex made that point and Alta wanted to jump in so I want to hear what she had to say but Alex made the point that it is Hopkins that is making the determination of equivalency.

PROF. CAPRON: I am asking. Is that the case?

DR. MACKLIN: I do not think that is at all the case. I do not think that is at all the case. The Johns Hopkins -- they may have an MPA from USAID but that requires them to say what they do at Hopkins and what they are going to represent to USAID in their MPA is exactly what they have to represent to the NIH and to OPRR. They are not going to have a different set of standards. They are already bound by the Common Rule.

So there is a point here that I really do not understand about Alex's response, and I am sorry, because what it sounds to me is not that Hopkins IRB is making --

PROF. CAPRON: I thought that was your response.

DR. MIIKE: Do not get so defensive. I am not

attacking you.

DR. MACKLIN: No. I just -- I mean, I think there is --

DR. MIIKE: No. What I am saying, though -- let me put it --

DR. MACKLIN: -- we have to clear up --

DR. MIIKE: -- in a bigger picture. USAID is a signatory to the Common Rule, right? Right?

DR. MACKLIN: Yes.

DR. MIIKE: So this is a case of to what level of detail is the sponsoring agency going to reach in, and NIH is reaching in, down to the -- wherever this country is. This is Nepal. Whereas, USAID, once you get the MPA from Hopkins is satisfied with it.

DR. MACKLIN: That is because --

DR. MIIKE: I see no other answer for that except to say that if USAID is reaching down to the local level then this is a question of quibbling over details of one reaching down versus the other reaching down. Right?

DR. MACKLIN: But, Larry, let me -- there is one clarification. They are both signatories to the Common Rule but --

DR. MIIKE: Right.

DR. MACKLIN: -- OPRR governs NIH and that is

why they got involved here. OPRR does not govern USAID.

DR. MIIKE: I understand that.

DR. MACKLIN: And that is --

DR. MIIKE: I understand that.

DR. MACKLIN: Okay.

DR. MIIKE: But they are signatories to the Common Rule. And this is just a very clear example, well, what happens when you get below the level of the department where the department has said we signed on to the Common Rule but we are going to be the interpreters at levels lower than that in terms of their grantee agencies.

The question to me is the same one that Alex has raised, which is at what level do we say let's not bother going further and further and further down? It seems to me that in many of these areas the best we are going to be able to come up with is something like guiding principles that should be followed and leaving enough flexibility to the agencies or whatever level we decide we want to have the cutoff on, without having to get down to interminable levels where we are going to be crossing the -- you know, dotting the i's and crossing the t's at the individual institutional level.

DR. MACKLIN: I mean, I think -- would it be

useful if we can go to these other documents?

DR. SHAPIRO: I was going to recommend that.

DR. MACKLIN: Okay.

DR. SHAPIRO: That is what we are getting to at here one way or another.

DR. MACKLIN: I thought this was going to be sort of clear cut but apparently it is not but it is -- actually it goes to the question, what ought we to be recommending by way of the different options in equivalent protection. So I think that really is the next step.

The document here just before the options are stated, we have got three options, and just before the options there is a paragraph that describes what the U.S. -- the current U.S. Federal Regulations state. Okay.

This is what the U.S. Regulations state. If you remember the -- probably not all the details but one reason why the response from Tom Puglisi of OPRR is in this briefing book again is that we sought to find out in an early stage in this project how does this actually work.

Here is what the guidelines say about equivalent protections. How is it determined which countries do or do not or which institutions do or do

not have equivalent protections?

And in a series of carefully crafted lawyers' questions, we got the lengthy Puglisi memo, which in effect says there is not and has not been an attempt to find equivalent protections. There are no criteria. There is no mechanism.

What we do instead is use the assurances mechanism in lieu of implementing this provision of the Federal Regulations.

PROF. CAPRON: Rather than calling that current practice here, you could call it OPRR practice under options.

DR. MACKLIN: Under options. Yes. Well, it is the --

PROF. CAPRON: That boils it down. OPRR practice is to do an SPA rather than do an equivalency.

DR. MACKLIN: That is right.

DR. SHAPIRO: Right.

DR. MACKLIN: That is exactly right. So that is option one. And, of course, we are raising this in the larger context. Remember that title is "Enhancing International Collaborative Research." We have heard testimony from other people in the past months about some of the barriers and some of the difficulties.

This latest one, which I thought might be sort

of clear cut and is not, is just another example but what seemed a little strange is that involved two different funding agencies from this same country, each of which uses a different mechanism.

So what we did was just prepare some options to get these on the table and have the commissioners think about these alternative options and that is why we are here. I mean, why this is here. Option 1, option 2 and option 3, or other. I mean, any combination.

DR. SHAPIRO: Alice, I am not sure what you said. You made a comment before about what we have here was two options but there are really four options.

MS. PAGE: Well --

DR. SHAPIRO: I did not quite understand that.

MS. PAGE: -- there are not really four options. These are the -- they have an MPA, which is -- that is -- if you want to call that an option for equivalent protections. I mean, that is not listed here. That is pretty straight forward.

USAID has developed their own procedures in addition to the Common Rule in terms of how they do these things. And the example -- the case example from Hopkins is one mechanism by which they will, in essence, make an equivalent protections determination.

They will accept the determination of the academic institution's IRB. That is not on here.

These are the other two that are in their procedures that are a little bit unique. One is this acceptance of U.N. agency determination which apparently USAID relies on quite heavily. This option B is USAID's own procedure for making equivalent protections. They require the substantive application of what they lay out as the three pillars of human subjects protections.

And then the difference really between what USAID does and what we would presume OPRR might do is that USAID will look at all the circumstances, as they say, in toto to determine whether there are equivalent protections as opposed to going through a checklist and saying, well, the IRB membership requirements are the same.

I mean, USAID would not necessarily require that the make up of the IRB be precisely what is specified in the Common Rule in order for there to be a determination of equivalent protections. That is the big difference.

DR. SHAPIRO: Thank you.

Alta?

PROF. CHARO It strikes me that there are two

interesting lessons that can be learned from this particular case study that affect the kind of recommendations we make.

First, I think it is worth noting the overlap with the domestic research report because the possibility of this kind of disagreement on a procedural level as to how one documents equivalency by any standard is a manifestation of the absence of a single regulatory authority that sits high enough up in the Federal Government to have authority over both NIH and USAID simultaneously.

What we are seeing here is a perfect example of what has been described on many other occasions of departments going in different directions in their interpretations and implementation of the Common Rule.

Second, on a substantive note as to how one would appropriately identify equivalency, as has been said, the OPRR model is extremely prescriptive in practice, although it is not necessarily so by policy. They have no policy and practice is very prescriptive, and the degree to which it is insulting or annoying to foreign governments or even just foreign institutions is apparent.

Whereas, the AID model that is described here on page 2 of the materials here, is one that is really

-- it is extremely general. I mean, it identifies three pillars of human subjects protections as review by proper committee, meaningful informed consent and meaningful assessment of risk benefit.

I can imagine that a middle ground might be a process that is somewhat iterative, that is somewhat more -- a somewhat more extensive explanation of what we mean by what the goals are of the review of a committee. And one of those things might be to say one of the goals is to make sure that there is review by people who can put themselves in the subject's position.

And another goal is that there is review by people who are technically competent to provide advice as to the particular degrees of risk and benefit and methods of minimization, et cetera.

So a little bit more specific than what we have here but iterative in the sense that those goals are then sent to the foreign institution with a set of questions saying how is it that at your institution you achieve these goals. It can be sent back to the United States now in a -- it is now much less insulting. It is a this is how we do things. These are the substantive standards we use. If you share them, how is it that you achieve them?

And it may be that under some circumstances it will have to go through several iterations before there is enough information for people to be comfortable with it.

And if that kind of iterative process were uniformly incorporated into the MPA's that are negotiated in the United States and uniformly used by all agencies, we could, in fact, allow for a fair amount of delegation and kind of cross authority and buying into somebody else's prior approvals with some confidence that you have the same substantive standard being used. One that is achievable, flexible and yet is not so vague as to offer up the possibility of evasion or mistake at a very high frequency.

DR. SHAPIRO: Eric, did you have a question?

DR. CASSELL: I was not exactly sure what the function of the example was. Now I have heard about five different functions of the example. But it did seem to me that it was related to what we are trying to talk about, which is how, in fact, to get a set of standards in a different setting. And that in this instance what we were being told was that it is the nature of the standard that counts, not exactly which agency oversees it so that if they meet our procedural standards, even though they may be the equivalent of

Rotten University in 2000, by 2010 they may not be. So I took that as an example of that rather than as an example of all the other things which so got me confused I just could not keep my eyes on it.

DR. SHAPIRO: Eric?

DR. MESLIN: I just wanted to remind commissioners when we spoke with Tom Puglisi from OPRR and asked him a number of questions, all of which are repeated in the briefing book, about how knowledgeable the parties are that the negotiation of an assurance is actually a negotiation. His answer was, "They probably do not realize that it is in negotiation."

So Alta's point about this middle ground, while well taken, and I am not arguing OPRR's point but they might say that is what we do now. We do have a discussion. That is what the context of negotiating an assurance is. We do it domestically and we do it internationally.

As a point of information, commissioners are probably aware that OPRR is undergoing a review and a revision of its assurance process so there will only be two of these, a domestic and an international. It is unclear whether that procedural simplification will change the fundamental question or issue that you have raised, Alta, which I take to be for the commission's

consideration should there be a directed recommendation that says here are the kinds of disclosures that the individual organizations who are negotiating the assurance must mutually make to each other. Or at least these are the disclosures that the Federal Government on behalf of the assurance making process and the equivalent protection granting process must make to the other party.

This is a negotiation. You are allowed to change the terms of the negotiation if by mutual -- I mean, I am not a lawyer but it would seem that in Tom Puglisi's responses, he evidenced a potential solution. It is not simply let's find some common ground. What they have been telling us is the reason they do not fully disclose that it is in negotiation is if it turns out that they grant equivalent protections, they are giving up the ability to oversee, monitor and assure compliance with U.S. regulations.

And given that framework, it is not surprising that they do not share widely or go out of their way to disclose what they give up by negotiating the terms and conditions of that equivalent protection model.

DR. SHAPIRO: Alex?

PROF. CAPRON: Two points. First, I think we need to have a UNAID --

DR. MESLIN: USAID.

PROF. CAPRON: USAID. USAID to tell us what their understanding of a situation like the Hopkins situation is.

You gave one answer that led me and Larry to have one impression as I understood it, and then you said but that was not what you were saying. I would just like to be clear.

Beyond that, it seems to me in terms of organizing the materials, I have suggested to you a moment ago that you change current practice to OPRR practice. I want to take that back and say that we set out as one model the SPA model, which we can say in the text is something that OPRR is using now.

Another model is this delegated recognition. In other words, that is what USAID uses vis-a-vis the U.N. recognized agencies, if I understand you. It is also what I understood your description to be the Hopkins example. If Hopkins has an MPA and recognizes this, that is the delegation model.

And the third one is the development of criteria, which I think Alta was doing a nice job of suggesting what those could be. In other words, using the language of the existing regulations to come up with something.

Eric, I would disagree that that is just a matter of whether or not that is a negotiation.

There is a whole difference in tone of what Alta was saying versus here are regulations, how do you comply.

One says here is what we are trying to achieve. These are the considerations that we look at. What do you do?

And then the judgment can be reached that is it or I have to ask you more or we have decided we could ask you if you could do something else because we do not see anywhere in your process something that is of importance to us.

And that, to me, would be something which, as she says, could then either be applied at the agency level or it could be applied at a different level if we thought that Hopkins with this kind of guidance in its MPA could do that as a delegated function. That would be different than what I was just describing a moment ago as the present -- my understanding of what you said -- is the present delegated thing, which is basically we think you do a good job and if you find it equivalent that is fine.

Because unless we have spelled out criteria we do not know what either the agency or the institution

is using to reach its judgment.

It seemed to me that that was a useful approach and it is more, Eric, I would suggest, than whether or not you know it is negotiable.

DR. MESLIN: We are not -- well, I will let Alta make her point.

PROF. CHARO I have got to say actually that was not exactly how I heard what Eric said.

DR. MESLIN: Right.

PROF. CHARO I thought he was explaining a little bit more about OPRR's stance.

DR. MESLIN: Right.

PROF. CHARO But these things -- I must say they suggest a few other things to me as I am listening to this.

First, as a commission that sits to think about questions of ethics but in the context of public policy, I am never sure when we have kind of exceeding our jurisdiction and our capabilities because the OPRR practice, which has been fairly prescriptive, is one that is premised, in part, at least, on the concerns about administrative feasibility.

It is simply easier to have a checklist so that you know whether or not what you have is an equivalent beast or a nonequivalent beast. The SPA

mechanism, which then, in turn, refers back to the very detailed requirements that are set forward in the Common Rule provides such a checklist.

And bureaucracies, even well funded bureaucracies, tend to like this kind of certainty. It allows for tasks to be done in a fairly mechanistic fashion with a high degree of consistency from one event to the next.

What it sacrifices, as we all know, as individuals who have been the victims of many bureaucratic procedures that seem to be not quite right for our situation, is that it is also inflexible, occasionally insulting, and often infuriating.

And the iterative process that I was describing is labor intensive. It requires a lot of judgment and it involves a lot of trust.

Now it seems to me that there is a question as to whether or not it is within our capabilities to make an assessment as to whether or not the bureaucratic concerns, which are legitimate, because the government cannot run without something to make the work just kind of churn along, whether those really are -- whether they rise to the level that they are, in fact, more important than the loss of flexibility and respectful relations that seem to be entailed in it.

The second thing is that if one wanted to move to a system that was based more on this kind of judgment call by agencies or IRBs, that the responses they are getting to a list of questions about how do you accomplish your goals are adequate, but that again relates back to the work being done on the domestic side of the commission.

Because to the extent that we move towards a system in which we certify IRBs or accredit IRBs, we have more freedom to move to a system that revolves around trust because we have the ability to test the IRBs in the accreditation process like we do under the Clinical Laboratories Improvement Act where you send samples to a lab and see what rate of errors come back. The accreditation process may have sample protocols that involve a kind of created set of letters back and forth with a mythical foreign IRB and they allow the IRB that is looking for accreditation to react to them and to be evaluated by the accreditors.

So the more that we work on that end to strengthen the ability to have confidence in the IRBs, the more I think that we can move away from the prescriptive practices that we now seem to be saddled with.

DR. SHAPIRO: Let me make a couple of comments

here. One, it seemed to me -- when I read this I focused on another issue, a completely different issue as to how I felt about these things.

I focused on what is probably an irrelevant issue from everyone else's point of view, namely whether the demanding equivalence was what you wanted to stick with.

That seemed to me to be the most important issue here. Not whether we thought that was a good idea, a bad idea. So I think we ought not to rush past it. It may be easier to decide, yes, that is good or at least equivalent. Whatever the language says in here. But it seems to me we ought to be comfortable with that first.

What we have been discussing is how on earth do you go about figuring out whether it is equivalent. And we seem to have a couple of different processes here. One is either an SPA or an MPA process somehow that you sort of apply for a license and you get licensed to do these things.

One is, I guess, US -- that is USAID uses -- calls U.N. procedures equivalent just by definition, as I understand what is said in here. And the other is various ways to figure it out case by case basis or class by class basis.

And so I would like to see if anyone has any concern, first of all, about the equivalence. First of all, whether that is the right criteria for us because that is going to feed back in a much more important way to what we have to do in these other chapters. Whether we really think equivalence, substantive equivalence, not procedural equivalence, is really the right criteria. That is going to determine a lot about what happens elsewhere.

Now maybe there is no issue here so maybe we just want to --

PROF. CAPRON: What is the alternative?

DR. SHAPIRO: Well, the alternative is, as will come up in other chapters, is that you go to other kinds of countries where you have competing ethical requirements and not just this ethical requirement, and they interact with each other in different ways. So I do not think it is at all obvious. I actually am uncomfortable with equivalence myself but I do not think it is all obvious that that would be the case.

PROF. CHARO You know, actually I think that the discussion about the procedures one would use for checking how other people do things could be used both for a system in which we are demanding substantive equivalence or for a system where we are demanding

something else. That is really about how you figure things out.

DR. SHAPIRO: True enough.

PROF. CHARO But it is possible that the word "equivalence" has been misleading and that a more appropriate word would be simply "adequate" protections.

Because I think what we are trying to find here is the core set of values that we will not relinquish and a core set of concerns that -- the core set of protections without which we would not permit American investigators who are somehow covered by U.S. law or sponsored by the U.S. Government to collaborate.

And it may be that that is considerably less than what is now considered to be equivalent. But if we could identify that core -- and in some ways I think that is what the AID's substantive application of three pillars was an attempt to do. They said, this is what we think the core is.

But maybe we should not call that equivalent. We should just say this is the "adequate" set of protections, beyond which we think it is bells and whistles.

DR. SHAPIRO: Larry?

DR. MIIKE: I was prepared to argue with your

characterization of your point that we have to do substantive equivalency rather than procedural equivalency because I get lost between the difference when we actually look at the application.

I guess what we are forgetting is that -- in this discussion about equivalence is that when we talk about other specific policies and recommendations in our international report we are not talking about equivalency, at least between the U.S. standards and foreign based institutions. Because we are looking towards flexibility in giving them autonomy rather than just sort of bulldozing over them.

So that is one thing that we have got to keep in the back of the mind in this discussion about equivalency about what we are doing in the other areas because it is -- to me, we are not going to be able to say "equivalency" given the direction that we are going in, in the other areas.

The other part is that what draws heavy on me in this discussion is that our oversight process of a project is going to greatly influence what we can say in this project because I would move more -- since we seem at the same time in the oversight project to be saying we want to expand the range of activities that should be covered by the Common Rule, at the same time

we want to relieve the IRBs of burden.

So like, for example, my unanswered e-mail was that I threw out as a proposition all minimal research is expedited review. I mean -- so, you know, we -- in many of the kinds of things that we are going to recommend in the oversight process, I mean the project, we will relieve the kinds of burdens that we think we might be imposing in the international sphere.

As long as we are not -- we do not sort of try to juggle those two in our minds, I think we are going to be sort of stuck in this international project because we are not really considering, in a systematic way, a way of streamlining the process so that we can focus on some things in this area.

Because clearly what we have got to do is say which are important areas of research that need a lot greater oversight and which are the areas that we can have more like a checklist process for that.

DR. SHAPIRO: Alex?

PROF. CAPRON: To answer the question that you posed and Alta's alternative about adequacy, I guess my sense is that we have to see the regulations we are talking about and the process we are talking about as part of the governmental system.

This is a system in which we are gathering

together resources for what we consider activities in the common good and we expect them to be expended in ways which meet standards which have undergone some kind of a publicly accountable process.

It took ten years to come up with the Common Rule and years before that, in part, because it was a process that a lot of people consulted on and had a certain amount of transparency and went into the Federal Register and got a lot of comments.

And the people's representatives in their oversight function over the Department of Health and Human Services, and all the 20 other agencies that sponsor research, have a way of holding the people who do this function on an administrative level to some standard. And they can look at that standard and they say it is spelled out here.

Now you have got something else, we are spending our money abroad, and we recognize there are going to be differences. How do you know if that is all right?

The notion of equivalence, as vague as it is -- if we say that all these standards and rules and procedures that we have are aimed to achieve a certain ethical result, then with more or less refinement as to how you get to the conclusion, you end up with a

conclusion that somebody else is doing something that is the equivalent.

If you use the word "adequate" in here then you put back into play the thing that took all those years to refine. What is an adequate system? Once you come up with it, why not use it rather than open up again to each new person's even broader ad hoc judgment?

Well, I think this is adequate. Well, no, I think that is adequate. No, that is more than adequate. You do not have to require it. Do you see what I am saying?

It seems to me that it is -- these rules have to be seen in the context of an administrative delegation, a legislature has given along with the funds that go and the employees that go with this, to an agency. And the agency has spelled it out.

To the extent you back off to vaguer language, you give the people, who are ultimately trying to exercise oversight on behalf of all of us, much less to go on as to know what that is going to mean as it plays out.

So, I guess, I would not reopen the equivalency, the at least equivalent language, Mr. Chairman, at this point.

DR. SHAPIRO: Could I ask a question? Just from the point of view of having to move us forward on this. What is the substantive benefit from having to choose one of these options?

I can imagine them all working. I can imagine any one of them working. Item three, of course, we would have to develop the criteria. If you wanted to develop some new criteria but would have to specify them. But if we stick with equivalent -- I do not want to get into that. I actually prefer the equivalent also.

But without worrying about that argument, why is it necessary for us to say an SPA or an MPA process is not so good, a USAID type process is good? I am just sitting here -- I can imagine them all to work.

DR. MACKLIN: I hope I can answer that.

DR. SHAPIRO: Okay.

DR. MACKLIN: Okay. But again just to step back to put it in context. This is the chapter on "enhancing international collaborative research."

We have heard from this possibly ill chosen illustration, but also testimony in the last six months that there are barriers, there are things thrown up that make life difficult for otherwise well meaning people who want to adhere to ethical standards, and are

seeking to do so.

But that the particular process, which is almost idiosyncratic because it involves a few individuals making determinations about -- as we have heard -- rather than either a set of criteria or as I would describe the USAID model. I am not sure how it works but under this three pillars.

These are what I would call criteria of adequacy for equivalency. They are not equality, which is what -- well, I mean, that is a sort of philosophical term.

DR. SHAPIRO: Yes.

DR. MACKLIN: But it is not equality which is what OPRR is looking for in making its determinations. You have got the same number of people on your IRB, do you -- that is equality.

DR. SHAPIRO: I agree with that.

DR. MACKLIN: Equivalence is, therefore, looser. And one of the advantages of our choosing is to ask whether the -- what is described as the de facto practice, is so rigid, so inflexible, that it is throwing up barriers where they need not exist and they are not helping to protect human subjects. That would be a reason for saying look at all these problems we have with the current system.

Albeit difficult, the third, development of criteria need not involve this body getting down and doing it but it could be, as in other recommendations -- other reports, recommending that someone develop these because they would be -- these criteria would be likely to ensure the protections we think should be there without requiring the equality and what seems to be -- to a lot of places to be an imperialistic imposition.

PROF. CAPRON: And, also, I mean if the SPA approach is too rigid, the uncriteria equivalency may be too --

DR. MACKLIN: May be too loose.

PROF. CAPRON: -- loose.

DR. MACKLIN: Yes.

PROF. CAPRON: So, I mean, the criteria says, well, we are -- again, I get to this delegated function. I know how you are going to make the judgment. I do not have to oversee your judgment every time. But I know how you are going to do it. You have told me how you are going to do it.

But what are you going to look to?

DR. SHAPIRO: It seems to me that -- I mean, I agree with the point that you make regarding equality and equivalency. I think the way you have described the

current -- if I can call it the current process or the SPA process, whatever we are going to call it -- it just means that it has been carried out in a kind of mindless way.

Any one of these things carried out in a mindless way will look mindless at the end of the day. So maybe we can construct language that would allow for a certain amount of flexibility here but lay down, I guess, some criteria or some language that would say, you know, thoughtful judgment is what makes these things work well.

DR. MACKLIN: But, Harold, excuse me. But that actually goes to the question of whether we think equivalent protections should be the criterion.

DR. SHAPIRO: Yes.

DR. MACKLIN: The regulations say equivalent protections but the office that does this has side stepped that language or that approach.

DR. SHAPIRO: I understand that. I agree with that. I agree with you.

DR. MACKLIN: And that is why we might be able to recommend something if we think that one of these is superior to the other.

DR. SHAPIRO: I am going to say this one more time because I am not expressing myself very well. I

think the so-called SPA approach is not bad in principle. It is just the way it is currently operated is inane. That is how I would describe it. That is to have this kind of attempt at equality, if you like, is the wrong thing to do. It is not equivalence. Just as you have said.

And they have gotten themselves into a way of dealing with it, if I understand what is being said here, that is just not very wise. It is not that in principle it could not work well. It is just that they are implementing it in a way -- and that is a problem always with any kind of agency which has to administer things over time.

So I would argue for -- I guess it is item 3, with flexibility. I think there are lots of ways to go at this which get you equivalence. And we ought not to try to narrow it too far.

I mean, I like the idea of giving some notions of things that we really care about but we ought not to narrow it too far and let people -- even different agencies find equivalence in different ways providing there is some criteria around on which they can center their judgments.

I mean, that is my reaction. I have said enough on this.

DR. MACKLIN: Could I --

DR. SHAPIRO: Yes, go ahead, please.

DR. MACKLIN: Well, I do not want to respond to that now but I just want to point out with our relatively short period of time --

DR. SHAPIRO: Okay. We will --

DR. MACKLIN: -- there were two more pages we thought we might look at here.

DR. SHAPIRO: Fine. Excuse me.

DR. MACKLIN: That is okay. No, I mean -- I do not know if we have heard enough.

DR. SHAPIRO: I think we have heard enough.

DR. MACKLIN: Because you know what we have to do is we have to now write something.

DR. SHAPIRO: Right.

DR. MACKLIN: For the next meeting.

But we certainly collected the views and have those notes.

Now I am prepared actually -- I do not want to deal with the wording of this. I am a little hesitant. But the very next page, that is page 3, goes to two different concerns. The first, which is a very -- merely procedural and we would have to spell out a lot more, which would be recommendation number one. I am just going to walk us through this and then come back.

DR. SHAPIRO: Okay.

DR. MACKLIN: The inclusion of a new section applicable to research sponsored by the U.S. in resource poor countries that takes into account the context and circumstances in those countries that differ from those in industrialized country sponsors.

Now what that is -- I mean, it is hard to take this in isolation but what this would be is right now we have the U.S. Federal Regulations. They say nothing at all about what you do when you do research in other countries, particularly the resource poor questions -- countries.

In one of the clarifications and explanations that is going to be in the first -- in chapter one, which arises from the many confusion and appropriate questions that have been raised, is how many of these recommendations that we have throughout these chapters should apply in general. Or which ones should apply in general and which ones really are geared to resource poor countries. That is where there is a great difference between the wealth and what can be done in other countries.

So if there were -- and one way of doing that, which we hoped to spell out in chapter one, that is to say some of the recommendations in this report deal

with any kind of collaborative research. Whereas, others are specifically geared to what happens when the United States supports research in other countries.

So what this would be, would be simply a recommendation for an inclusion of a section in the research regulations that would then be able to implement some of the specific recommendations that may come out of this report that are peculiar to the resource poor countries and do not apply generally.

Now we cannot act on this now until we finally decide on all those recommendations but this is a suggestion for how to carve out an area.

And the second, not unrelated but it has to await some kind of consensus here, and it should be number two. It is at line eight. There should be a number two. That is the second way in which there may be a recommendation to expand the regulations.

The use of equivalent protection mechanisms to ensure that the U.S. recognizes the legitimate authority of other countries to follow their regulations and guidelines that afford equivalent protections to research participants even if -- and this word I want to underline -- even if the procedures in those guidelines differ from those in the U.S. regulations.

So if there is some spirit -- if we can get the spirit of that, we do not have to tinker with the wording, but this would be the recommendation.

Now that is all I want to say for the moment about the recommendations.

The last item here is questions arising from the chart. All right. And here because we saw the chart, Stu highlighted some things, and we have these. Now we have to say what do we do about these things that we found. Do we ignore them or do we do something about them?

And here are the three areas once again that Stu highlighted when he presented these. The first area is substantive ethical principles or standards articulated in other documents that are absent from the U.S. Federal Regulations. And we might have to go through the entire list. Stu gave us a little sample. And ask are these principles or standards reasonable and desirable? If so, should the U.S. Federal Regulations be amended to include them?

And this is again mindful of the fact that our regulations or the current ones we are using were drafted in -- well, they were written before 1991. I mean, it is basically from 1974. So we have got 25 year old regulations and all these other documents are

more recent.

Then there is the second and third obvious. Ones that are articulated in U.S. Federal Regulations absent -- I am sorry. Yes. Absent from other documents. And the third, the categories that are present in other documents.

So that would require, of course, a very detailed look but there is an in principle question here. Do we want to deal with this at all in this comparison and see whether some places have done things better or have things -- have principles and standards in them that we do not know.

DR. SHAPIRO: I have some comments on all of those things. With respect to the latter, that is the sequence of questions to come out of the chart so to speak, I think it would not be responsible not to catalogue these and decide which were important and substantive and needed these questions to be answered because we cannot assume we know everything or got it all right the first time.

And it seems to me that we ought to review it. I mean, it takes a little work but we should review it and decide which are important differences. There must be small differences which we could put aside just for purposes of not -- you know, not having time to get to

all the details here. But if there are ones that appear important, we should make a decision regarding these various numbers that you got listed here because they all seem like sensible questions to me. And I would certainly like to know the answers to these questions.

Now what will end up in our report I am not sure.

And Larry wants to ask a question but I want to make one more comment.

With respect to the earlier recommendation -- part of the recommendation, which you do not really want to deal with now, that are on the top of this page, page number three -- I will just give you my own quick reaction to them.

One is the second one, which is that we would recognize that if other people have ways to get equivalency, that was fine with us. I certainly feel very positive about it just as a reaction to that.

The first one is the one that has given me trouble right from the start and I have not -- still do not have it worked out in my mind, and that is my problem because I do not know that anybody else has a problem. And that is I think one needs a well articulated rationale for dealing with resource poor

countries in some different way.

Now there may be a very good rationale but that is what I am waiting to understand. I have not found one yet. And so I would just leave that out there for the time when it comes to the talk about that.

Larry?

DR. MIIKE: Well, I agree with the use of equivalence in the discussion that we had prior to this very end. I do not agree with the use of the word "equivalence" in these areas because what they really are --

DR. SHAPIRO: Which areas? The ones on the bottom?

DR. MIIKE: The ones on the bottom here because what we are really talking about here is that there are some documents that include these things.

DR. SHAPIRO: I agree.

DR. MIIKE: It does not necessarily mean that we --

DR. SHAPIRO: Absolutely. I agree with that.

DR. MIIKE: And I think that we -- I think we have gone over actually your last point in the past discussions about what makes these undeveloped countries special that we might treat them in a

different way.

DR. SHAPIRO: Okay.

DR. MIIKE: But I think also that when we address these issues they need to be stratified in at least two or three ways. One is that -- whether we say that these should be formally adopted in regulations that become the force of law and others where we might want to urge certain kinds of things.

For example, one that comes to my mind is the compensation issue. I do not know if -- I see some in here that I would say we do not need -- we should not address it.

DR. SHAPIRO: I did not mean to say that we should start including everything that is in there. We should just look at it and decide whether, you know, that is something we should pay attention to or not. I mean, I agree with that.

DR. MIIKE: And I also would add what everybody has said, which this is really helpful. It just sort of takes that enormous amount of information down to some readable level.

DR. SHAPIRO: And they are sensible questions to ask. Okay. Any other comments on this particular aspect?

Okay. I am going to suggest we take a ten

minute break and then come back and -- do you want to move next, Ruth, to the chapter four?

DR. MACKLIN: Yes.

DR. SHAPIRO: Okay. So we will move back -- we will move to chapter four after the break. Let's try to assemble about 20 till.

(Whereupon, at 3:28 p.m. a break was taken.)

DR. SHAPIRO: Okay. Let's move on with our discussion. We want to turn to the material in the draft of chapter 4 and I am going to turn to Ruth in a moment.

Before I do so, Eric, you have a comment you want to make?

DR. CASSELL: Let me wait until everybody is back.

DR. SHAPIRO: You want to wait until everyone is back.

PROF. CHARO And when you do, would you use the microphone? It is a little hard to hear you.

DR. CASSELL: I am going to do that, too.

PROF. CHARO Thank you.

DR. SHAPIRO: I may not call on you again, Eric. This may be your last chance.

DR. CASSELL: It may be after I say what I say. It may well be my last chance.

DR. SHAPIRO: All right. We will wait until later.

Why don't we then begin our discussion of chapter 4?

Ruth?

OBLIGATIONS TO SUBJECTS, COMMUNITIES, AND COUNTRIES IN WHICH RESEARCH IS CONDUCTED

DISCUSSION WITH COMMISSIONERS

DR. MACKLIN: Well, I was hoping I would not have to begin the discussion.

DR. SHAPIRO: Well, what would you like us to do?

DR. MACKLIN: Chapter 4 is now -- I believe the commissioners had seen an earlier -- a shortened version, half -- about half of it. I am sorry. About half of it with some attached -- some recommendations that were imbedded in it.

That section is almost unchanged. It was the first 18 or so pages. And what we have now is the proposed complete chapter and the new section, quite lengthy, to which we owe a debt of gratitude to Alice Page, who did all of the research and all of the writing basically.

It is the section that begins on page -- prior agreements. What page is it actually?

DR. SHAPIRO: 17.

DR. MACKLIN: 17. Okay. So I think what would be useful is if we focus the discussion on prior agreements, that is on that entire section discussing the background, the arguments against prior agreements, the rebuttals to those arguments, the current examples of something that look like or approximate prior agreements, and then also before we are finished today go back and look again at the recommendations that are imbedded in this chapter.

Because in order to complete any chapter we need to hear once again what the recommendation should look like but I think it would be useful to start with the new section, which simply follows from the rest and then go back to the recommendations.

DR. SHAPIRO: All right. So let's begin our comments, as Ruth suggested, on the material following page 17 up until roughly 35, if I remember correctly, which is where the recommendations are. We will come to the whole subsequently. Presumably we come to the recommendations, that will take us automatically back to the first part of this chapter because the recommendations -- at least some of them come from that area.

So let's go to the prior agreement section.

Eric?

DR. CASSELL: Well, this is sort of an antecedent to that. I just want to confess that I have lost my sense of the direction of this report. I think it is one of the most crucial reports that will give as a commission.

This chapter is primarily -- seems to be primarily about resource poor nations and it has us as distributing the largesse of others besides ourselves in a way that I think is unrealistic but that is to be argued later on.

So this is one section. I cannot see how it entirely relates with the equivalency discussion we just had in another section. I would -- it may be but I would feel a lot better to see if a few pages that say this is the focus of this report. We want to do this, this and this, and we already have enough to know what it is the report should accomplish in those few pages. What it is it is trying to accomplish without the arguments that back up that. The arguments are in the chapters themselves.

I do not know. Maybe everybody else is absolutely clear about all of this but I certainly am not.

DR. SHAPIRO: Well, I will not test everybody

else on the commission right now but I think we can expect what I think is chapter one over the next few weeks, which will be in your hands.

DR. CASSELL: Yes, but I think even without chapter one or without the whole chapters, it ought to be possible, like you do in an introduction, or one mostly does before one writes chapters --

DR. SHAPIRO: Yes.

DR. CASSELL: -- to say this is what I want to say in this chapter and this is what I want to say here so that I, as a commissioner, have some idea of what the total direction of the report -- of this particular report is and what its main points want to be without the arguments that support them.

DR. SHAPIRO: You will have them.

DR. MACKLIN: Well, I guess the only thing to say -- I mean, really all of that will be laid out in chapter one, which is in a way an introduction but will have a lot of elaboration.

The only thing I could suggest at this point -- and I can see why you may get lost because we have not been going in order in some of these chapters -- is to go back to what was the original outline.

I am actually quite surprised when Alice and I work on this to see that we are pretty closely

following that outline. At the first meeting when this report was discussed, the commission looked at the outline, made some very helpful suggestions, and in principle seem to have endorsed the outline for the report.

So we have basically been following that outline with the understanding that the way it was laid out and the justification for doing it were kind of in there. Now I do not know, maybe I am wrong.

DR. CASSELL: May I follow up? Is that all right?

DR. SHAPIRO: Yes. Please.

DR. CASSELL: Well, I mean, in the last little while of our discussion, we have moved our position somewhat so that we now look at ourselves not as -- I am going to make this overly simple -- not as dictating what we want other people to do but it is to try and define the equivalence for the principles that we agree should be followed on the one hand.

And another time, unless I am mistaken, the conversations we have had before, we have been putting limits on the obligations of -- particularly drug company type research organizations -- to give benefits to the population on whom their work is done and follow-up and so forth.

And yet when I look at this stuff, I do not see those changes. I just do not see it. Now it must be that I am not reading it properly but the general tone has not changed and it certainly does not reflect my own understanding of the commission.

DR. SHAPIRO: I appreciate those remarks but even taking those into account, I do want to turn to the prior agreement section.

DR. CASSELL: Now, we turn to the --

DR. SHAPIRO: Yes. And then we come back to that as we have time for it.

So let's now turn our attention to the prior agreements part of this chapter, which is from 17 on, until the recommendations come in the mid 30's somewhere.

Let's see if there are comments or questions from members of the commission with respect to that aspect of this chapter.

Any comments or questions?

Alta?

PROF. CHARO In the section on prior agreements there is a really nice collection of arguments for their use and criticisms about their use. But implicit in that -- sorry. Implicit in that, I think, is a link to something else that may seem more

central to the commission's recommendations.

And that is the suggestion that has been made, and I think has been the subject of some consensus, that research done in -- at least in resource poor countries, and I put an asterisk on that, Harold, because I know you have got questions about why we focused that way -- but research done in resource poor countries should not be done there by Americans unless it actually addresses a genuine health need of that country.

In other words, we should not use these populations simply as surrogates for U.S. population that would be equally useful to answer a scientific question.

Now to say something is genuinely responsive to the health needs of that country, I think, incorporates the notion that it is not only responsive theoretically, that is we are going to find a new cure for chloroquine resistant malaria, but that it is also actually responsive in the sense that once that cure is developed, it will actually become available and be used. Or at least that there is a good probability of it for at least some substantial number of people there.

And in that sense the prior agreements which

focused to some extent on promises to make things available at a cost that is manageable, I think are part of what makes the research genuinely address the health needs of that country.

So I kind of see these things as linked. I see the arguments as being linked. I do understand that that does not incorporate things like suggestions that there be a buy off in terms of tech transfer or nonhealth related donations of other sorts to the country.

But on the issue of essentially wrap around care but wrap around care in the form of economic availability, I do think maybe we should not have to separate prior agreements so dramatically from what it has already become, a kind of central principle of how it is that we conduct research abroad, and that is only when it is actually useful to those people.

DR. SHAPIRO: Alta, could I offer even -- just to get it out once and then bury it -- an alternative perspective on that?

I have been trying to think through this issue of why it is ethically unacceptable -- to just put it in the grossest terms -- to do research in some country because it is cheaper to do it there even though it may or may not have anything to do with any health problem

in that country.

On way to argue this is to say, look, it is the -- it is what I call the -- it is another part of the issue of why do we make computer chips in Southeast Asia instead of Peoria. Nobody thinks that is unethical as far as I know.

And, therefore, why couldn't we do this somewhere providing we are not exploiting people? Okay. And providing everyone is appropriately compensated for whatever it is that they need compensation for.

And what is it about this medical research, which is different from access to health care, which is a different matter all together -- what is it about medical research that says, no, that does not operate in this case. Fully compensating people is not enough. That it has to have -- we want to achieve some other objective -- other social justice objectives here. I think those objectives are worthy. I support those objectives but I do not quite understand why we tie them together in this way.

PROF. CAPRON: Mr. Chairman?

DR. SHAPIRO: Yes.

PROF. CAPRON: Let me give a partial response to that.

DR. SHAPIRO: Yes.

PROF. CAPRON: Partially analytic and partially sort of phenomenological.

The analytic part would be I think it is possible to distinguish between paying people for their labor and paying people for their bodies. And that if you carried the view that you are pushing far enough, it would be possible through economic compensation, making it "worth their while" to use people for research that is highly risky where the benefit to them is that they are not able to feed their family or, better than that, educate their family or whatever.

And they enter freely into that exchange.

And that seems to me -- it is possible to say that there is a difference between that if it is working long and hard hours versus being injected with a substance which may cause you to become very sick and die from that injection.

The more phenomenological is just there is a way in which biomedical research carries into it something of the traditions of medicine itself. And in that context, again there seem to be relationships between the stronger party and the weaker party, the dependent party, and the other party, the knowledgeable party, the scientific party that are different than an

arm's length relationship between an employer and an employee.

And obviously even in the employer-employee relationship in the industrialized countries, we now impose limits on what offers can be made and the ways in which that relationship can take place and certain practices that are unfair, labor practices and so forth and so on.

But it seems to me that particularly in the ethics of medicine, we regard some things as being unacceptable even if you could get someone to agree to do it as a doctor.

DR. SHAPIRO: Right.

PROF. CAPRON: And we bring that into the research relationship. So there is a difference.

DR. SHAPIRO: Yes.

PROF. CAPRON: It may be a reason why we would say even if you could go and set up a factory there and pay wages which no American would accept but the people there would gladly regard as fair compensation for their time, you might not say that research which you could do much more cheaply there of a biomedical sort, but which has no relevance at all -- it is an entirely Western disease, a U.S. disease, and you are just testing out something there.

DR. SHAPIRO: Okay. I understand. I think I understand and appreciate those arguments, although I think that sometimes these arguments have their own little mystique about them that we sort of carry on over time. This kind of almost legend about how people -- how doctors and patients relate to each other and so on.

But I do think there is something to those arguments and so what that leads me to say is that we ought not to be too rigid about what we mean here with respect to obligations. This is a complex issue. It has some of those elements in it but it has other elements in it and, therefore, when we talk about the reciprocity that is undoubtedly a part of all this, we ought to have some flexibility in how we interpret it and not be too rigid.

PROF. CAPRON: Well, I mean, let me -- I do not think it is -- I am sure the arguments have -- carry with them ideas which are not carefully examined but let me just give you one that is relevant to this.

If we were talking in a medical context, I believe we would regard it as unethical for a physician to say I am going to stop treating you now because you cannot pay for this treatment anymore. As an

individual physician.

Whereas, if I am running a company and have been supplying you with parts, I gather it is quite acceptable I am not going to ship any more parts because you are not paying your bills. And there is -- I do not think that that is a mystique or surrounded -- it is something which is an explicit ethical requirement, which is actually backed up by law.

Abandonment of a patient is not acceptable in the middle of a treatment, providing your professional services. You can work your way out of it and transfer to somebody else but you cannot simply abandon and walk away from your patient the way two businessmen can walk away from each other because the one is not paying the other.

DR. SHAPIRO: Eric, did you want to --

DR. CASSELL: See, I think that there is a basis for this in benevolence. Along the moral basis for that is that there is a long history of benevolence and the action of the physician in taking care of someone does require that. Being stronger, the other person is sick and so forth. It creates certain obligations. Alex has actually mentioned one of them, that you cannot abandon a patient without making arrangements for the care that follows that up.

Now, on the other hand, in this particular instance it is -- we are talking about the treatment of persons with diseases, some of whom will get an active treatment, which we do not know whether it will help them or not but without that they will get no treatment. And the others will be as they were before, requires that they be treated humanely and that they have the right to participate, to give consent and so forth and so on.

But I also do not know why I am required -- I certainly would not be required in the case of an individual patient to keep on treating them and treating them and treating them. There are limits to it. Abandonment is if I just stop.

But if I say I can no longer treat you, you know that there is a limit to that.

PROF. CAPRON: I was not arguing for the obligation discussion at the beginning of the chapter. I do not think it carries the day. I was trying to say to the chairman I do not think his analogy to --

DR. CASSELL: It is not -- that is right. There is a difference.

PROF. CAPRON: The analogy to saying simply because we have no problem with a corporation deciding to manufacture some place where labor is cheaper, then

we could say we have equally no problem with U.S. researchers going to find the cheapest subjects that they can find. I think that there -- I have tried to suggest there are two differences here. One having to do with the body as opposed to labor and the other having to do with the fact that medical research is in some sense a subset of medical -- physician-patient relation.

It is not perfectly. In fact, one thing that I am strong in arguing for is the notion we ought to separate the actual person who does one from the person who does the other but that tradition -- that is why I say it is phenomenological. We do sort of carry it over. It is regarded as it is doctors who do the research and we carry over.

DR. SHAPIRO: I understand what you are saying but -- and I do not want to take any more time on this but it seems to me still that --

DR. CASSELL: Except it is the crucial underpinning of the chapter so it really deserves some discussion.

DR. SHAPIRO: But we want to get the prior agreements part. That is what Ruth wants to talk about. I just make a bigger distinction in my mind between research and care. But in any case, let's go

on to the prior agreements part of this.

Alta?

PROF. CHARO Well, actually what I wanted to say by way of response to you is pertinent to the prior agreements. Because although I do not necessarily disagree with what either Eric and Alex were saying, I come at this from a slightly different point of view that is somewhat divorced from the medical context. And as equally applicable in the labor area as it would be in research.

You said that you wanted to hear arguments about why it should not be acceptable so long as you are not exploiting people. Well, that is a premise now.

DR. SHAPIRO: Correct.

PROF. CHARO So the question is what constitutes exploitation.

DR. SHAPIRO: Correct.

PROF. CHARO At the risk of repeating something I think I might have said a number of months ago at the earlier stages of this project, people like Werthheimer and others that have written, I find, very useful pieces on the nature of exploitation make a distinction between offering people opportunities when they are in dire straits that are not caused by the

person making the offer. That is there is somebody who is in a bad condition. I had nothing to do with it and I give them an opportunity. Versus having created somebody's dire straits and then offering them a Hobson's choice.

So that in some sense the fact that we observe the people in some of these countries are in dire straits, economically and physically, requires us to answer the question as to whether or not we, who live very comfortably by virtue of our birth in the United States, do have responsibility for the creation of those dire straits.

And I think there is room for legitimate disagreement in the degree to which people view themselves as complicit in the conditions in those countries. I can say that I never consciously made an effort to make conditions in those countries worse.

At the same time I have benefitted on a daily basis from those conditions because much of my lifestyle stems from the ability to take advantage of these differentials in things like wages to produce consumer goods that I then purchase at a nice affordable price. This has been at the center of, of course, some of the discussions in the context of sweat shops.

Because I personally view myself by virtue of having benefitted from these conditions, just like I view myself as having benefitted from histories of discrimination against certain populations of the United States, I then see myself as being no longer permitted to make offers without having to take some responsibility for the situation people are in when they are asked to make a choice as to whether or not to accept the offer.

So for my point of view, to give somebody the chance to make money by being a surrogate research subject, a surrogate for somebody who is better off and better educated and better positioned to say no, is, in fact, to exploit them because it is to take advantage of a condition I am in part responsible for.

That is why offering through prior agreements some kind of long term connection between the research and what will benefit that population takes away the exploitive capacity. We are not just using people because they are surrogates but we are, in fact, only working on things that are pertinent to them and not necessarily or primarily pertinent to us.

But I completely understand where people could disagree with that analysis because they do not buy into the responsibility.

DR. SHAPIRO: I have nothing against putting any of this in a prior agreement. If that is a prior agreement, that is fine. But I am trying to separate in my own mind what arises here because we have obligations that arise from certain considerations of social justice and deal with those as -- and do not load that all on to the medical research phenomenon.

PROF. CHARO But you see the -- for example, China does not recognize the international patent conventions and it is able to, therefore, within their borders reproduce drugs at a very, very low price for its citizens because they choose not to enter those patent agreements.

DR. SHAPIRO: Right.

PROF. CHARO Other countries, however, have not felt free to exempt themselves from those international agreements because of the threat of trade sanctions in various forms.

So those countries, in fact, are being bound by international conventions on intellectual property, which you may make an argument as an economist would benefit the entire globe eventually, but there is a bit of a trickle down theory --

DR. SHAPIRO: I do not want any insults here.

PROF. CHARO No, no.

(Laughter.)

PROF. CHARO But it has got a bit of a trickle down theory feel to it, because in the short run, these countries would be benefitted by not recognizing those intellectual property rights and freely borrowing from the now publicly available information about how to make these drugs and cure diseases, and do it at a price that they cannot get from the companies that are now -- because they have got patent rights or are the licensees of the patent holders -- able to sell it at a profit to plow into their next R&D budget.

I mean, I am not saying that there is not an economic argument for the good sense of intellectually property regime but I am saying that the reason -- not for the background poverty, right.

But the reason why the medications that are often needed to cure the diseases that are caused by the background property are so unavailable in some of these countries is, in part, the fact that they are stuck in an international trade situation where they have -- they have a stick aimed at them and the stick is trade sanctions.

DR. CASSELL: That is unarguable.

PROF. CHARO Right? So that is one of the reasons why they -- the availability after the research

is --

DR. SHAPIRO: Then one ought to -- yes, then one ought to say that you are using -- I mean, in my view, I am not going to say anything else, but in my view that you ought to say, well, the reason you are going to do this is because of all of these other issues which raise a level of social justice issue in our mind. We are going to use this vehicle as a way to help resolve these important social issues. And separate it out from something which is intrinsic to the activity itself.

PROF. CHARO I think Alex would argue that there really is something intrinsic to health, to bodies and to research and to medicine.

DR. SHAPIRO: I understand.

PROF. CHARO I would be happy to see both sets of arguments laid out because I think both are subscribed to by different people.

DR. CASSELL: I would also point out that it says on page 21, line 19, few would probably disagree that at least in theory prior agreements are a good idea and should be encouraged. Who can argue with that? That is absolutely right. And the host country has got leverage to try and get such agreements.

But the next thing says they are ethically

desirable, yes. And necessary to fulfill the major premise that research should be responsive to public health needs in developing countries.

Wait a minute. How did that get to be the major premise? That is -- that can be a premise.

PROF. CAPRON: That does not borrow from the physician-patient obligation. That goes back to the risk benefit requirement as I understand it, which is part of our regulations. And that is the pivotal argument about where you do research, and that is what I understood Harold to be challenging. Why isn't it equally -- why isn't it just like any other economic activity?

Because we have had a moral requirement which constrains researchers in a way in which businessmen are not constrained to achieve a favorable risk benefit balance. And that has usually been taken to be with reference to the population in which the research is done. Not, however -- it is not taken to be the risk benefit balance has to be favorable for any individual subject.

DR. CASSELL: Yes. But, I mean, for example, there are instances where the disease in question occurs only in this particular country or the patients have something which makes them -- but that does not

help the public health needs of that nation.

I mean, I understand why we should help solve public health needs but that is a social justice issue again. If this is what it is about, then let's make those arguments absolutely clear and see if we can sign on.

But if this is actually about ethically acceptable research and why we encourage prior agreements for which there are many good arguments, particularly for the host country, that is separate. And it is that conflation.

I have no objection -- I mean, I am a professor of public health. Of course, it is good to help solve the public health problems of other nations.

But the argument of why this structure of ethical -- the ethical structure that we are proposing depends on that as a major premise is not at all clear to me.

PROF. CAPRON: But aren't we here trying to say what happens when you apply the present U.S. regulations to research conducted abroad?

DR. CASSELL: Thank you.

PROF. CAPRON: They require informed consent, favorable risk benefit balance and, according to the

Belmont principle, something about justice.

There is a quote in here or there is a paraphrase in here from that article by Leonard Glantz, et al., about would we feel in the United States comfortable with having research conducted on a population which was going to then have no access, no access, to the results of that research.

I think the answer is no. I believe the general view is, for example, when you are doing a study, you should not have a situation in which the only subjects are going to be poor clinic patients as opposed to also looking to patients in private practice settings and so forth. Partly for that reason.

But if we went into this -- if somebody said, "I am going to develop a drug and I am going to go to the ghetto and get poor kids, and they are never going to get access to this," I do not believe an IRB -- any decent IRB in this country would approve that research.

DR. CASSELL: I am not so sure about that.

PROF. CAPRON: And I do not think consistent with the Belmont report they could.

DR. CASSELL: I do not think you --

PROF. CAPRON: At the outer limits. We skirt that by the fact that there are a lot of people who do not get mainline health care in this country. But that

is on the basis that -- well, but they get what they need, you know, and at the margins, and in an emergency and everything else.

But if you could say as an absolute premise I know this drug will never get to this population, never, not for 50 years, not until it has been superseded by generation five of the improved drug will it ever get to this population.

I cannot imagine an IRB in this country approving that research.

DR. CASSELL: I cannot imagine somebody putting that in the protocol -- in their protocol.

PROF. CAPRON: Well, fine, but if it were known, you would say, wait a second, this is going to be a $10,000 a dose -- okay. But I was just handed a note. I do not know what the Ely Lilly research on the homeless alcohols in Cincinnati was. But if there was such research, the very fact that you know of it probably is because people regard it as something of a scandal.

PROF. CHARO It was. That is why it was in the newspapers.

PROF. CAPRON: Well, I do not remember the details but that is my -- I agree with you, Alta. If it was in the newspapers, it was regarded as something

which raised serious problems and was hard to defend.

And that is the difference. I mean, it seems to me if we say you are going to manufacture VCR's in some poor country and they are never going to buy VCR's, they are never going to be able to afford them, we can say who cares less. They got a job. Because we are not using them. We are paying them for their work. That is fine. They can manufacture something and they never know.

DR. SHAPIRO: Well, I do not think those distinctions are really quite so easy to make myself. I mean, I understand the point you are making. I think there are some valid aspects to the point you are making. I really do. I certainly appreciate them. It is not like making sneakers or something else. I think there is something different. There is something different going on here which needs to be taken account of. I agree with that.

And -- but the issue as I mentioned to Alex at the break -- I was trying to think of a scheme that would at the end of a trial not make the participants have any higher moral standing than everyone else in the -- or anyone else who had similar needs to that.

PROF. CAPRON: To me that is a separate issue.

DR. SHAPIRO: I understand. It is a separate

issue.

PROF. CAPRON: I have not been addressing that and I actually do not agree with what the chapter says about it.

DR. SHAPIRO: Well, that is another matter but the -- but in any case I think there are some things that are separate and that are different. But I just think -- in my own view, I would feel better if we just articulated them and laid them out and made the arguments.

Larry?

I am sorry. I am talking too much. I am not going to talk any more.

DR. MIIKE: Just a comment for Eric. We do have a process for expressing your views, Eric, and you should be asserting something that says I do not know why we are doing this international project. It has no importance whatsoever.

And you should listen to me when I am talking to you, Eric. You did not hear a word I said.

(Laughter.)

DR. SHAPIRO: I will tell him later, Larry.

(Laughter.)

DR. SHAPIRO: Call him on his phone.

(Laughter.)

DR. MIIKE: He has got an unlisted number, I think.

DR. MESLIN: Now let's be polite.

DR. SHAPIRO: All right. Let's go back to aspects of the -- that anyone would like to raise with respect to these prior agreements.

Ruth, are there aspects of this that you particularly would like us to address of the prior agreements?

DR. MACKLIN: Not at the moment. And here is why: People say, well, it sounds like it is a good idea, prior agreements. Who can argue against it?

DR. SHAPIRO: Yes.

DR. MACKLIN: What people are much more exercised about is other recommendations and the so-called major premise, which as it says here was discussed in some length at other -- in other chapters.

Now we can -- I think what we should do is look at these other recommendations.

DR. SHAPIRO: Okay.

DR. MACKLIN: Because the prior agreements --

DR. SHAPIRO: The ones on page 35?

DR. MACKLIN: Yes. They are on page 35. And see to what extent, if any, any of these is acceptable.

DR. SHAPIRO: All right.

DR. MACKLIN: I would like, though, at some point -- and I hope perhaps today but we may need to look at the chapters and the arguments, which are not before us -- to go back to that major premise and ask where does it come from and do we need to justify it.

Sometimes there are rock bottom premises that are very difficult to justify or to say anything further about because a beginning ethical premise has to start somewhere. It is not going to start with a set of facts. It has to start with a conviction that can be supported by arguments but perhaps others might respectfully disagree.

So I think we should come back and ask about that major premise. Where does it come from and who signs on to it? I believe, if I am speaking accurately of all the people who have testified, every one of those researchers, including people who have conducted or are supporting some of the research that some people who have testified find to be unethical, all buy into that major premise. Everybody whom we heard, from the NIH, the CDC and the individual researchers said, "We are doing research in countries that is responsive to the health needs of the people in those countries and it would be unethical to do otherwise."

Now the conclusions and the twists of argument

that may come from that are a little bit different but that was the premise with which everybody who spoke before this commission started with.

Now, if we have to go back behind that, I do not know where we are going to go to find the conviction. We can look at some documents like the CIOMS document and others, but then anyone who is skeptical is going to say, "Yes, but where did they get it from? You know, why should we believe them?"

So at some point I would like to know what the Commission -- what more we need to say in order to endorse that premise that the research should be responsive to the health needs of the country.

But first, I think, it would be more useful since we want to write these chapters and have acceptable recommendations to look at each one of these and see which ones in the present or altered form might be acceptable, and which ones commissioners want to throw out all together.

DR. SHAPIRO: All right. Let's just go through these one at a time. They are not numbered but the first one is on line 11 on page 35. For the benefit -- I do not know if the people who are here --

PROF. CAPRON: Read it.

DR. SHAPIRO: I will read it out loud.

"Sponsors and researchers have an obligation to disclose to research subjects prior to their enrollment what will and will not be made available to them following their participation in research."

Does anyone have a comment?

PROF. CAPRON: Hard to take exception.

DR. SHAPIRO: Hard to take exception.

DR. CASSELL: Hard to take exception.

DR. SHAPIRO: All right. Let me ask does anyone take exception? Even I do not take exception.

Diane?

DR. SCOTT-JONES: I do not take exception to it but I would prefer if there were a qualifier that would say something like as much as is possible because you cannot anticipate everything that will happen as a result of participating in research.

DR. MESLIN: It is not what will happen. It is what will be made available.

DR. SHAPIRO: Do you have in mind then -- I just want to make sure I understand the question. You have in mind that there might be things they have to make available or should make available that cannot be anticipated at this time? Is that the kind of thing you have in mind or is it something else all together?

DR. SCOTT-JONES: Well, participating in

research of the kind that we have been discussing might result in some unanticipated illness. It might result in all sorts of things that cannot be determined ahead of time.

DR. SHAPIRO: Right.

DR. MESLIN: Diane, this recommendation is really referring to what will happen.

DR. CASSELL: At the termination of the trial.

DR. MESLIN: After the study is done.

PROF. CAPRON: Diane is quite right.

DR. MESLIN: I understand.

PROF. CAPRON: The phrase "what will be made available." I think we are reading it as out of the research. That is to say what of the goods that may come out of the research will be available.

One way of dealing with the unanticipated aspect is to say what the sponsors and researchers are committed to make available.

DR. SCOTT-JONES: Yes, something like that.

PROF. CAPRON: And then they can make more available if it becomes necessary because of circumstances but they are already committed.

Are we talking solely about the products here or are we referring to also the compensation issue if you are injured?

DR. MIIKE: That is what I was going to raise is that is the other leg of what she is talking about. We just got through with a discussion about treatment and compensation.

PROF. BACKLAR: And, also, Arturo mentioned -- things like information, like the Chinese study that you are going to --

PROF. CAPRON: Information about how we injured you.

PROF. BACKLAR: Well, that you would not keep things from them if something went awry. It is a broader order than just we are giving you medicine to follow things up.

DR. MACKLIN: Clarification here. Let me just whisper it here. You know, these recommendations were all imbedded in the text. They are not going to appear in this isolated form. When they first appeared in the text there was a preliminary discussion leading up to them and then there was a justification. So it made it quite clear what it applied to.

Unfortunately, because we pulled them out and put them at the end with the intention of taking all recommendations from all chapters as the commission has done in other reports, putting them in a final chapter, but with the appropriate context and justification,

everything everybody is asking for should surely be in there. What are the limits and what does this refer to?

Unfortunately, the wording as it is fit where it was placed earlier but, of course, does not explain it now. It was meant strictly to apply not to compensation, not to treatment, not to anything that happens in it, but -- and I think it is good to put it in the active voice. Researchers and sponsors should make clear what they will make available and then the context should make clear that it is any products from the research that may be needed by these participants afterwards.

DR. CASSELL: And this follows from the concept justice is reciprocity that you discussed earlier.

PROF. CAPRON: No, this --

DR. SHAPIRO: Full disclosure.

PROF. CAPRON: Full disclosure. This is only telling what you are going to do. It could be zero. We are going to make zero available to you and that would fit this recommendation.

DR. CASSELL: That would fit this.

PROF. CAPRON: Yes.

DR. SHAPIRO: So that is, I think, the sense

of this -- I mean, the spirit of this is just full and honest disclosure.

DR. CASSELL: Disclosure.

DR. SCOTT-JONES: Right.

PROF. CAPRON: We are committed to getting on the plane and getting out of here as soon as possible.

(Laughter.)

DR. SHAPIRO: So there is no misunderstanding, at least to try to eliminate any misunderstanding, what happens after the trial. Even though you may be fully informed about the trial, you also want to know about what is going to happen after that since it is the spirit of this I take it.

DR. MESLIN: Yes.

DR. SHAPIRO: And I think, as people said, I do not think we find that in an way a problem.

Let me read the second recommendation. "Researchers and sponsors have an obligation to continue to provide the beneficial intervention, free of charge, to the participating subjects if they can benefit from it."

Diane?

DR. SCOTT-JONES: This recommendation does not make clear who would decide whether participating subjects can benefit from continuation. How would that

be decided?

DR. MACKLIN: It is a medical judgment. Strictly medical judgment. I mean that is what intended. In other words, there is a -- there are participants in a trial. In the context of the trial they start getting better because you are giving them this medication, let's say it is for malaria or maybe something else, a more chronic condition, and they still have the sickness but the trial ends. It has already demonstrated that they can benefit from it.

DR. SCOTT-JONES: Okay. I have an idea of what you are saying but in my -- I thought we wanted to look at these as they are written. And in my view it is not clear. It does not rule out the possibility that I as a participating subject could say I still can benefit and I expect to continue to get this. I think it is not clearly worded to say what you just said.

DR. SHAPIRO: Other comments? I know that quite a few hands went up.

Arturo?

DR. BRITO: One of the issues I have with this, and I ran across this -- I cannot remember. It is written on the text somewhere. I wrote on my notes. But this kind of problem is a problem of coercion.

Whenever you -- if at the beginning you have prearranged you are going to say to participants in a poor country, resource poor country, that you are going to provide these benefits or intervention only to participating subjects, then at what point does that become coercive and unfair? So then, therefore, if you do not participate, we are not going to provide this. So I have a little problem with this.

DR. MACKLIN: Could I clarify here? This was actually an item that arose in chapter three where we talked about what should be provided to people during the trial. And that point was raised there and we had a lot of argument.

DR. BRITO: Right.

DR. MACKLIN: We will come back to that chapter when we see the whole report but that was a question of whether or not it is an undue inducement to provide something during a trial.

This is now talking about what is owed after the trial and I guess you are making the same point.

DR. BRITO: The same point because it is a prior agreement. You know, if I am living in a resource poor country, you come to my community and you say, "Oh, and the ones that participate in this, you are going to get this free of charge for the rest --

you know, for however long, for the next year or two years if we find it is beneficial."

DR. CASSELL: How could I say no to the proposal?

DR. BRITO: How can I say no if I cannot -- if there is no chance I am going to get the health care. So I am just saying that it is -- I just think it is no less coercive than what we discussed in chapter three.

DR. CASSELL: Could we solve it a different way maybe?

DR. SHAPIRO: Okay. Eric, then Bette.

DR. CASSELL: If we go to the next recommendation, it really carries the same substance as that recommendation but it implies, as is common in many other trials, that if the intervention is beneficial it will continue for the period of time required afterwards. I mean, that is a common thing in trials. We see that in the United States commonly. People are not cut off from their medication. If the new medication is not licensed, they still may get their medication afterwards. But it puts a time limit on it and it puts limits on it. Not necessarily time.

DR. SHAPIRO: Alta, and then Diane.

DR. MIIKE: What about Bette?

DR. SHAPIRO: Oh, Bette, you were next.

Excuse me. I am sorry.

MS. KRAMER: All I wanted was a point of --

DR. SHAPIRO: Unfortunately, I made a mistake.

MS. KRAMER: Just it was just a point of information. I want to know is that the practice in domestic trials as well?

PROF. CAPRON: Doesn't that vary?

DR. CASSELL: It is commonly done.

MS. KRAMER: Pardon?

PROF. CAPRON: Doesn't it vary as to where you are in the trial process?

MS. KRAMER: So it is not -- are we -- would it be then the intention if this guideline -- if this guideline, this recommendation were followed, that we would be creating a more stringent recommendation for international research than we have domestically?

DR. SHAPIRO: I believe so.

DR. BRITO: International research in resource poor countries.

MS. KRAMER: Well, what about resource poor people here?

DR. CASSELL: In the United States if the medication is beneficial, it is common to provide it if it is not licensed. In other words, if it cannot be obtained any other way, it is common to continue to

provide it.

DR. MACKLIN: And once it is licensed, people get it through their insurance.

PROF. CAPRON: Or not.

DR. CASSELL: The ones who can. And the ones who cannot, do not get it.

DR. MACKLIN: And that is an injustice in our system.

DR. CASSELL: Yes.

DR. SHAPIRO: Okay. Alta?

PROF. CHARO I am sympathetic but I have a feeling that across a variety of situations in some cases this may be unrealistic. I think I want very much to distinguish, and I am going to refer now back, by the way, to page 6 where you discussed why it is that ceasing to provide medical benefits that have been conferred during research is to render the subjects worse off after the conclusion of the research than they were during the research.

Okay. I think that that is an argument I am comfortable with if you had, for example, a life extending drug for somebody who is an extremist. I take the example of somebody with Lou Gehrig's disease and you have finally found a drug that is going to extend their life somewhat.

And if you were to stop giving the drug, they will die immediately. Because in a sense what they have lost is the uncertainty of dying slowly, with not knowing exactly when it is going to be, because now the withdraw of the drug actually precipitates an event. And that is a psychological harm even if there is a kind of net numbers of life gained.

There are other situations where they would not be made worse off than they were before the research. Right. Only then during. I am thinking now of some chronic conditions where what is being tested is a superior therapy to one that existed before.

Here I guess I think that there may be a need to have some nuance as to how much of a difference there is between the tested therapy and the existing alternatives. Something that controls your asthma a little bit better but not dramatically better is different in my mind from something that has a vast difference between where you were before in research and where you were during it.

And because this kind of recommendation really does not entail some potentially significant financial commitments by the trial sponsors when they are looking at chronic conditions, I just want to be a little bit more careful about exactly the situations where we want

to trigger this and those where it is less urgent.

DR. MACKLIN: But could we -- I mean, we do need a lot of nuance. Could I just ask, Alta, if it would make a difference if we inserted here, because this is really what I think we had in mind, in cases where the participants do not otherwise have access to an established effective treatment.

PROF. CHARO That would go a long way to clearing --

DR. MACKLIN: I mean, that is the asthma example.

PROF. CHARO Right.

DR. MACKLIN: Okay.

PROF. CHARO That is right. Well, of course, established effective by their local country standards.

DR. MACKLIN: Well, we have established effective in another chapter --

(Simultaneous discussion.)

DR. MACKLIN: -- but we are struggling to get a meaning for that.

PROF. CHARO Right.

DR. MACKLIN: But I am now trying to address what you just raised, which I think is an important question and requires a qualification. Would that go

part way?

PROF. CHARO It would absolutely go part way because it would clear out a lot of situations where the financial commitment may not be necessary to leave people in a condition where they do not feel abused, which is, I think, a good goal.

Whether or not they are entitled to feel abused is separate but I think that it is a good thing for them not to feel it, whether or not they are entitled to feel it.

DR. SHAPIRO: Larry?

DR. MIIKE: A couple of things that are really reactions to what have been said. On Arturo's point about undue influence, I thought we had -- we have made a conclusion that these kinds of things are not by themselves undue influence.

Just the fact that people participate in trials, even if there is no iota of benefit, there is a therapeutic misconception anyway. So I thought we had laid that whole issue to rest and I have no problems with it.

My reaction now is just really -- the second one is really to what Alta said. I really am opposed to recommendations that start to weasel and qualify and condition and do things that begin to obscure the basic

message. Those kinds of things can be written in the explanations about what we mean by a particular recommendation but the more clauses that we have within a recommendation, it makes it more obscure from my point of view.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: Well, in light of what Larry just said maybe I should not put in the qualifiers.

(Laughter.)

DR. SCOTT-JONES: But I am going to anyway.

DR. SHAPIRO: You and Alta can take care of Larry over there.

DR. MIIKE: I will never invite you to my house again.

(Laughter.)

DR. SCOTT-JONES: We will have to discuss that later, Larry.

(Laughter.)

DR. SCOTT-JONES: I read back on page six what I thought was a very strong statement that there is no ethically defensible argument for cessation of continued medical treatment of subjects in a resource poor country. I agree in spirit that people in resource poor countries need more medical care. I think that no one can argue with that point but I think

there could be problems if we put this as a recommendation without some qualifiers.

I already raised the issue of who decides whether the person can benefit from it. A second is who would administer the treatment and under what conditions? In a very poor country there may not be the people with the training or the conditions of hygiene necessary to continue to administer whatever it is that was benefitting.

Assuming that the U.S. researchers will come back home, they will not be there or necessarily continue to administer it. And then would you have this enforced for all participants from all experimental conditions or just from the one -- for the ones who got that particular treatment in the experiment?

And then, finally, I believe that this in itself promotes the therapeutic misconception so that people when they enter these trials are going to not distinguish being in a research project from getting medical care that they so desperately need.

That is not to say that we should have this recommendation in some form but I think we should write the recommendations with care and with probably more care than we would if this applied to us in the U.S.

because we are dealing with people whose every day lives are so dramatically different from ours.

I think that we are losing sight of our lofty goals by not writing this very carefully.

DR. SHAPIRO: Alex?

PROF. BACKLAR: And actually, of course -- I am sorry.

DR. SHAPIRO: Alex?

PROF. CAPRON: No, let Trish go.

DR. SHAPIRO: All right. Trish, go ahead.

PROF. BACKLAR: I mean, this actually goes to the heart of the problem in the sense of why are we doing research in these countries if it is not going to be addressing issues that are of concern to them, which is your point. Are we only going to do it if we are going to address issues of concern to them? If it is not of concern to them -- if it is of concern to them, then we have some obligation somewhere in here to help, and they have some obligation also to help themselves out with what we find that will benefit them.

It is not -- if we are going to do it just to benefit us then this becomes a problem. Because then if we are going to do it to benefit us, then surely we have to set up things for them before using them as subjects for our benefit.

DR. SHAPIRO: Alex?

PROF. CAPRON: Given my comment before in response to the argument you raised, I think some people anticipated that I feel differently about this than I do. I share Diane's sense. I thought she put it very well about the ways in which the therapeutic misconception is enforced here.

And I would go beyond that, which is kind of a statement about a psychological state, to say that there is a difference between deciding at the outset that researchers are bound by slightly different rules than businessmen who are engaging in an arm's length relationship and saying that researchers are bound by the same relationship that they would have if they were giving medical care.

I do not think that the two line up.

I was particularly puzzled by this recommendation beginning with the word "researcher" instead of all the others which begin with "sponsors." I would like to suggest that we separate out in our thinking, and maybe -- and this has nothing to do with the wording. It just made it leap off the page, Alice. So I do not -- I did not take that actually to be intentional. I thought that it was probably adventitious.

But I have a sense that in the back of our mind we have Pfizer and Merck and so forth in mind, and statements about the enormous profit that drug companies make. And we are sort of engaging in a form of ad hoc taxation in saying that in the world these are sources of payment. I guess my sense would be why not Toyota and GM. I mean, why aren't they paying for drugs or Nike or anybody else who is doing business in the world who has profits.

If we are talking about governmental sponsors, we have one set of issues. If we are talking about private sponsors, another set. If we are talking about researchers as individuals -- in this statement whenever you have an "and" you ought to be able to drop it out.

Researchers have an obligation -- a life long obligation to the participating subjects to provide free care? I mean, that just -- that statement falls on its face it seems to me. There would be no way that anything that we have said comes anywhere near to supporting that conclusion.

If it is this -- new separate point. If it is the subjective sense that Alta was talking about -- I mean, clearly a person is better off at the end of research to the extent that they have been better off

during the research even if it stops and they do not get any further benefit.

They have had the benefit of whatever has come to them. But those are the people who are getting the active intervention. Many of these will be situations in which there will be an alternative given. Whether it is a placebo or the presently not very effective intervention, whatever that is.

Are those subjects now entitled to it? I think our sense is that they are in the same position. It was a random chance which they were -- they are not in the same situation psychologically. It is not as though they have been doing great and you are going to take away their drug and they are going to do poorly.

So the psychological argument has to be seen for just what it is. It is not a moral argument. I mean, it may be one of discomfort. My God, you are well today but I am going to make you ill tomorrow. The other person is ill today and I am leaving them ill if I do not give them treatment.

So, I mean, I -- the rationale has not been provided here for this. And that is why -- I mean, I would love this report to be called the Madison Report. And it would set forth high principles and a company would say, "We are going to follow the Madison

principles, and we are going to take it on, we are going to write agreements, advance prior agreements, prior prefaces, voluntary agreements, and we are going to negotiate, and we are going to face some tough Ministries of Health" who are going to say, "You want to come and do the research here but this is what we are going to extract from you." And they will say, "We will do it because we believe in the Madison principles."

And there are others who are going to say, "Well, we cannot go that far." And that would lead to change. I mean, as George Andreopoulos was saying to us, in time that will lead to change and the companies that do not adhere to it will fall away. They will not be able to get away with it any more.

To continue, people who are not convinced that there is an obligation on whoever happens to have sponsored -- some little biotech company that happens to have sponsored some research some place to provide free care to the whole lot of the people, and maybe drug at a reduced price to the entire country in perpetuity. It just does not -- it does not convince.

DR. SHAPIRO: Eric, then Arturo.

DR. CASSELL: Well, I think that I want to

follow up on that. You see the -- our objective is not only that we protect human subjects in this research but we would like to see change occur like that. That would be a very beneficial thing. And then you say, "Well, how do you make that happen."

And, in fact, laying out principles that would be a desirable thing so that countries negotiate this when -- and then you do begin to get the change. Because for me -- I am not going to say the word but I think that over the period of time that is exactly what has to happen.

And then, in fact, you get ethically defensible research and beneficial to populations. That is how it happens. It does not -- this will not do that. Leaving anything else aside, it will not do it because it cannot be done. What Alex says is absolutely right. It just cannot be done.

DR. SHAPIRO: Arturo?

DR. BRITO: Something you said, Alex, concerns me a little bit about -- that I think is also important in the wording here. It is that the assumption that the intervention, the active -- let's call it the intervention or the new intervention is actually going to be beneficial.

And I think this is where wording is very

important here because it may be -- even with a placebo, it may be that the placebo is actually a better intervention. So it depends on these prior agreements how it is worded because there may be absolutely nothing provided except to leave the community alone or the participants may actually be worse or the ones getting the active ingredient may be worse off than --

PROF. CAPRON: Sure.

DR. BRITO: Okay. So I just wanted to make sure -- this relates to this about what Diane -- going back to what Diane was saying, being a little more specific, I guess, you know, about what it is that is being promised, if anything at all, in these prior agreements.

DR. SHAPIRO: Alta?

PROF. CHARO Again, in the spirit of trying to disentangle different kinds of scenarios to see if we have different reactions. In the spirit of trying to disentangle situations so we can see have different reactions to different situations, I am thinking now about the discussions around research with people with impaired decision making ability.

And the discussions about the consequences of trying a new psychiatric drug and then at the

conclusion of the trial facing the dilemma of removing somebody from that drug and allowing them to go back to the drug they had been using previously with the kind of interim period of significant kind of decompensation and interruption. Which is not even to talk about the kind of qualitative difference between the experimental intervention or the research intervention and the clinical therapy.

And in that case we did advocate for some kind of attention to that dilemma and to some provision for wrap around care. I do not recall that we suggested that we needed to have provision for a lifetime commitment at no charge. But we did say that there was some need to avoid creating problems by virtue of the withdrawal of a research intervention.

I wonder if we can draw some guidance from that as to exactly what the core concern is and see how far that extends in these settings.

PROF. CAPRON: That was a suggestion that staff look at that document?

PROF. CHARO Or that we just think about it ourselves since we all voted in favor of all those recommendations.

PROF. CAPRON: Well, actually at the -- I am sorry. Go ahead.

DR. SHAPIRO: My own view of this -- one, I think the -- just as I told Ruth before -- I think the recommendation as it stands, I cannot find a way to defend it on ethical grounds or any other kind of grounds, but there may be a way. Maybe I can get convinced.

But I have convinced at least myself that anything that is this blanket and seems that straight forward is just incorrect. It is just -- the situation is just much too difficult.

What we need to do -- I sort of sense in my mind that we need to encourage certain kinds of approaches, certain kinds of thinking about this, and for people to understand there may be good arguments and certain obligations, for example, in the next recommendation to be sustained. But there are not -- there are just very different situations.

First of all, there is a lot of very low risk trials. There is a lot of trials that do not make anybody any much better or any much worse and what do you do with those. There is only a small proportion of the trials that are actually the product. Okay.

We are probably now talking about a -- I do not know what the percentage is but it is probably pretty darn small.

And so it seems to me better as a way of going about this to try to put as much of the reciprocity as you can in up front. There may be some left over. I understand the point. There might be some reciprocity left over which might indicate something like recommendation three or some other version of two. Because you just cannot find any conceptual way to deal with it except after the trial.

But I look at that as okay. We lack any -- we lack the capacity or we just -- there is no way because of the circumstances to get the compensation or reciprocity. I am using compensation but I do not mean only money. Whatever the compensation turns out to be.

And if there is some left over, all right, you have to be conscious of it and you have to see what it is you can do to eliminate that obligation or to live up to that obligation.

So I think that the second one here is just much too broad and there is too many problems with it. I mean, a lot of them have been raised here by Diane, Alex and others.

Larry?

DR. MIIKE: I often come to these meetings thinking that we do not have any context in which we

discuss it at a current meeting because everybody seems to have forgotten what we discussed at the previous meetings.

So I would like to get some indication from the rest of you here notwithstanding the problems with the specific wordings here. Did we not agree that in these countries that we are talking about that if there is a benefit to the participants in the research there was an obligation to provide that benefit. And we can argue about how long, at what cost, et cetera. But did we not reach that conclusion?

I thought we did. I thought it was pretty clear if there was a beneficial -- if there was an intervention which improved the clinical situation for those patients that at least for those who are actually participating -- and I think we even discussed about those on a placebo arm.

PROF. BACKLAR: Right.

DR. MIIKE: Yes. So we are in agreement at least on that and it is a question of --

DR. SHAPIRO: What is the obligation? I am not sure if --

PROF. CAPRON: Who has the obligation?

DR. SHAPIRO: Yes. I did not understand the last part of your sentence.

DR. MIIKE: Whoever is paying for the study and that will benefit in a financial way from the drug that would then be sold had the obligation for those participants within the research protocol -- I am not talking at this point in time about the country or some of the populations -- that we had come to the conclusion that they had an obligation -- they should have an obligation to continue providing that intervention to those patients.

DR. SHAPIRO: Forever.

DR. MIIKE: Yes.

DR. SHAPIRO: Free of charge.

DR. MIIKE: Yes.

DR. CASSELL: I do not remember doing that. But I think we did agree that -- I think the sense of it was you could not go in and just do a trial, do your thing, and walk back out as though you had no responsibility to the participants in your research in the same sense that you cannot do that in this country.

Sometimes it happens that you say that and then you see, well, this is what it looks like when you spell it out. And you say, well, if we do feel that way, this will not fly. And if we do feel that they have an obligation, we have to figure out how do we

express that.

DR. MIIKE: I understand that. I phrased it a different way. I said regardless of how these are framed right here, did we not agree that if there was an intervention that was beneficial, at least to those who participated in a trial, they would continue to receive it.

DR. CASSELL: Yes, I think we did.

DR. MIIKE: Yes.

DR. SHAPIRO: I just do not remember. Maybe we did. I do not --

PROF. CAPRON: Could I just --

DR. SHAPIRO: Yes.

PROF. CAPRON: If we agreed to that, which I do not recall, I do not agree with it. I do not agree with it as a blanket statement at all. And I want to respond because I think Alta's suggestion is a good one. Looking at what you described, I would say that an IRB facing a protocol to test an antipsychotic medication, which if it is successful will do something which present drugs do not do and in its absence, the person is in a very bad condition.

You could in those circumstances say that the risk involved in the research includes the risk of getting better and then being thrown back into that

condition. And that risk is an unacceptable risk. It is avoidable by the sponsor agreeing that the drug will be continued to be provided until such time as it becomes generally available as a licensed drug and available through a prescription.

That would be a matter of the individual judgment of an IRB about the risk benefit ratio. They would not have to reach around to some ethical principles that say you would have to do this as an obligation even if we did not think it through and make that a requirement at the beginning.

PROF. CHARO On what basis would an IRB conclude that that is an unacceptable risk?

DR. CASSELL: Well, if it would throw somebody back into a major psychotic break.

PROF. CAPRON: And I think there are some peculiar things. We were talking at the break, Trish and Harold and I, about a situation in which you would have a drug that was life saving. I mean that I could be feeling fine but about to drop dead of a heart attack unless I am taking a pill every day. And that is what the study shows and now I am taking the pill, and you want to take it away from me.

And in a certain way I can actually believe that it is easier for me at the outset being told this

is what the study is going to do, this is what we -- if we find that this is what this drug will do, do you agree to go into the study knowing that we will not provide it to you until it is generally licensed. It is too expensive or too complicated or we are just not willing to make that commitment. Do you agree?

I can understand that being a situation in which a person could give a consent. Whereas the person who is now suffering from a -- but is in a tiny window when they are able to make consent, let's say, but they are basically suffering from this debilitating condition, could not make that choice because the prospect of going from health right into that psychotic state when the pillars were drawn, is a trace which they cannot imagine, whereas I can imagine the situation because I am already in that situation of apparently being on the brink of death every day from a heart attack.

If you see the difference and that you could say that one is a choice in which a person has enough information to make a choice about it and the other one is not. Therefore, an IRB would make a judgment about one, one way, and one the other way. I could also imagine the IRB in the heart case saying, no, no, if it turns out that that is the thing that stops you from

dying tomorrow, it also may not be withdrawn. It is just wrong to go into research that creates that.

But it seems to me that the mental condition as we have said in that report raises additional complications and questions about the consent process so you might feel that you have to put that restraint on there. It is an act of paternalism and, in effect, say we are not going to let people who might be willing to go into it without this price being paid on the part of the drug company to agree to do so because it is a situation where they are just too vulnerable.

DR. SHAPIRO: I think -- I am sorry. Arturo and Trish.

PROF. BACKLAR: I just want to add to that because it was interesting that you brought this up, Alta, because this is exactly what we were discussing before. But as I recollect our report on persons with difficulty with decision making, that we made this recommendation in a rather oblique fashion. It was not merely that there would be after care and some kind of wrap around services. But it certainly was not as bold as this.

We were quite cautious in how we recommended that and it was exactly that issue of somebody having -- being psychotic and then having it relieved and you

do not want to put them back in that state of becoming psychotic again.

DR. SHAPIRO: Arturo?

DR. BRITO: I just want to mention one aspect very quickly about this recommendation that I had written in my notes a long time ago and I do not think I mentioned this before. So, Larry if I did, I apologize but I do not have the memory. All the meetings are running into each other and what I read runs into each other so I cannot distinguish.

But one thing that we have to be also careful with the wording is not going -- the pendulum swinging too far the other way. Is that if our recommendations are written in such a way and they are, you know, they are taken up somewhere, and they are written in such a way that the language is so strong that researchers -- I mean, the sponsors of research in foreign countries which have done -- you know, one thing we forget or fail to mention enough is that there has been a lot of beneficial research to foreign countries done by the U.S. and other westernized or industrialized countries in resource poor countries.

And can it be counter productive if the obligation is too much. In other words, therefore, you are going to scare off pharmaceutical or academic

institutions from going into certain countries that have very different cultural differences that -- and they are very resource poor, and you are going to scare people off from doing that because they are afraid they cannot meet any or all of the obligations that you are promising.

So I think we just have to be real careful not to forget that there has been a lot of beneficial research.

DR. SHAPIRO: Ruth, it seems to me that as you think about these problems or at least as I think about them, I should say, it is very hard to escape the anguish that is going to be involved in various cases. There are close cases. There are difficult cases. It is very, very hard to write anything down that is going to escape all that.

But I kind of like the idea -- I think maybe Alex mentioned it -- that an IRB as it reviews a proposal kind of tries to make an assessment of the benefits and risks that are involved here and makes sure that the protections and/or reciprocal compensations are adequate to meet that situation, which may involve wrap around care or something equivalent to it.

But it would not seem to me that it would

necessarily involve it. That is where I get stuck.

DR. MACKLIN: It has been my experience IRBs never look at this. We may want to make another recommendation about what IRBs should take into account in making their determination but basically the assessment of the risk benefit is not an assessment of whether anybody is actually going to get this in a poor country. It is an assessment of whether or not the research design is of sufficient quality and caliber and the methodology is good enough and it is good science so that it is going to yield some benefits, meaning contributions to science wherever the chips may fall.

So it would be -- we would require another recommendation for what IRBs have to look at that would go way beyond what they currently do.

DR. SHAPIRO: Well, it seems to me -- I mean, I am not prepared to make that suggestion. I have not thought it through enough. But it seems to me that if that is -- given that that is the case, they are making the easy decisions in the IRB and we are trying to make the hard decisions by writing a recommendation, and a simple recommendation at that.

It seems to be upside down in the sense that the lack of -- you know, we do not have the same kind

of information that they would have and so on.

Now that may not be the right way to go about it. I am not making any recommendation. But there is something attractive about that line of thinking.

Alta?

PROF. CHARO Well, first, I want to say I share that sense that -- thinking about the possibility of the sudden loss of something that one has gotten accustomed to as a risk makes sense.

I do think, though, that there is still another half of the equation that we need to handle. I am not sure exactly how to handle it. Because when you go back to the earliest stages of this project and some of the stories coming out of the research trials in other countries, one of the things that emerged from those stories was the sense of abandonment.

The researchers swoop in. They set up a clinic. Some group of people suddenly find themselves with lots of attention. And not only are they getting some, you know, trial of some antidiarrheal or antimalarial, or whatever it is, but they are also getting full check-ups and they are getting nutritional status evaluated, and they are getting infections treated. And then the study ends. The researchers pack up, boom, gone, and the clinic goes away.

Not only the actual investigational drug or device -- notice, by the way, all the research we are talking about here is in the medical model. But also all of the ancillary stuff. It just goes away. And that this is really quite disturbing. This phenomenon.

And I really sense that if we go back to what this recommendation started with, I think it was an effort to address that sense of abandonment.

I think it might be fair to say that we want to have a principle that says that sponsors may not abandon the subject populations.

Now as we know in the area of medical care, not abandoning a patient does not necessarily require, as Eric said earlier, that one continues exactly the same care under exactly the same financial terms as before or even for free.

It can mean appropriate referrals. The creation of some alternative mechanism for obtaining care. I mean, in this context it may be a wider range of things than just the provision of the investigational drug or device. Indeed, in some of these trials I suspect it will be the ancillary attention from the clinic that is going to be far more determinative of somebody's health status than will be the presence or absence of the investigational drug or

device.

So I do not -- I am not prepared to actually go into enough specifics to be able to write something and propose it for a vote but I am wondering if maybe we can think with a broader range of variables at how to get at this problem with a two prong approach, the identification of the risk of loss of a benefit that you have gotten used to. And, second, a wider range of things we can consider and kind of we will not abandon people.

DR. SHAPIRO: Given the time it is now, I would like to at least spend a few minutes, if you do not mind, just going on to the next recommendation. Not the next one which Eric already referred to. It is a similar one to the -- but the fourth one down, which deals with capacity building.

That recommendation says sponsors and researchers have an obligation to build capacity in developing countries for designing, conducting and providing scientific and ethical review of research. Capacity building programs should accompany research projects so that host country researchers can be full and equal partners with industrialized country researchers or sponsors.

That is the recommendation. Comments,

questions?

Diane?

DR. SCOTT-JONES: I agree wholeheartedly with the spirit of this recommendation but again I wonder how we can make this recommendation without thinking through the implications of it, Because if research is done in countries that are resource poor, to meet this goal in any way would require so much in the way of resources.

It would require providing computers, training medical students or graduate students. It would require so much that it is just hard to imagine how this could happen in countries where capacity is very limited. This goal would be very far off and could not be accomplished in the near future.

I do not know how the recommendation could be written to maintain this wonderful spirit of helping without putting a burden on researchers and sponsors that could not be accomplished in any reasonable way.

Then the other reaction I had when I read this recommendation is that for the first time in this set of recommendations the phrase "developing countries" is used. It is not used in the prior three. I think we should be clearer whether we are talking about developing countries or whether we are talking about

all countries with whom the U.S. might collaborate.

If we are talking about developing countries, I think we should be more straight forward throughout that that is our focus and not international research more broadly.

DR. SHAPIRO: Thank you. Other comments?

Eric?

DR. CASSELL: Well, I do not know where the obligation comes from. If this is justice is reciprocity then it is what my father-in-law used to say. 50/50, your rabbit and my horse. It is not clear what the -- I mean, if you have an obligation then you have an obligation because of a reason in this context anyway. I do not know what that reason is.

DR. SHAPIRO: Alex?

PROF. CAPRON: I would like to distinguish the two sentences here. The first sentence is a statement about obligation. The second is a statement about what should happen. I would like to drop the first sentence. This is going to sound a little long because I am sort of taking some of the references out of the first sentence.

But if we said programs to build the capacity of developing countries for designing, conducting and providing scientific and ethical review should

accompany research projects to enable these countries or researchers in these countries to become full and equal partners with industrial. Then it is a statement of something that should happen.

We do not claim it comes from an ethical obligation but it is something good that should happen.

DR. CASSELL: Yes.

PROF. CAPRON: And again I have -- you know, I would think that a company or an NIH institute or anybody else or a researcher says I am for that, I am going to try to implement that, and look this recommendation has urged me to do that and I am going to do it, we would say you are moving in the right direction.

We do not have to worry about whether or not we can construct a moral obligation that makes this true across the board.

DR. CASSELL: The Madison principle.

PROF. CAPRON: That is what I like. I will give you that revised wording.

DR. SHAPIRO: Any other comments or questions?

DR. MACKLIN: Can I just ask Alex and everyone else, since the problem seemed to my amazement to lie with the word "obligation," even though there is an ethical "should" in the next sentence, I would like to

know whether the vast problems that were discussed over the last half hour with the preceding recommendations could be somewhat mitigated if we took out the words "obligation" and put in "should" instead.

PROF. CAPRON: Well, it is not just there. It is --

DR. MACKLIN: No, no. I want to know whether the -- I am asking a very specific question about the language of obligation versus the language of should.

PROF. CAPRON: I understand.

DR. MACKLIN: And ask whether if the preceding two that we discussed at some length were altered to have the word "should" instead of obligation, would that eliminate some of the difficulties that were -- or not all maybe. Not the ones that did not --

PROF. CAPRON: Ruth, you started off by telling us that these recommendations are merely summary of conclusions that are reached earlier in the report. Earlier in this chapter you give us a fork in the road. On one side you say lies obligation. On the other side lies virtue. To me virtue includes should. You should do this to be a virtuous person or a moral person or whatever the standard you are using. It is a should.

If you -- and then you say but we are going to

take what you call the more difficult path, which I gather to be a way of saying we are going to try to construct an argument that leads to obligations, that shows that this is obligatory. It is not something that you should do. It is something you must do, that you shall do it under ethical command.

If you would change that and make these as arguments which show that this is a better state of the world, if this were the case, then if it is not, yes, then a should here would change.

If you are just going to put the word "should" instead of obligation here but you are going to have all the argument before, which is all around trying to construct a case that this is obligatory, that moral obligation makes it necessary for a researcher in this situation to build capacity of a developing country, then I have problems with it. Then you have not changed anything but the wording and you have not changed your argument. You would have to change your argument, too.

DR. SHAPIRO: Eric?

DR. CASSELL: I can see once again just following what you say but with what Alex says. Recommendation three, which I think has "two" in it. Sponsors -- researchers -- sponsors -- it would be

desirable for sponsors to provide and so forth. It is desirable. They should.

But there is no way to make it -- I mean, I cannot see how you can make it an obligation. First of all, it is not going to happen. But even leaving that out. Sometimes we say things that we know will not happen because they may be prescriptive in a sense for the future. But this is a cannot.

Alex gives you a way out of this, which I think is a very good one.

DR. MIIKE: But I thought we heard some testimony the last time around that people are doing it. They are, in fact, doing it.

DR. CASSELL: Well, virtue exists.

DR. MIIKE: But you just told me they cannot. I am just telling you that there is empirical evidence that people were doing it.

DR. CASSELL: No. Sponsors and researchers have an obligation to build capacity in developing countries for designing, conducting, providing research. That is fine. Capacity building programs. Now aside from vaccine programs, which is a very different animal -- let's pick a complex drug and I like the example where capacity building programs exist.

DR. MIIKE: The discussion that we had around this issue was not this big grandiose thing. What it was, was that we should build the capacity in that country so that we have researchers in the country participating as equals.

DR. CASSELL: Yes.

DR. MIIKE: Or doing the research themselves. That is not an unattainable goal.

DR. CASSELL: Absolutely.

DR. MIIKE: I think that we heard testimony that people were doing that.

DR. CASSELL: I agree with you.

PROF. CAPRON: It is a good goal. The question would be suppose X, Y, Z company and X, Y, Z country agreed to do a program in which that did not happen. They said for the purposes of this program it makes sense for us to come in and do this but we are not going to engage in capacity building.

I mean, there are people from your country who are now in our country as graduate students or they are professors. They are going to come with us to run the program. So we are going to have people who know the country, who are indigenous from here. But they are going back with us. We are not building capacity here.

Now I would say that is not as good a program

as the one that we are --

DR. MIIKE: But we have not answered that.

PROF. CAPRON: Am I going to say that it is morally wrong to have done that or it is just that was a choice?

DR. MIIKE: I understand, Alex. But the way I interpret that and the way I would like to see it is what we are actually aiming for, is that if we are talking about a single research project, that is quite different from a company or an institute that sets up a long-term multiple project going on. They have a bigger obligation.

Even in the single research project -- and I will speak from personal experience. In the Hawaiian community lay people wanted to participate in research because of all the issues you hear about. People coming in and out.

It took them seven years to convince NCI that a lay person could be a co-project director for a cancer prevention study. So that even on individual research project, capacity building may be simply dealing with communities so that they can be better informed. I mean, we are not talking about a big gold standard industrial complex in that country. Capacity building ranges across a whole bunch of things.

As we talk about progressive -- what was the words that we used just a few hours back?

DR. MACKLIN: Progressive realization.

DR. MIIKE: Progressive realization.

I think that was the spirit of this and clearly if you are talking about a company is going to set up a multi-year, multi-trial type of thing, then from my standpoint they have a -- they have to have a bigger obligation in terms of building capacity in that country versus a company that might go in because there is one particular trial that you want to do.

DR. CASSELL: I think you are absolutely right. I think that, in fact, this should reflect that. The ethical basis for it is really what Alex talked about and what is in here as an alternative ethical basis. Virtue is not a bad basis for action. It has been considered for quite some time.

Yet we want to make it clear that that is a good outcome. Not an obligatory outcome but a good outcome because it leads to something in the future which is very important. The capacity of the nation to do its own research and so forth.

But then it has got to say that.

DR. SHAPIRO: My own sense on this one, Ruth -- and then I want to just spend the last few minutes on

the last one. We do not really have enough time. I know that. Is that I also have hard time thinking of this as an obligation, especially it is so broadly drawn here that it seems very difficult for me to understand it in that way.

If we had -- even if it said things like have an obligation or should assist in developing or something that was a little more modest in scope, it would seem to be both more effective and more convincing than the language that is used here.

Let's go on to this last recommendation. We have talked about obligations. Let's go to this last recommendation, which talks about -- it is too long to read. So those of you who have it here can read it. Are there any comments or questions regarding the last one?

This is the one regarding --

PROF. CAPRON: This is the country.

DR. SHAPIRO: That is right.

PROF. CAPRON: Well, I will say that in the discussion itself, wherever that was, the argument that political lines were important did not have much follow-up. What page? Do you know what page that is, Ruth?

DR. MACKLIN: I am sorry. I am not sure what

you are referring to specifically.

PROF. CAPRON: The language on page 36 is other relevant populations in the country.

DR. MACKLIN: Yes.

PROF. CAPRON: So you are making an argument that the country is the relevant unit.

DR. MACKLIN: Yes.

PROF. CAPRON: And somewhere in the text -- what I am saying is I do not remember the page but maybe you do. There is an argument about why the country is the relevant unit and I just --

DR. MACKLIN: Yes. Well, there were -- it was an argument about why it is because even though it may not make either logical or ethical sense in some way of thinking about it, it is the -- these geopolitical boundaries are drawn and it is probably the most practical from the standpoint of the negotiation that has to take place because the negotiation is going to be with some Ministry of Health or appropriate officials in that country.

PROF. CAPRON: Right. But whenever you get to the point of negotiation it seems to me you are back on the alternative ethical model, which is that a negotiation process that yields this particular result has yielded a better result than one that does not as

opposed to it would be wrong for the Ministry of Health in a country to agree to a research project in which this obligation was not fulfilled. You see what I mean.

I did find it. It is on page 14. You say, for example, if a vaccine trial is conducted in Uganda, all of East Africa is too large an area. And how do we know that? Since national boundaries provide some geopolitical rationale and no other logical candidate for drawing the line is apparent.

Well, that is a non-sequitur. I mean, the "since" does not tell us why it is too large an area. It is probably too large an area because the country -- the company is unlikely to commit to taking all of their future market and make it an area where they are going to sell the good at no profit.

DR. MACKLIN: So I mean, I am not sure if you are asking for more by way of justification or by changing it from the country to something else.

PROF. CAPRON: I am just saying I do not think you can provide a justification for it being the country other than practically that is how negotiations are going to happen.

DR. MACKLIN: Fine.

DR. SHAPIRO: Any other comments?

Alta?

PROF. CHARO The comment on this is also relevant to the previous two sections that we talked about. Particularly the one about the free of charge, number two.

If we look back at the memo that the staff provided, the one that Stu Kim presented earlier, in part five there are examples of language from various countries that talk to this kind of issue. In some cases the language seems to encompass both the individual participants and also the host country or some larger region in terms of access at the conclusion of the trial to a successful product.

Now I see here two examples that interest me particularly. The language in the Ugandan law is one that is quite specific about providing to individual participants, in that case also without charge. It strikes me as the kind of thing where a host country is making a political decision on whether or not it wants to lose a competitive edge in attracting trials by putting into place this kind of provision.

It is making a political decision on behalf of its own citizens. We may have some qualms in some cases about the democratic processes or lack thereof that yield that decision but nonetheless it is made by

people who have all of their own interests on the table and they are being balanced against one another.

By contrast, we see in the case of the Canadian commentary to Article 7.2 something that is kind of equivalent to our discussion here, which is the creation of this obligation on the part of the sponsors and it precludes host countries deciding that they would rather keep a competitive edge and attract more trials.

I would find it tremendously helpful when we speak with Professor Dickens to find out how that is operated in practice. You notice in Canada they say that if it is impossible to assure the continued access that provisions are taken to insure an adequate replacement.

I would really be interested in understanding how this has worked out because it would help me in evaluating how strongly we can word these kinds of recommendations on our own and expect there to be an actual possible implementation and what the cost would be. Because the alternative is to encourage countries to follow the Ugandan model. And if they all do it collectively they can through collective action force this requirement upon sponsors but there is the free rider problem of, you know, the one dissenting country

that then becomes the attractive place to do all your trials.

I do not think this is as much of an issue as it is in other economic situations because these trials are not based only on the fact that the countries are poor but also because of the prevalence of certain diseases or certain environmental conditions. So it is not a pure example of that market issue.

But we have a choice here of encouraging collective action on the part of these countries or taking it on ourselves. I would like to hear more about the Canadian effort to take it on themselves.

DR. SHAPIRO: We can ask him.

PROF. CAPRON: It is not a free rider issue. It is another issue.

DR. MESLIN: As a point of information, the Tri-Council policy statement is not uniformly adopted by every Canadian institution. It is a graduated mechanism now. The MRC has now been disbanded. There is now a new overarching federal funding agency and they are now trying to implement that policy throughout. But it is still worthwhile to ask Bernard about this.

You will not get evidence of how effective and what cost because it is too new and too soon to know.

PROF. CHARO Interesting. Okay. Yes, I know it is not free rider.

DR. SHAPIRO: With respect to just a few small comments with respect to this last recommendation, I am always uncomfortable with words like "all". Like "all" relevant people and "all" relevant -- it just is always -- it just makes me a little uneasy. It sounds to me like a mountain out there. I do not know who it is that considers themselves relevant to these decisions but that is just a small comment. I just always am uncomfortable with trying to be so comprehensive.

With respect to the recommendations themselves, I have kind of a mixed feeling. I am not going to go over the arguments of what again we have about whether they should make these products available and so on again, but this -- as I read this recommendation I kept thinking that we are encouraging people to be teachers. I kept thinking that we are encouraging American sponsors over there to go over and teach people somewhere else how to take care of themselves. And how to manage their own best interests.

I just had some concern about that. I am not against paternalism in all cases but I just -- that was the flavor I had which sort of bothered me a little

bit as I read through this thing and maybe I over read it so I will just pass it on.

Diane? Then we are going to -- Diane, you are going to ask the last question today.

DR. SCOTT-JONES: Okay. I had a comment about number four about the recommendation that the sponsors and the researchers would help to build the capacity to have distribution plants for the drugs or the products of the research. I just wondered, I read back over what was said in the text about that, and once again I think that is an important goal but it seems to me a difficult one for researchers to take on.

DR. SHAPIRO: Okay. I think we have spent enough time today creating problems.

DR. MACKLIN: I have to ask how we are going to find the solutions.

DR. SHAPIRO: Wisely.

DR. MACKLIN: I mean, this is -- I mean, in terms of the next steps in what we have to do. I mean, it is a really serious question because one thing we could ask for is alternative wording for these recommendations. Another, we could ask for suggestions -- whether certain recommendations be entirely eliminated.

What worries me a little bit as I spent a

couple of minutes looking back at the notes from previous meetings where we discussed these same recommendations is that there is some inconsistency from one meeting to the next and Larry pointed this out, I think, quite accurately.

DR. MIIKE: I have not been paranoid.

DR. MACKLIN: Pardon? No, you have been absolutely on the money. And, therefore, it is a little worrisome since I have -- I mean, we have also the transcripts in case anybody wants to see them but, you know, I take notes at these meetings. Therefore, what is a little worrisome is even if we -- I am not sure what the -- if there is a consensus. We know there are a lot of objections. I am not sure there is a consensus.

But what worries me especially as we reach near the end of this process and are going to be coming up with full chapters and recommendations that taking into account what was said here and fashioning them into the next set of recommendations, we can come back with another chapter and I say this with some hesitation, there can be objections again or objections to this.

So I would like to know if anyone based on the history and the work of this commission has a

suggestion for what to do about recommendations when there seems to be not only -- I am not worried about the tinkering with the words, but I mean the substance of these recommendations.

DR. SHAPIRO: Well, I would like to see these side by side. I do not have quite the same recollection but I am sure it is not as careful as your's and other's.

Then just ask -- I do not know if we need to wait until the next meeting to ask people what their views are, which of these that they prefer.

DR. MIIKE: Can I suggest that -- just from what I heard, I guess there would be two questions for me. One is that do people object all together in the direction -- whether it is obligation or virtue or whatever. I do not have a sense that people are objecting all together to the direction of it. It is the strength and the requirement side that we are arguing about.

DR. SHAPIRO: That is my sense.

DR. MIIKE: If that is so then it is easily resolvable in terms of -- I am saying that because you are going to do it, Ruth. It is not us. It seems to me it is easily resolvable just in terms of rewriting the recommendations. Some of these are redundant. For

example, the last one sort of includes some of the earlier ones. But just in terms of -- I would split these up into what should be done for the people that need the product and then the other one is the capacity building element.

I did not hear -- I saw heads nodding in terms of they are agreeing this is the direction to go but it is just the strength of the recommendations.

DR. SHAPIRO: Arturo?

DR. BRITO: One suggestion, Ruth, something Eric said earlier, is that it would help me a lot -- and I am not sure how other people feel but if we did go back now to that introductory chapter and rewrite -- I have the -- with me, with all the notes I took, but I really have lost a little bit just like Eric said. I have lost a little bit of the direction and it does help to have that introductory chapter now to kind of think about these recommendations in that context.

DR. MACKLIN: Thank you. It is coming.

Well, I mean, you never saw an introductory chapter.

DR. BRITO: Well, the proposed outline.

DR. MACKLIN: I mean that was a couple of pages. I mean, what we really need is the full chapter and that should be forthcoming.

PROF. CAPRON: I think you also were right, Ruth, that we are going to have to ask the question of what is described in here as that premise about relevance to the local situation because without that -- I mean, the chairman gave you the challenge. Why is this any different than going in and conducting a business? We do not require relevance to the local situation for that. There is a lot that depends on that.

As to why you might get reactions differently, I believe that at previous meetings I personally have expressed the same questions that I have now but let's suppose I nodded my head at the previous meeting when Larry gave the summary that he gave of what we had said there and then I read what it looked like when it was on paper.

It can be that I had a sense there ought to be an obligation but when you tried to show me how it was explained ethically, I said, well, I guess I am not convinced. Let's just say that I was in that situation. That is the way I feel about this chapter where it tries to build the ethical obligation. I am not convinced by this presentation.

If there are more arguments -- if you rewrite it, you might convince me but I do not -- on the face

of it -- think that. So I am inclined to go the other direction of saying --

DR. MACKLIN: The other meaning?

PROF. CAPRON: The other direction saying this is the way -- the world will be better if it were this way not because people are obliged and a country and a researcher who agree to proceed without this have not done a moral wrong. But if they did it, it would be better overall.

So we end up establishing -- and as Larry says, we can cite examples. They went into this country and set up capacity building. They went in there and continued to provide health care after they left, you know, et cetera, et cetera. We could -- and these are all good examples of people who have done it. It was affordable. It made the world better and the health minister from X, Y, Z country, as Alta says, says I am going to adopt the Ugandan position and so am I and so am I. You are not going to find someone who will be the cheap one on the market who will do it without these requirements and they become requirements. But not because they were derived from an ethical obligation a priori.

DR. MACKLIN: One more point. Not about this but about what we did earlier today. And that is

because of the collapsed time frame from now till the end, we do not have the leisure -- correct me if I am wrong, Dr. Meslin -- we do not have the leisure or the time allocated to this project at future meetings to deal with chapter five, which has not yet been written because we had to hear from our experts, which is what we have done.

We do not have time to do that and then at the next meeting in June look at chapter five and everything else in the same way that we have marched along.

So what I want to ask if the commissioners are prepared to do, is whether you will respond to an exercise that we will put up on via e-mail.

And the exercise will be what we did not get to this morning at the end of the morning, which was the thing -- the items on Stu's chart, the things that are not in the U.S. regulations that are elsewhere, the things that are elsewhere not in the U.S. regulations, and those categories, right. Because what I want to ask is if you will respond -- if we lay these out in some order of importance, not little trivial things, whether we can count on getting a response to the question, the U.S. regulations now do not have this provision, should they, or something like it. Okay.

Just kind of a straw position.

So we can then fashion a recommendation that will say something like the U.S. Federal Regulations should be amended to include this and why.

DR. SHAPIRO: I think we have to do that. I do not think it will get done if we do not. I think we just have to take it on as obligation for each of us.

DR. MACKLIN: Where does that obligation come from?

(Laughter.)

PROF. CAPRON: From our oath of office.

DR. SHAPIRO: Thank you all very much. We are adjourned for this afternoon.

(Whereupon, at 5:39 p.m, the proceedings were adjourned.)

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