35th MEETING

NATIONAL BIOETHICS ADVISORY COMMISSION

Holiday Inn Georgetown
Mirage Ballroom
2101 Wisconsin Avenue, N.W.
Washington, D.C.

October 21, 1999

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I N D E X

P R O C E E D I N G S

OPENING REMARKS

PROF. CAPRON: I have been asked by the audio staff to tell you that if you speak into the microphone and it does not give you any sound it is because they have moved things around and you should simply wait a moment and he will adjust it. I mean, go on talking but your voice will come up louder and he will find out if there is a problem so we do not anticipate problems but if there is one he is aware that it may occur.

I want to welcome our new commissioner, William Oldaker, and ask if he would engage in the process of self-introduction for us with a few highlights and his involvement with the field, and how glad we are to finally be at full strength again.

DR. OLDAKER: Thank you.

I am Bill Oldaker. My involvement in the field originates with my founding a company along with several other people about three years ago called Neurostem Biopharmaceuticals, which holds a patent on

isolating neurostem cells. I became interested as we have gone through this area and the whole issue of bioethics and realized its importance, and the number of unanswered questions compared to the very few answers questions in the whole area.

I am a lawyer by training. I have practiced law in Washington, D.C., for over 30 years. I have held a number of different government posts, none in the areas related to this but at one time General Counsel of Federal Election Commission and prior to that I was a civil rights lawyer for a number of years.

I currently have a law firm in Washington that as a practice has a base in ethics although it is more government ethics than it is bioethics and I also represent a number of candidates on election law and other issues. We also have a litigation section that does general corporate litigation and we do a number of other things that people do in Washington, which is represent corporations, trade associations and unions who have issues in Washington.

But I look forward to this. I am quite excited about the appointment and I will listen today and try and learn as we go on. Thank you so much.

PROF. CAPRON: Welcome. I am sure that throughout the day there will be opportunities for us all to come and introduce ourselves and, as I say, we are very delighted to have you with us.

I have the sense if you had joined the commission a little earlier you would have immediately probably had to recuse yourself because we have spent all this time so you are joining us now as we have just completed the stem cell report. It is perfect timing.

Our Executive Director, Eric Meslin, has a brief report for us.

EXECUTIVE DIRECTOR'S REPORT

DR. MESLIN: Welcome, everyone, to the meeting. As you can see from Professor Capron's appearance to my right, Dr. Shapiro is delayed this morning and has asked Alex to chair the morning's session. Harold will be here around lunch time or

shortly thereafter.

You have at your table folders a number of things that staff has added sort of at the last minute but hopefully you will be able to put it into the appropriate spots in your briefing book. Perhaps the most important is the revised agenda which is also available to the public outside the room.

The agenda has been changed in a couple of ways, hopefully not dramatically. We were originally planning on having background discussions on two of our background papers today. One from Lori Andrews and the other from Mark Sagoff. Lori will be here today. Mark will be here tomorrow morning and the agenda reflects that.

In addition, we are fortunate that tomorrow morning we will be visited by Dr. Neal Lane, the Director of the Office of Science and Technology Policy from the White House, and there are some other materials in your table folder there. A memo from me which will be inserted in your briefing books at Tab 4A, as in apple, and once we discuss it tomorrow

obviously we will make those documents available to the public.

The only other thing I would mention is that we have confirmed for the most part the next several meeting dates for the commission. That, too, is in your table folder.

We will next be meeting on the 2nd and 3rd of December and we are still trying to find which is the preferable hotel, either here in the Washington, D.C. area or in the Baltimore area.

We had planned on meeting in Baltimore but due to some circumstances beyond our control, including all the hotel rooms being taken up in Baltimore, we are meeting in this location and we do not want to deny our colleague, Carol Greider, the chance to have a local meeting, particularly perhaps for that meeting if she is here for that meeting but more on that later. Perhaps from Carol but not certainly from me.

I will not go over all of the dates. Some of them -- the locations have been selected but the

actual hotel space has not been finalized. You will also see that June the 5th and 6th has location to be determined. Some commissioners have already expressed an interest in it being in their hometown and we will say more about that when the time comes.

Finally, with respect to dates, we will get you the remaining dates for this current year and, hopefully, be able to schedule all the way through to 2001 so that we have both on our schedule, that is to say your schedule as well as our logistics contractors, dates so you can plan well in advance and know what you are doing.

The only thing I would say, and I am glad to say at this point, is that we have had a number of staff changes and I hope the commissioners as they both introduce themselves to Mr. Oldaker will also have a chance to meet some of our new and returning staff. They include Jodi Crank, who has graciously returned to be my assistance; Andrea Kalfoglou, a research analyst with us, who will be working on the reproductive technologies report.

PROF. CAPRON: Andrea, wave your hand.

DR. MESLIN: You will meet Andrea.

Many of you have met Stu Kim before. Many of you have met Kerry Jo Lee before. And if there is anyone else that I have missed in the audience -- I do not think I have -- you will get a chance to meet them.

So I am very delighted that some new staff have joined us and I think the commission will see a reinvigorated and a robust staff working on our projects. That is my report for the moment.

PROF. CAPRON: Very pleased.

I cannot tell you how disappointed I am that we are not meeting in Alta's hometown in January.

(Laughter.)

PROF. CHARO: That can be rearranged.

(Laughter.)

PROF. CAPRON: Just for me.

We will have a brief report now from Alice Page and we will be returning to some of the topics that Alice has on her own behalf and in working with

Ruth Macklin on the International Project after our discussion with the Panel on Informed Consent.

Alice?

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

OVERVIEW OF WORK TO DATE

MS. PAGE: Good morning.

Ruth is in Geneva and regrettably could not be here so I am going to provide an overview of the work on the International Project to date.

If you have taken a look at the documents that we have inserted in your briefing books you can see that we have been quite busy at work on the International Project since our last meeting.

There are four items that I want to raise with you at some point but I am going to only at this talk about two of them simply because they are informational and do not require a lot of discussion on your part.

The first thing has to do with a comparative legal analysis that is a piece of the International Project that is something that has just gotten

underway and this analysis will be comparing the ethical principles and guidelines that are found in various international documents, including the Declaration of Helsinki, the CIOMS Guidelines pertaining to both epidemiological studies and biomedical research involving human subjects, the ICH Harmonized Tripartheid Guideline, and in particular the Guideline for Good Clinical Practice, the U.S. Code of Federal Regulations for both HHS and the FDA.

We are going to be looking at two documents that the Council of Europe has produced, the MRC Interim Guidelines, the Canadian Tri-Council Policy Statement, and the French law on the protection of persons on whom medical experiments are performed.

We were looking at the possibility of doing some comparisons with other documents as well and if we decide to select other documents we will let you know.

Now the purpose of the analysis is simply to answer some questions about the differences between the ethical principles and standards that are

contained in the U.S. federal regulations and the guidelines and the laws of other countries, and these various international documents that I have mentioned.

We are also hoping that the analysis is going to answer questions about differences in procedures that are laid out in these documents and other items such as obligations to subjects following completion of clinical trials and the compensation of subjects which are contained in various documents.

Stu Kim is working hard on this analysis is and it is initially being prepared in the form of a chart. We hope to have something for you to look at with regard to this piece of the project prior to the meeting on chapter five, which has to do with enhancing international collaborative research, and I think that meeting will probably occur in February, which is where the material fits in substantively.

The other item that I want to inform you about is our December meeting. We are well on our way making preparations for that meeting and I want to give you a heads up as to what you can expect. I

think it is going to be a very exciting meeting. It is going to focus on chapter three of our outline, which has to do with the risk/benefit analysis. There is going to be lots of testimony from different people about some very controversial and difficult issues. It is going to be divided really into three parts.

First of all, we have commitments to testify about risk/benefit analysis from Robert Levine, from Chris Whelan, and I think we have got either Peter Lurie or Sid Wolfe from Public Citizen lined up.

I do not think that anyone of that group needs any introduction except perhaps Chris Whelan. He is a physician and an epidemiologist from Case Western University. He has done extensive research in Africa and in Uganda, in particular, and he is going to talk about ethical issues he has encountered as a researcher in designing clinical trials through two cases studies, both of which, I believe, have to do with TB and HIV infected persons.

One of the case studies was a placebo controlled study. It ignited a lot of controversy and

was written up in the New England Journal of Medicine a couple of years ago. The other is an ongoing study and it was commenced on the heels of the controversy surrounding that first study.

There is one additional individual who has been invited to round out that portion of the testimony. The invitation has been extended but we have not heard back from that person.

We are also putting together an expert panel to talk to you about clinical trial design methodology. Gary Chase, who is a biostatistician from the Henry Ford Health System in Detroit and from whom we were introduced by a contact at the Fogarty International Center has greatly -- has been a great help in assisting us in developing this panel. He is going to be a member of the panel.

And in addition to him we have a commitment to testify from Steven Lagakos, who directs the Center for Biostatistics in AIDS Research at the Harvard School of Public Health, which as many of you know is the center which designed and analyzed most of the

federally funded clinical trials in HIV and AIDS. He was involved in the ACTG-0076 trials.

My understanding is that both Ruth Macklin and Bernie Lo know Dr. Lagakos.

We have several other individuals from the FDA, from NIAID, and various academic institutions, all of whom have expressed an interest in participating, and we are just trying to finalize those details.

We also have a little bit out of substantive sequence. Dave LePay coming to talk to you from the FDA. He is the FDA representative to the International Conference on Harmonization and he is going to come and talk to us about the good clinical practices guideline.

Finally with regard to this meeting, we do anticipate preparing a set of findings and recommendations relative to risk/benefit analysis for your consideration. This is a much more difficult topic than informed consent and we expect that the recommendations that we make will not be as extensive

as the ones you have seen today simply because we need to have the benefit of the expert testimony before our work can be done but what we will plan to do is lay out for you the controversies and options relative to all of the areas that we think need to be addressed in the findings and recommendations prior to that meeting.

PROF. CAPRON: Thank you.

Alta?

PROF. CHARO: Just by way of a note of information, I recall, at what might have been the November or December '96 meetings when were still meeting at NIH, a really excellent presentation on protocol design with a special emphasis on why one needs placebo control trials even when testing -- even when doing comparisons of already approved drugs.

It might be helpful to try to pull out from the transcripts a summary of that and perhaps even -- I am embarrassed to say I do not remember who made the presentation.

DR. MACKLIN: I believe his name began with a

"T".

DR. CHILDRESS: Bob Temple.

(Laughter.)

PROF. CHARO: We are thankful to this person even though we cannot remember his name.

DR. CASSELL: No, it is Bob Temple.

PROF. CAPRON: Bob Temple is the name.

PROF. CHARO: Thank you. I could not -- if we could get perhaps a kind of refresh -- refresh our memories on Temple's presentation that would be helpful.

PROF. CAPRON: Yes, Larry?

DR. MIIKE: Just a comment, Alex.

The discussions seem to be heavily focused towards AIDS and I wonder whether that is going to be represented -- are we going to have information on what is the range of international research that is conducted so we have some focused perspective?

DR. PAGE: We are very aware of that issue and we are trying to bring in as diverse, you know, individuals as we can. For example, I mean Chris

Whelan, his emphasis is on TB but it happens to be that there -- there just are a lot of people that are infected with AIDS who contract TB and so I mean it is the thing that sort of ignited the whole controversy and we cannot stay away from it but we are also trying very hard not to just focus exclusively on that.

PROF. CAPRON: Rhetaugh, did you have your hand up?

DR. DUMAS: No.

PROF. CAPRON: Okay.

Yes, Bernie and then Jim.

DR. LO: That sounds like a wonderful agenda for next time.

I was wondering if there is any possibility that we could try and get some testimony from people from developing countries, how they assess risks and benefits? It is obviously a crucial issue and I think -- you know, I know it is hard to sort of schedule those things but I think some of the criticisms that Public Citizen made in the handout we got under one of our tabs, I think, really is on point here that we

would be wise to sort of hear directly from people who live in the country where this research is going to be done and who face the problems.

DR. PAGE: That is something we have considered and we are trying to work on bringing some of those people here to testify to you. I am not sure when it will happen but we are working on it.

PROF. CAPRON: I want us to come back to the bigger issue that lies behind that after we have had a chance to hear from our panel.

Jim?

DR. CHILDRESS: Since I will not be here this afternoon I wanted to make one point about an element of tone and this comes up in a couple of different places here, "and where ethics is not and should not be a barrier to the research enterprise." Now I agree with that and the way it is meant here but I think actually that is subject to considerable misunderstanding. That is to say ethics does and should set a barrier to certain research enterprises if they are poorly designed and so forth. That point

is made here but I just worry about the blanket statement "ethics is not and should not be a barrier to the research enterprise" and then the discussion of -- in the informed consent area of the way in which, well, if informed consent requirements are a barrier to research then we need remedies to get around those barriers.

I worry about that kind of tone but I agree with the point that is being made. We need ethics in the very beginning, et cetera, et cetera. But I think that we could find a different way to state the point.

DR. PAGE: Okay. We will do that. We actually rewrote that in response to something that a researcher told us, that ethics was a barrier to research so that is how that came up.

PROF. CAPRON: Well, I think that as we began the enterprise, I think, there was a sense that misunderstandings about ethical objectives or requirements ought not to be a barrier and that if there were different ways of achieving the same results one of the questions was do the present U.S.

regulations permit use of alternative methods to achieve a result, what is the equivalence of the result when different methods are used and so forth, and that tone, I think, is appropriate but I would certainly agree Jim that we do not want to sort of say that the major objective is getting ethics out of the way so that the research can go forward.

I am sure others will have ideas about potential speakers, avenues to pursue and the like on the two topics that Alice has already described and I encourage you during the meeting or by telephone or e-mail to be in touch with Alice and Eric about those points.

And now it is our opportunity to hear from our panelists if they are both here.

Welcome to you both.

The biographical information about Sam Avrett and Sana Loue are in the materials. They both have not only substantial academic background in the topics that they will be talking to us about but a great deal of practical experience.

Taking nothing away from Mr. Avrett, I was particularly intimidated reading Sana's CV since she, having already become a master's in education and a lawyer, then took a master's and doctorate in public health, and is now on her way to becoming a medical anthropologist, and so we are obviously hearing from someone who speaks from a great many fields of background.

We will start with Sam and then Sana.

PANEL ON INFORMED CONSENT

MR. AVRETT: Great.

Alice asked me to talk about the importance of community consultation as a supplement to individual informed consent so what I would like to do is just say who I am and then why we need community consultation, what community consultation is in my mind and some of the successes and challenges that I see.

The perspective from which I speak, I have been an advocate and educator on HIV for nearly ten years now. I am also a person at risk for HIV. I am

HIV uninfected. My partner of the past seven years is HIV positive so I am a consumer of prevention and I am also a demander of research. I am desperately interested in AIDS research to provide new tools to keep my partner alive and I am desperately interested in research to provide vaccines to keep me HIV uninfected and that is why I have become an HIV vaccine research advocate.

I am not a trial participant right now. I am a member of a community that is vulnerable simply because of -- in many states in this country I can get arrested for fooling around with the wrong person at the wrong time but I must say that I am not representative of all vulnerable communities and I do reiterate what was said here. If you are going to be talking about community consultation and informed consent with international clinical trials there is a question to be raised about who are you talking to, who are research participants from poorer countries, and from vulnerable populations.

Community consultation -- I guess that it all

boils down to when you have got people studying people you need communication between the people who are studying and the people who are being studied or it will not work. And that to my mind is the roots of Nuremberg and Helsinki and the Belmont report.

You need communication with people being studied. You also need communication with local citizen opinion leaders, gatekeepers and advocates who might have useful perspectives on the design and conduct of research.

In AIDS research there has been useful community consultation, with people with AIDS and HIV, with community leaders, with public health officials and community docs here in this country.

I think of the two reasons why you need community consultation as, one, we are trying to do ethical trials in an unethical world. You need a collaborative process because even the most perfectly designed research trial is being implemented in an imperfect undesigned world and especially in international trials clinical trials are recruiting

vulnerable populations in a range of global health priorities and situations.

Clinical trials increasingly, and in the case of preventive HIV vaccine trials, are recruiting people who are vulnerable because of poverty, because of illegal or stigmatized activities such as drug use or homosexual sex, and vulnerable because of power dynamics affecting their autonomous decision making, some women in many parts of the world, military, students and government employees even.

We also -- the second reason is we need community consultation to supplement individual informed consent because although I believe that individual informed consent is always possible we are social gregarious animals and knowledge, attitudes and beliefs are always formed in a social context. If we want the individual to have sufficient knowledge and comprehension for that person to provide fully informed consent then knowledge must be enhanced by a robust community education and community debate.

The local -- in this country there is a

network of vaccine trials, trial sites, called HIVNET and the community educators of those trial sites with the community advisory boards put together a set of best practices for community consultation and what they essentially said was in best practices for clinical research sites you need to do a bunch of things.

You need to first and immediately set up local community advisory boards, national community advisory boards and international community advisory boards.

You need some sort of infrastructure for open dialogue between the researchers and the people being studied and community leaders.

You need to demonstrate solid plans for protection of research participants and communicate those.

You need to provide full and honest information about your research plans as early as possible. Do not invite community to the table after the research plans are already set.

Treat this as a true collaboration. Again do not invite people in after the fact, as an after thought or as an adjunct to the research. Bring people in as soon as you know that you want to do research in the community to discuss what the goals are, what the potential benefits are, and what the risks are.

Engage in a significant community education effort. In New York, where I am from, we have three trial -- vaccine trial sites right now and one community educator, who is full time trying to run around doing community forums and generating some awareness, and articles and media.

And be capable of engaging at a national level on debates and issues as they arise. Oftentimes, I think the researchers do not have the capability of responding to things in the media immediately and engaging in that dialogue.

There have been lots of successes from the AIDS advocacy experience. I think that we have had some really good success in figuring out good

implementation of trials but it has required a lot of ongoing consultation.

Public citizens have had a hard won voice on the relevance of research plans and trial design to help research needs. Early on there was community input on inadequate focus on opportunistic infection research and AIDS, inadequate focus on women and AIDS research, and more recently a voice on whether U.S. Government funds should be spent on gp120 efficacy trials.

Communities have had a voice here in the United States in discussing the feasibility, acceptability and relevance of preventive HIV vaccine trials.

Public citizens in the United States have had a role in vaccine trials in their implementation and identifying unforeseen risks of trial implementation such as social discrimination against participants and advising on trial design such as recruitment criteria and advocating on selection of research subjects and inclusion. There has been a good amount of advocacy

to try to include women in preventive vaccine trials in this country.

I think one of the greatest challenges is that we need more local community advocates for the community side of the consultation and this is particularly true internationally. Research cannot be about pharmaceutical priorities and on market priorities. It cannot be about hypothesis driven science priorities purely. It cannot even be driven purely by global war on disease priorities.

It has got to be driven, I think, by local public health needs and local public health priorities, and you need to have the local voice to be able to express that.

So I guess that I think all of our goals -- the goal of all of us is to get good clinical trials. For any ethics panel it is difficult to dictate absolutes and dictate absolutes across every country, every trial and for every person.

If we want to be lowering risks and maximizing benefits through informed consent and

community consultation then we have got to realize that lowering risk cannot be framed in absolutes. It is a continuum or, in the phrase that I hate, a slippery slope and the best test that we can do is empower people so that they can stand steadily and knowledgeably on that slippery slope and negotiate it, both as individuals and as teams of researchers who are engaging in research in individual countries.

And to that question about ethics as barrier I think that we cannot let risk and the avoidance of risk paralyze research. Again it is a continuum.

And I guess that -- yes. To repeat, we have got to work to empower people and teams of people to be able to negotiate that continuum of risk and continue to work for maximizing the benefits of trial and minimizing the risks.

That is it.

PROF. CAPRON: Thank you.

We will have questions for Mr. Avrett after we hear from Dr. Loue.

We have an article which she co-authored

three years ago in the Journal of Law Medicine and Ethics among the things that we have looked at and I think part of what she will be talking about is that background from the Ugandan experience.

DR. LOUE: Good morning and thank you for inviting me to testify. It is a pleasure to be here.

I am going to focus my remarks on Uganda's application of international principles governing informed consent to the Ugandan context.

In July 1997 the representatives of the National Consensus Conference on Bioethics and Health Research in Uganda voted unanimously to adopt what is now titled the Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda. I will be referring to that as the guidelines. This really -- this will give you an update of where things are now from the time of the article that was referred to.

This particular consensus conference included representatives from a wide range of governmental and nongovernmental agencies, including the Ministry of

Health, the Ministry of Defense, the Ministry of Education, the Attorney General's Office, the Uganda National Council of Science and Technology, the National Drug Authority, the National Cancer Institute, McKerere University, which is one of the two medical schools in the country, various medical associations, including religious based medical associations such as the Islamic Medical Association and the Protestant Medical Association, nursing and pharmacist organizations, various churches, legal service agencies, human rights organizations, and media personnel. The public was also invited to participate in the national conference.

The vote to adopt these guidelines, which was unanimous, really represented the culmination of a three-year examination of Uganda's practices and policies regarding research involving human subjects.

The newly adopted guidelines made significant procedural and substantive changes to the process of bioethical review in Uganda and I will be focusing on the ones that pertain specifically to informed

consent.

To some extent I will be reading because I do not want to confuse the provisions that I am referring to.

Previous ethical review of research proposals have required the informed consent of individuals but had really failed to enunciate the basic elements by which to judge the adequacy of any particular proposal or any particular research undertaking.

The guidelines mirror to a significant degree the provisions enunciated in the then-existing, because we are talking about 1997, U.S. regulations and guidelines one through four of Science Human Subjects in paragraphs one, 10 through 13, 26 and 47 of Science Epidemiology, and the Nuremberg Code.

The guidelines include, for example, a prohibition against exculpatory language and mandated description of the risks and benefits of the research, and statements that research is to be conducted, that participation is voluntary, and that the participant may withdraw at any time without a loss of benefits to

which he or she would be entitled.

However, the guidelines depart from paragraph five of Science Epidemiology by specifically prohibiting an investigator from relying on the permission of a community leader for the participation of community members in research.

In all situations other than those specifically excepted, such as minor children who are unable to give consent, the investigator must obtain the individual's consent to participate in the research.

The development and adoption of this requirement of individual consent essentially necessitated the re-examination of various aspects of Ugandan customary laws. Unlike many Western cultures, Ugandan traditional practice really demanded the subordination of an individual's wishes such as an adult son or a wife to those of a specified family leader such as the father or the husband. And subordination of an individual's wishes could be further extended to those of the community or the

tribe.

DR. CASSELL: Could you slow down a little bit?

DR. LOUE: Sure. Thank you.

The rejection of a leader's permission as an adequate basis for an individual's participation in research really stems from Uganda's own recognition of its past history and its experience with tyranny, torture and the elimination of targeted groups. Perhaps what is most well-known to people in the United States are the historical eras of Idi Amin and Obote.

The guidelines attempt, however, to defer to some extent to Uganda's customary traditions and laws by including a provision that allows potential participants sufficient and adequate time to confer with anyone else of their own choosing in order to discuss the particular parameters of the research and to minimize the possibility that they may be subjected to undue influence or coercion.

The guidelines also reject a requirement of

written informed consent and again this stems from Uganda's past experience of torture and persecution of individuals who are found to be associated with particular entities or particular enterprises and reflects the sensitivity to individual's reluctance to necessarily sign a piece of paper that attaches their name to an enterprise.

The guidelines set forth additional protections for six classes of individuals: Pregnant women, children, prisoners, the mentally ill and behaviorally disordered, soldiers and refugees.

In general, the provisions are consistent with the Nuremberg Code, with various provisions of the Helsinki Declaration, as amended, of guidelines five, six and seven of Science Human Subjects pertaining to research involving children, the mentally ill and behaviorally disordered, and prisoners, as well as regulations adopted by the U.S. Department of Health and Human Services.

However, there are several differences from the U.S. provisions that I think are noteworthy.

Now until very recently United States regulations restricted the ability of pregnant women to participate in clinical research. The guidelines prohibit pregnant women from participating in research only where the clinical research is not designed to meet the needs of the mother. The fetus is to be placed at a risk to the -- at a minimum risk to the extent that it is necessary to meet those needs.

The provision potentially permits the health needs of the mother to override any potential risks to the fetus in balancing them.

The requirement of the father's consent to the woman's participation which would have been required under Ugandan traditional law and is premised on a recognition of joint parental consent for the health of the fetus is eliminated in situations where the clinical research is designed to benefit the mother and meet the needs of the mother.

The Consensus Conference's decision to adopt this position reflected an awareness of women's social vulnerability and their vulnerability to disease

transmission as a result of numerous traditional practices in Ugandan society, which includes polygamy, wife inheritance, and the acceptance of male infidelity but not the acceptance of female infidelity.

After an examination of policies and regulations and procedures in the United Kingdom, Australia and the United States specifically, the new guidelines distinguished between consent and assent in the context of children's participation.

Assent requiring a lower level of understanding must be obtained from the child in all cases as a condition of his or her participation in research in addition to the permission of the parent or guardian where the parent or guardian can be identified and located and they have not abandoned the child. This requirement of assent again constitutes quite a departure from Ugandan tradition, which normally would not have considered the voice of the child in making these decisions and the child would have been subjected to the complete authority of the

male parent or guardian over his children.

Like the United States, Uganda provides for the participation in research of children who are wards. Unlike the United States, the guidelines permit research involving such children to be conducted only where it is specifically related to the children's status as wards and there are additional significant differences that exist now between the two country's provisions.

First, the United States provision is limited to children who are wards of the state or any other agency, institution or entity. In contrast, Uganda's provision encompasses as well children who have no identifiable parent or guardian or have been abandoned by their parent or guardian.

As currently written, the Ugandan provision would permit a child to participate in research prior to the assumption of responsibility for the child by a guardian, institution, agency or governmental entity. It is not clear that U.S. regulations would allow this.

The Ugandan provision fails to provide guidance, though, as to which individuals or entities are responsible for working with the child to render that decision in view of the child's inability to consent.

United States regulations permit the participation of children who are wards in research involving greater than minimal risk with no prospect of benefit to the individual participates as well in research that would not otherwise be approvable but is expected to yield findings critical to the understanding of disease or its prevention. Now in these circumstances the U.S. regulations provide additional safeguards, including the appointment of an advocate for each child who is a ward in order to provide a perspective in addition to that of a parent or guardian and that advocate is required to act in the best interest of the child.

In contrast, Uganda's guidelines explicitly prohibit the participation of orphans and street children in research involving greater than minimal

risk regardless of any benefit that may be derived from the research. This prohibition stemmed from a concern for the growing numbers of children who had been orphaned or abandoned as a result of HIV infection.

The guidelines also provide additional safeguards for the protection of prisoners and I will not detail those here. They are very similar to those in the United States.

An awareness of the need for provisions the protection of the mentally ill arose from the observation of increasing numbers of individuals who were suffering from HIV related dementia and pursuant to Ugandan tradition these individuals would have otherwise been deemed able to consent to participation in research by virtue of their age and their family status so these protections really represent something new.

They also encompass persons who are behaviorally disordered due to the inability to distinguish between those who may be behaviorally

disordered and those who are mentally ill because of diagnostic difficulties.

Research involving the mentally ill or behaviorally disordered is consequently prohibited absent the informed consent of the prospective participant to the extent that they are able to provide consent and the permission of an incompetent individual's guardian, conservator or other authorized individual. This requirement then prohibits the participation of incompetent individuals who do not have a guardian or a conservator.

And additionally the consent of a guardian or a conservator or other authorized person must be supported by evidence of legal authority to make that decision for the individual. Again this is new under Ugandan law. That was not previously required.

Research involving mentally ill or behaviorally disordered individuals is prohibited if the research can be carried out with individuals who are in possession of their full mental capabilities,is not relevant to the health needs of those with mental

or behavioral disorders, involves more than minimal risk or is potentially no more advantageous to the individual than currently existing interventions.

The newly developed guidelines encompass -- provide additional protections for two classes of individuals that are not encompassed by United States regulations. The first pertains to soldiers and the desire to protect soldiers stemmed, in part, from concerns for potential abuse by Ugandan leaders and these concerns again come from a history of fears that were imprinted by the Idi amin and Obote regimes.

In addition, these concerns came from members of the Consensus Conference's experience or their actual knowledge of the involuntary participation of soldiers in research that had been conducted by the United States. Most notably the LSD experiments of the 1960's and the radiation experiments during the Cold War era.

So the guidelines were framed to apply to all military personnel regardless of rank and the requirements for approval of the protocol are similar

for those for research involving prisoners. The institutional review committee, which is a new phenomenon under these guidelines and is similar to the United States Institutional Review Boards, must include at least one enlisted soldier where the proposal being involved involves soldiers and may not otherwise include individuals currently associated with soldiers in the military.

Unlike the U.S. regulations, Uganda's guidelines specifically enumerate refugees as a class of individuals marrying additional protections. This stems from Uganda's direct experience with refugee populations seeking refuge from political turmoil and genocide in Rwanda and what was Zaire.

Research involving refugees may not be approved unless the research question is answerable only with the participation of refugees. The research is relevant to the health needs of refugees and will benefit refugees as a class and no more than minimal risk is involved.

At least one member of the IRC must be a

representative of a human rights organization that has as its primary focus the protection of refugees and refugee populations.

The guidelines, as I said before, were formulated following review and consideration of the principles in the Nuremberg Code, the Helsinki Declaration, and the laws of the United States, Australia and the United Kingdom.

At this point it is anticipated that there will be an annual or biannual review of the guidelines to reevaluate their soundness in what is now a continuously changing context and to further develop and elucidate the ethical principles that Uganda wishes to apply.

Thank you.

PROF. CAPRON: Thank you very much.

Just by way of information, have you had further direct contact with the implementation of these guidelines?

DR. LOUE: Yes, I have. I am working -- actually Chris Whelan's name was mentioned before. He

is the principal investigator of a training grant that Case Western Reserve University has with Uganda and one component of that training grant is this bioethics component which is the one that I have been primarily responsible for. At this time we are working on developing a presentation that can be introduced to researchers in Uganda, in part, through educational sessions and, in part, through the media that will both explain the guidelines and the need to conform to individuals as well as train the media to help us do that, and to disseminate information regarding the guidelines to participants in research.

PROF. CAPRON: And is the basic infrastructure in terms of these IRC's in place at the medical schools yet?

DR. LOUE: No. And that is one of the basic problems, is that unlike the United States, for instance, there is no greater infrastructure that really has oversight authority and enforcement authority and that is true both at the institutional level with the IRC's and at the national level.

At this point in time there is still significant controversy, for instance, between the National Drug Authority, the Uganda National Council of Science and Technology, and the Ministry of Justice as to exactly who should assume responsibility for that oversight function.

On the institutional level it still remains a problem in terms of providing adequate training to individuals. The notion of an unbiased, uninvested review committee is still something that is quite new to Uganda.

So, no, those structures are not in place.

PROF. CAPRON: Thank you.

Questions?

Alta?

PROF. CHARO: I think this kind of follows on the kinds of things that Alex was asking. It is just more information if I may.

I am going to presume that the guidelines that you have described would be enforced both for publicly financed research and privately financed.

There is not the distinction that is made in the U.S.

DR. LOUE: Right.

PROF. CHARO: Here the only enforcement mechanism we really have is the withdrawal of funding eligibility in the context of regulatory violations. What kinds of enforcement mechanisms have been proposed for these guidelines? What would happen to somebody if he or she did not follow these guidelines in the course of doing research?

DR. LOUE: There have been a number of potential consequences that have been written into the guidelines. One includes the prohibition of ever conducting any research in Uganda. One includes the termination of a specific research project. Another is the temporary suspension of a research project pending further investigation and where the Ugandan Government is actually providing funding or support, the termination of that funding or support.

I think to a large degree the framers of the guidelines contemplated that the media would act as an enforcement mechanism in the sense that it would be

through the media that violations would really come to the attention of both whatever enforcement authority is actually put into place and the attention of research participants.

Unlike, the United States, for instance, communication in Uganda can still be somewhat difficult. Many people do not have telephones, transportation infrastructure is no where comparable to what we have in the United States so that the media really can serve an important function that is beneficial -- it may be beneficial in the United States but is really critical in Uganda.

PROF. CHARO: The second part of the question has to do with the mechanisms for identifying problems that might result in a need for an enforcement measure.

In the absence of consent forms that have been signed, which provide a documentary trail that can be used for audit and oversight, what other mechanisms have been proposed in the guidelines to allow people after a research trial to go back and ask

was everything done appropriately?

DR. LOUE: I think this is a problem area that really requires further modification in the guidelines. The guidelines do specify, for instance, that if someone does not want to sign their name, they can sign an X. The problem then, as you suggested, is that if someone wants to do a post-audit of the investigation and make sure that everything was done according to the guidelines it becomes very difficult to know who actually participated in the study.

Again I think the framers of the guidelines are hopeful that the media will play a critical role in helping to inform research participates of their rights in participating in research and the mechanisms that will be put into place for them to file complaints directly.

PROF. CHARO: Do you think this is realistic, the reliance on publicity as the main form of enforcement?

DR. LOUE: I think at the present time given the absence of adequate funding it becomes the most

critical component. I do not think it can be the only component and I think a great deal of trust is being put -- placed on investigators' integrity and I think to some extent even the representatives of the Consensus Conference were uncomfortable with this given Uganda's past history.

Again absent sufficient funding to develop an adequate infrastructure it really does become almost the most critical component.

PROF. CHARO: Thanks very much.

PROF. CAPRON: Bernie?

DR. LO: First of all, thank you both for your presentations. I want to carry on the tradition of asking a double barreled question to get the most out of my speaking opportunity.

The first question really has to do with the role of public representatives, and it is really addressed to both of you. How feasible is it in developing countries to have the kind of activism that Sam was talking about in the AIDS community in the U.S.?

Dr. Loue, you talked about the composition of this commission and it was striking to me that most of the people were officials, public leaders, and I do not know how feasible it is to sort of get down to the level of people who are actually going to be subjects of studies. So comments on that would be useful.

And, secondly, in some of the other materials we have received on informed consent in research in developing countries there were concerns raised that some of the things we take for granted as being part of a consent process in the U.S. really are antithetical to the way medicine and society work in some countries so that the notion of telling a person they have a grave diagnosis in order to allow them to give informed consent for research is standard here and yet in countries where you do not tell people they have cancer, do you then change the rules because it is now a research project?

And another objection or concern raised was that to tell people that -- to tell potential subjects

that the choice of therapy in a randomized trial will be determined by chance and the doctors do not know what is best sort of undercuts the -- in some situations a social kind of agreement that the doctor always knows what is right and so do we include -- do we insist on including those provisions as part of the information that must be disclosed so that people can give consent or do we somehow modify what we would do taking into account sort of the traditional practice of medicine in that culture?

I thought it was interesting in your presentation how it sounds like this discussion of research ethics has really helped change the way Ugandan law thinks about power relationships and the rights of individuals and so forth.

So if you could address those two issues it would be terrific.

DR. LOUE: Sure. I would agree with you. I think that this discussion really has changed in many ways the way many people are applying Ugandan law and thinking about Ugandan law. I think that has also

been fueled by a number of changes, for instance, that were effectuated by Uganda's new constitution, which specifically recognizes the rights of women and minorities, which heretofore had not been recognized.

In terms of community advisory groups or activism the way that we know it in the United States, I think it is quite difficult, for instance, for something like that to take hold in Uganda and that is really for a number of reasons. I have had students, for instance, from Uganda who when they are in the United States they are focused on their research and when I have said to them, "Well, what will you do when you go back to Uganda when you have finished your doctoral training," and they have said to me, "I will try to figure out where I am getting clean water from." So I think we have no real understanding of the impediments that people face on a daily basis.

Many of the people who participate in trials in research may have to travel extraordinary distances to get there and they spend all day there and then travel back. People who go for care in hospitals very

often if their families do not come with them and provide them with meals in the hospitals they are not going to eat in the hospitals. It is very clear. So to ask that people who are eking out a minimal living who have significant transportation difficulties, financial difficulties, who in addition to caring for their own families may have assumed responsibility for nieces or nephews or grandchildren, relatives who have died or who have become very ill themselves with either HIV and/or tuberculosis, I think is not really very realistic.

I do not rule out the possibility that it may happen but I think under current circumstances with the exception of perhaps people living in Kampala, which is the major city, it would be very difficult, for instance, for people who are in a nearby suburb of Kampala or a village of Kampala to not only travel in to participate in research but to also serve on advisory boards or assume an activist role.

One of the other barriers that I think we do not think of when we speak of Uganda because the

official language is English is that the majority of people who do not have formal education do not speak English and they do not read English and they do not write English. Uganda has a very high illiteracy rate and that is particularly true among females.

Until very recently families were required to pay for public schooling for individuals and when the children reached university age if they were accepted into a university, at that point it became free education. What has been the practice is that when the family has to choose who will be educated the practice has been to choose the oldest male child so that the majority of younger children in families and certainly the majority of women are uneducated and would be -- they would find it extremely difficult to assume that kind of role in addition to the other roles.

In terms, for instance, some of the medical practices that attend participation in trials, I think for me a telling experience was when I was visiting with one of the leading OB/GYN practitioners in Uganda

and a woman had come in for a pelvic exam, and I noticed that he did not perform a pap smear and I said, "Why are you not doing a pap smear?" And he looked at me as if I were absolutely out of my mind and said, "First of all, we cannot afford to do pap smears. And, second of all, what good is it going to do if I discover she has cancer? There is nothing I can do for her so why am I going to tell her that and have her know -- have her worry about when she is going to die? She knows that some day she will die like the rest of us."

And I thought that that remark was really quite telling and I think it does illustrate what you are saying, that things that we take for granted as part of sort of ordinary medical care in the United States are really seen as extraordinary in Uganda.

This has really posed, I think, a difficult challenge for representatives of the National Consensus Conference to deal with in the context of clinical trials. There is clearly recognition that when an individual agrees to participate in a clinical

trial that regardless of how we might perceive it, Ugandans perceive it as being coercive. There is no choice. There is no other possibility for obtaining a higher standard of medical care. Whether you are given placebo and whether you are given experimental treatment, the care that will go along with that for the condition under study is far superior to anything that Ugandans will be able to obtain within their medical system unless they are one of the very privileged and monied few.

Trying to balance that then with creating a situation to minimize the risk that individuals will be exploited because of those circumstances I think has posed great difficulties. What the National Consensus Conference has devised have been a number of provisions to attempt to address this problem.

First the guidelines specifically permit placebo controlled trials under specific conditions. One is that -- the condition of clinical equipoise, which I think most of us are familiar with. The second is that the placebo group is to obtain the

standard of care that is recognized as the local standard of care. You can imagine the kind of debate that went on at the Consensus Conference trying to decide whether this was to be the best practice that existed anywhere globally or whether this was to be local practice and the consensus finally was that it was to be local practice again because of the coercive influences.

In an attempt to balance that, though, what the Consensus Conference also devised as part of the guidelines was essentially a three-part requirement for any investigator coming in to do clinical trials. One is that the investigator must provide medical care to the research participants during the course of the study for the condition that is under study.

In addition there must be a follow-up period of care, which the exact time of that period is going to be dependent on the particular disease under study, the particular treatment, and the particular conditions at the time of the trial, and this was because there was a sense that participants in trials

were feeling abandonment.

Again this goes back to your comment, I think. In the United States we have the possibility of negotiating with our health care providers. In Uganda what the health care provider tells you is really seen as unquestionable authority. The provider knows best. You accede to the wishes of the provider and then when that provider is no longer there and treatment ends at the end of a trial the patient is left with a sense of abandonment.

The second requirement is that an investigator must use their best efforts to make the treatment if it is found to be successful available to the community following the close of the trial and this was not made mandatory.

There was recognition, for instance, that investigators may not be able to do this, that there may be financial constraints. There was also recognition that this if it were made mandatory, it would essentially require a benefit for participants in developing countries that is not now guaranteed to

even participants in developed countries.

So, for instance, if a drug is found to be successful in a trial in the United States there is no guarantee that that drug will then be made part of the formulary for the AIDS Drug Assistance Program. So there was recognition of that.

The third requirement is that the investigator must provide proof of insurance and must provide participants with information relating to any damages that will be available as a result of any injury or death arising out of participation in a clinical trial. This, I think, is really quite a departure from what is now required under U.S. regulations where we simply require that the participant be informed.

Uganda now requires that there be such a provision in place, that there be an insurance policy to cover any injuries or deaths arising out of that trial prior to the initiation of the trial and that the participants be made aware of that compensation.

DR. LO: If I could just follow that up?

PROF. CAPRON: Bernie, yes, a quick follow-up. I have now Steve, Diane, Eric, Larry and Trish on the list and now Alta.

DR. LO: That was really wonderful. There is one part of my question I wanted you to address that had to do with what do you actually have to disclose in the consent process. One of our other papers in the briefing book talked about an adjuvant therapy trial for breast cancer in Vietnam and the argument was you do not tell people there they have cancer so that should not be in your consent form. You do not tell people the doctor is not sure what the best treatment is so you should not put that in the consent form.

In your Ugandan guidelines do you have to disclose the diagnosis, do you have to disclose the fact of equipoise?

DR. LOUE: You do have to disclose the fact of equipoise. You do not have to disclose the diagnosis but you have to offer the diagnosis to the individual.

PROF. CAPRON: Okay. Steve?

MR. HOLTZMAN: No.

PROF. CAPRON: Steve passes.

Diane?

DR. SCOTT-JONES: I have a question about the research that is done in Uganda. What percentage of research done there involves collaboration or ties with United States researchers or researchers from England or other developed countries? What I would like to know is how isolated is the Ugandan research community from the international research community? I would like to know to what extent is research done in Uganda?

DR. LOUE: I cannot answer the question unfortunately with specific statistics and I apologize for that. I would say that I think that the Uganda professional research community is very well connected to other members of the international research community. There is significant research being done in collaboration with the United States, with England, with quite a number of the Scandinavian countries, I

believe with Germany. I think with the Netherlands as well so I think there is a -- I think there are very good linkages with resources there.

In addition, I think that as a result of those linkages within -- I have been going to Uganda now for five years and even within the five years I think you can see an increasing sophistication in terms of the knowledge of the international principles and guidelines and increasingly complex discussions arising out of discussions of the Ugandan context and how these principles apply in the Ugandan context.

Whether the majority of research is being done with international funds is unclear and I should probably describe a little bit more about what happens with research in Uganda.

My conversations, for instance, with individuals from the Ministry of Justice and with the Uganda National Council of Science and Technology, have indicated that they actually have many fewer difficulties with researchers coming in from outside of Uganda than they do with Ugandan researchers

themselves and the reasons for that are many.

Uganda law specifically recognizes what we would call traditional medicine. What has happened in the context of the HIV epidemic is that individuals who are traditional practitioners as well as some individuals with medical degrees are now marketing the products which they claim cure AIDS as a result of tests that they have conducted.

Up until now, and currently, the "trials" of these products have not come under the jurisdiction of either the Ministry of Justice, the National Council on Science and Technology or the National Drug Authority. They have been specifically exempted from governance under Ugandan law and this was a hotly contested issue at the Consensus Conference.

The ultimate decision is that these trials which many believe constitute the majority of "research" in Uganda should come under the jurisdiction of whatever agency assumes jurisdiction for the enforcement of the guidelines. Clearly the traditional practitioners are unhappy with this. The

traditional pharmacists are unhappy with this.

Some believe that that really -- that these particular types of trials really constitute a large proportion of the research that is conducted in Uganda but no one really knows to what extent that is true or not true. I think everyone at the conference had heard the litany of horror stories that had come out of individuals availing themselves of these kinds of products.

There are studies that are conducted in Uganda by Ugandan researchers outside of this traditional context, for instance through the medical schools, that although they traditionally have not been subject to the parameters that are enunciated in the guidelines conform to a much greater degree, for instance, to the Nuremberg Code and the Helsinki Declaration than the traditional research.

PROF. CAPRON: Sam, do you have anything to add to that?

MR. AVRETT: All I was going to say is responding to the previous question and following up

with the comment about increasing sophistication of the dialogue about research in Uganda, I would say in the previous question about what is the chance of an active community voice in Uganda and other countries, I would say there is a very good chance and, in fact, it is already happening.

And that my -- from watching from the United States on the progress of a Phase I HIV vaccine trial in Uganda, the media has been very active in talking about those trials. The AIDS Service Organization in Uganda has leaders who have been very engaged. And that there has been a voice from politicians, from community activists that has focused attention, and from the media that has focused attention and shaped public opinions, and that in recent debates internationally about UNAIDS guidelines for vaccine trials, the perinatal short-course AZT and so forth, the activists from Brazil, from Thailand, from elsewhere have not been silent at all so I would not discount the voice.

DR. LOUE: If I could respond. I think we

may be defining activism somewhat differently in the sense that I have real questions, for instance, about the extent to which a journalist who generally in Uganda has significantly better education than someone living in a village or the extent to which someone who plays a leadership role in one of the nongovernmental organizations can truly represent the thoughts and experiences of individuals from the outlying villages who may be traveling to participate in trials.

So when I speak of activism and how difficult it is I am really referring, I think, to people who clearly know that they have whatever disease or condition is under study who are not part of this smaller educated cadre in Uganda and who quite honestly will never be part of that small educated cadre.

I truly do not know the extent to which individuals in those positions can represent -- can claim to represent and embody the voice of these other individuals.

MR. AVRETT: I agree with that.

PROF. CAPRON: Eric Cassell?

DR. CASSELL: I found this -- I found both your presentations and your article very, very helpful.

I mean, one of the things that we are supposed to -- we are protecting human subjects and it is important for us to remember what we are protecting -- what we are trying to protect. We are trying to protect from harm in research. We are not trying to protect their rights. Although in the United States often it comes down to protecting rights as though that automatically assured protection from harm because it allowed a person to express their own desire.

In the United States prior to the present era, that is through the late -- through the early '60s the protection from harm was primarily the obligation of physicians to their patients and the large well-developed ethics -- we now call etiquette but ethics at that time was devoted to that. That then became paternalism and you all know about that.

But the minute we move towards emphasizing the autonomy of persons who cannot really exercise their autonomy, at the same time we allow physicians to get off the hook. After all, they are not responsible anymore as much as they were before. So I am interested in what the ethos of physicians in relationship to patients is in Uganda and -- of course, they are educated and so forth, and I think you know what I am talking about.

DR. LOUE: Yes. I think that is a great question. In Uganda generally physicians demand or they command a great deal of authority. When a patient goes for a clinical examination -- even outside of the research context it is assumed that the physician knows what he or she is doing, that whatever recommendations the physician makes are going to be -- are the best recommendations and that they are in the patient's best interest.

I think it may be more difficult. I think we in the United States sometimes have difficulty in a research context separating the clinical function from

the research function. I think that may be true to an even greater degree in the Ugandan context where when someone goes to see someone with a white coat they are a doctor. The fact that this is research and not clinical care -- even though it may be explained to the best of anybody's ability to explain it and even though individuals may signify that they understand -- I do not know that there is always real understanding of that or remembrance of that.

Some individuals, for instance, have suggested that participants need to be reminded on a periodic basis that this is research, that this is not their new doctor. That has not been incorporated in the guidelines but it was certainly an issue that came up for discussion.

One of the difficulties that was discussed in the context of the Consensus Conference was the obligation of the researcher vis-a-vis the participant in the context of research when autonomy is defined or when it is attempted to be applied in the Ugandan context you are still talking about a population where

the overwhelming proportion is illiterate in any language where many people do not have television, where there is no telephone, where there is minimal access to transportation. So that saying an individual has the freedom to make their own decision and the knowledge to be able to do it signifies something very different than when you say that in a developed country with the exception perhaps of certain ancillary communities.

The question that arose in the context of the Consensus Conference then is should there be a greater burden placed on the investigator to justify the research than there might be, for instance, on a research proposing to conduct research in a developed country. And it really became a question of how do you simultaneously maximize autonomy and beneficence in a Ugandan context without becoming paternalistic and essentially completely overriding autonomy but it clearly takes on a different meaning in the Ugandan context given the relationship between care providers and patients and given the Ugandan context itself.

I do not know that that has been answered. The guidelines attempt to begin to answer it but I think that is going to be an issue that continues to be explored into the future.

DR. CASSELL: Can I just follow-up just briefly?

PROF. CAPRON: Briefly.

DR. CASSELL: You see I am struck again. Even Western medicine has imported into Uganda although it has been quite some time and with that came an ethos that was appropriate to Western medicine on the way in. Is the traditional relationship between the healer or the caregiver or whatever you wish in Uganda such that it might be dependent upon to protect the patient? To say that the person is a researcher has not changed their obligation to protect the patient that they are treating. Is that traditionally there?

Remember our job is to try and figure out how do you move over protection of human subjects into international context and so --

DR. LOUE: I would agree that that is there, that there is the assumption clearly that if a person is a physician their obligation is to protect the patient from harm. I -- whether they are a researcher or not. I think the real problem that has arisen in the Ugandan context -- and it arose because of the HIV epidemic -- is that again you have medical doctors who are marketing cures for AIDS that clearly are not cures. Because of their education, because of their position, because of their respect that they command people have bought into these claims and have sold their property, have lost everything relying on these cures, and obviously they are not curing them so that -- I mean, people are cognizant of the position -- of the traditional relationship but they are also cognizant that these kinds of things are happening and it is really an attempt to try and find a balance.

DR. CASSELL: Thank you very much.

PROF. CAPRON: Larry?

DR. MIIKE: Yes. I wanted to ask Mr. Avrett a question that Alex had initiated but first I really

need -- I think I need a comment on Dr. Loue's presentation. I think it is very useful for us in terms of the kinds of recommendations that we can make in terms of improving the international situation and I was pleased to hear you describe what were really challenges to the political and social norms in Uganda with the kinds of changes but I was totally disappointed in your answer about community involvement.

Your answer was, "Well, journalists do not represent them." Well, the people in outlying villages do not really know what to do. There is no organization. You could have said that about the United States thirty and forty years ago. You could have said that doctors were in control, patients had no say.

So I was wondering what Mr. Avrett thought about this from a community perspective listening to this discussion that has been going on because to me it seems to me that what you have just described is the beginning of a long process and I would have

expected your answer to have been what is the next stage that we find ways in which we get community involved rather than saying, well, that is why I am sort of disappointed. In some parts the status quo is successfully challenged. Whether they get implemented or not is a different question and yet in some of the other areas you accept the status quo so -- but I am really more interested in Mr. Avrett's perspective.

MR. AVRETT: In the United States with HIV vaccine trials there are sites that recruit women at high risk in the South Bronx and active i.v. drug users in North Philadelphia and Chicago, and you could say that because of poverty or for whatever reason that the ability to provide informed consent or the ability to be activists and have input into the trials is limited. However, I think that is not the case and there has been -- there have been very active community -- there is a very active community advisory board in the South Bronx vaccine trial site.

Those participants are able to understand the risks and benefits of those trials. There has been

some very good work to assess the level of comprehension and information that those women have about the trials and the motivations that they have for joining the trials. And those women have provided very good insights about the appropriate language of the informed consent, about the design of the associated service referrals and all of that.

I wonder with Ugandan -- I have a question about the Ugandan situation, which is has there been a concerted effort in monitoring the informed consent to look beyond the signed forms or any kind of paper trail to assess in -- to assess the level of comprehension that trial participants have?

DR. LOUE: I think it is fair to say that -- well, at least to the best of my knowledge there has been no attempt and ability to monitor informed consent to date so there is no infrastructure in Uganda, for instance, like the FDA or like DHHS that has authority to come in and say let me audit your records and see that you have followed informed consent procedures. I mean, I think it is important

to recognize that until three years ago Uganda had no informed consent procedures that were formally adopted apart from what was expected of Uganda in conjunction with foreign sponsored research so this is really quite new.

It is not a question, I think, of necessarily accepting the status quo but I think it is important to understand what the status quo is and how new this really is in the Ugandan context.

PROF. CAPRON: Okay. We have two more questions before our break. Trish and then Alta.

PROF. BACKLAR: I want to thank you both very much for your very interesting and useful presentations and the material that you submitted to us.

I want to go back to something that Diane brought up at the last meeting, and you were not here so I am going to restate it, all the conversation appears to have been today about research that was of interest to the subjects. I am really quite concerned about what this would mean if this research was not of

interest to the subjects because I was -- one of the things that I noticed to start off, Dr. Loue, is that I was interested that you said, of course, that subjects perceive entering this research as no choice. In effect, it is their only avenue to care.

An in this country we are very interested in the therapeutic misconception and it seems to me that in Uganda, as you describe it, this is not a misconception so that it does not exist. This is the only way to care and, therefore, it is not a therapeutic misconception. You are going to get health care by being in research and you will not get it otherwise.

What does this mean, though, when the research is not addressing something that you need? That is point one.

Point two: Both of you discussed the community voice and I think Dr. Loue picked up on a concern I had when Mr. Avrett was discussing things. He was talking about a voice -- an educated voice and I still am not certain at all -- I am trying to get my

question -- of how one really would access the voice of the subject who is being used in research which is really of no interest to them.

One other thing -- I am sorry -- by the way also in terms of the power of the physician. I do not think -- I think that the physician even in this country today represents a very powerful force. Most of us know that when we have relatives or we, ourselves, are ill, when we are changed into the role of patient or someone we love becomes a patient, we do not feel that we have much voice.

DR. LOUE: To whom are you --

PROF. BACKLAR: To both of you actually.

DR. LOUE: Okay. In terms of what if research were addressing something that the patient or the subject did not need and the concept of clinical care, I think individuals -- I should clarify something. Individuals in Uganda can always get care outside of a trial but I think it is generally believed that the care within a trial is going to be vastly superior.

PROF. BACKLAR: So there is a therapeutic misconception?

DR. LOUE: For instance, someone can go to the local hospital for treatment of a condition. Let's assume the person has HIV. They can go to the local hospital. What will happen at the hospital is that they will be given symptomatic treatment. They will not be given antiretrovirals. They will not be given protease inhibitors. If they have pneumonia maybe they will be able to get the proper antibiotics. Sometimes the drugs that are needed are not available. The country has simply run out of the drug supply. This is true even within the National Tuberculosis Program. So, theoretically, someone can get care outside of a trial but the quality of that care is going to be vastly different and I think that that is what the knowledge is.

In terms of how to truly access the voice of the research participant, my greatest concern in being able to do that in Uganda is how to overcome the daily logistical barriers to be able to have that happen.

I do not dispute that -- I mean, clearly, for instance, communities have advisory boards. In Cleveland, for instance, the HIV Planning Council has as a number of members women who were injection drug users who are not -- who have very little, if any, formal education who have been able to at least periodically stop using drugs and have become active voices in the community.

I think what I see as being one of the greatest differences between the U.S. context and the Ugandan context is that someone in that situation in the United States, however difficult it may be to access support systems and rehabilitation, and I am not in any way implying that that is necessarily easy because I think in many communities it is not, those systems still exist.

There are support systems in place. There is Narcotics Anonymous. There is Alcoholics Anonymous. There are social services. There are governmental safety nets that will provide medical care to people, for instance, through Medicaid. Those systems,

nothing comparable to that exists in Uganda, absolutely nothing.

So there is an AIDS organization named TASO, which I think has done extraordinary work given its limited resources but the reality is that for someone who is HIV infected they have to overcome before they ever get to the point of activism, they have to overcome where do I get the water for the day, where do I find my money to feed myself and my family.

How do I get the 26 miles from my village to the hospital to get any kind of care? And we are not talking about do I take a bus or do I take a subway. We are talking about do I rent a ride on a child's bicycle handlebars or do I walk or do I take the local form of transportation, a metatu, after I walk for 10 miles to get to the metatu.

I do not know how to overcome these logistical barriers. I think certainly if they could be overcome there would be the interest in having a greater voice and in participating but I simply do not know where you would even start and as I mentioned the

whole concept of having formal guidelines is itself quite new to Uganda.

So to talk about activism -- the other thing I think that is very different in the Ugandan context that we may not fully understand and I certainly do not pretend to understand it is the legacy that has been left by years of repression and torture under Idi Amin and Obote.

Almost everyone that you talk to has had some family member who was killed or tortured under one of those two regimes. People remember when someone was an activist in years past that that had severe political repercussions so that there is still -- and we see this, for instance, even in the process of signing a written informed consent. People do not want their name attached to movements.

There is also significant tribal and religious diversity in Uganda. Many of the educated class in Uganda belong to the Baganda Tribe, which is the largest tribe in Uganda, and this was traditionally the privileged tribe under the British

Colonial rule so that when we talk about educated and noneducated we are also talking about a tribal distinction.

We are also talking about a distinction in who owns the political power and all of this, I think, has implications for who is willing to become involved as an activist and this again is in addition to the layers of logistical barriers.

So, although, I do not -- I am not saying that it cannot happen, I am saying I simply do not know how to help it happen given the Ugandan context and given that I cannot begin to comprehend the kind of legacy that has been left from those kinds of regimes which -- where we have had nothing comparable in this country.

In terms of the power of the physician, I mean I would have to agree with you the physician really wields extraordinary power and again I think we have to recognize that there is a -- when we talk about physicians vis-a-vis patients or vis-a-vis research participants we are also talking about

economic and class and tribal differences as well.

MR. AVRETT: But I would ask the question differently in response because you are saying what if the research is not important or what if you cannot access the voice of the participant but I would say both of those underline informed consent.

I mean, surely if the local -- if the researcher is doing research, that research hopefully is compelling and it is important at some level and that it is asking some compelling scientific question. And the basis of informed consent in my mind is the researcher is challenged to be able to explain that in a way -- to explain the compellingness and the importance of the research to the participant so that they understand it.

Whether it is locally important or not, at some point it has to be compelling and the researcher needs to explain why they think it is important. And the participant, I think, has to understand that and conversely as difficult as it is for a participant to get a trial site and to understand the concepts of

research, at some level the participant has to knowingly and willingly be able to agree to participate and the researcher has to be able to hear that from the participant. I think that just underlies the --

PROF. CAPRON: Alta?

PROF. CHARO: First, again thank you. This has been very, very, very helpful.

A lot of what has been discussed focuses on the idea that access to a research trial is a net benefit in the end and specifically and most controversially it is a net benefit because of care you get independent of the actual research interventions. I know you appreciate the difficulties that are inherent in this notion.

I mean, it really gets us right back to that old notion of charity hospital patients who have the choice of opting into research if they want charity care or going without care.

But putting aside the kind of long tradition we have had discussing the same problem in the U.S.,

if that is, in fact, the kind of analysis of risk and benefit that is being brought to bear in the Ugandan context, why is it then that orphans and street children are specifically excluded as research subjects, which I believe you said very early on.

It would seem to me that that is exactly the population that has the least access to even the most minimal care because as you said, and as I have observed myself in other hospitals in other parts of Africa, without family support access to hospitals is pointless. It lacks food and it often lacks drugs or even sheets.

And so wouldn't they be the first people rather than the last people that should be enrolled as research subjects if one genuinely believes this is an opportunity and not exploitation?

DR. LOUE: I think that that was really an attempt to try to find a balance between the benefits that might come from research and the perception that is also coercive if you have no other choice and the possibility of exploitation.

There was great concern that because the population we are speaking of are children to begin with and are street children and orphans so that there is an additional layer of trauma that is added in that context that they would potentially be subject to phenomenal exploitation.

There were a number of members of the National Consensus Conference, for instance, that were aware of the trials that went on at Willowbrook and they wanted very much to prohibit that kind of thing from ever happening in Uganda.

So I think that the idea was that any research that is done with street children and orphans can be no greater -- can involve no greater than minimal risk.

PROF. CHARO: But I -- if I just -- I just really want to understand this because it feels to me like there is a kind of cognitive dissonance here.

In other settings with adults who are impoverished and have no access to better than minimal care the system trusts the integrity of the researcher

because the researcher is also a physician who really is thinking more as a physician and, therefore, is putting the patient's interest first even though the patient is actually a subject in a research trial and as a matter of individual decision making this individual ought to be given an opportunity to say of all the bad deals available this is the best bad deal, all right.

So we trust the integrity of the investigators and the kind of notion of personal protection of your best interest in that situation but not where the need is the most desperate as if the integrity vanishes under these circumstances or is it that there is just -- is it that these people, in fact, are not cared about as much so that you can ignore their need to get access to care for a trial? I mean, it just -- it is something that just does not feel like the people are being consistent.

DR. LOUE: I understand what you are saying but I would not say that people do not care about this population. That was really not the sense at all that

I got from the discussion at the Consensus Conference. If anything, I think there was more a sense of we have to protect these children no matter what. So it may reflect a heightened concern where adults, for instance, would have a greater voice to be able to say something is --

MR. CHARO: I am sorry, Alex.

But just protect them from what since the whole point is that the trials are a good thing?

DR. LOUE: But any harm that may arise from the trials.

PROF. CAPRON: It sounds as though Dr. Charo is laboring under the therapeutic misconception.

PROF. CHARO: No, but that is the whole point of being able to enroll people there, is the assertion that the trials are therapeutic in the end.

DR. LOUE: But there is --

PROF. CAPRON: No, as I have understood it -- I would like it if we could get this clarified. As I have understood it, it is the quality of concomitant medical attention that is going to be higher.

PROF. CHARO: Yes.

PROF. CAPRON: The trials may have all the usual problems and, indeed, with the strong statement of a requirement of equipoise the sense that you may be well off being in the trial or you may be poorly off -- poorly served being in the trial but the lure is the lure of having the medical attention.

PROF. CHARO: It is more than a lure.

PROF. CAPRON: As was true in Willowbrook, as is true for prisoners in the United States --

PROF. CHARO: Right.

PROF. CAPRON: -- and it -- what I have found so fascinating, if I may say so, by this is that the Ugandan Consensus Conference participants were so aware of problems and pitfalls that we had discovered here. We went into all of this with the background of the FDA saying that, I believe, only with one institution have they been able to establish that their -- the prevailing standards in whatever country it is are equivalent to our's and, therefore, they can get some of this deemed status and yet it seems -- not

in terms of implementation maybe but in terms of analysis and principle the Ugandans have incorporated into their own process our mistakes as well as our "successes."

PROF. CHARO: Alex, you really did misstate what I was saying.

PROF. CAPRON: Okay.

PROF. CHARO: I apologize. But I was -- but the point that I am taking home here is that an awful lot of the justification here is not that the research interventions are therapeutic and that is not what I was suggesting, that the overall experience of participating in a trial, being exposed to the research intervention and the concomitant care is on balance overall beneficial to the individual as compared to other options.

PROF. CAPRON: When the individual can make that judgment and yet with a child that individual is not able to make that judgment.

PROF. CHARO: That is not the point.

PROF. CAPRON: Is that the gist of your

answer?

DR. LOUE: If I could interject something. I would have to agree with what you are saying and I think that that was the thinking. For instance, that is the reason that there was such a strong voice that when researchers come in to do a trial they must now have proof of insurance to cover injuries or damages because there is the recognition that although there may be the concomitant care there is still the possibility that someone may die or the possibility that someone may be injured.

PROF. CHARO: My point is not to try to prove these kids should be put in the trials. My point is to try to explore the reality of whether or not this notion that the concomitant care being beneficial offsets a variety of other concerns about people's enrollment is valid and I find it highly problematic and very reminiscent of the pre-New Deal Era in which the idea that people could get extra pay, which was in their short-term interest, if they took on hazardous employment was tolerated as making the best of a bad

deal against background conditions in which you had no other options for high paying jobs.

And we have been through a very interesting debate in the U.S. that has not yet been resolved. We still debate minimum wage and the Supreme Court first upheld and then struck down notions of a fundamental right to make the best of a bad deal when they considered the Lochner case.

So I just -- I find this whole notion of the concomitant benefit being pertinent to the equation extremely troubling but at a minimum I would love to see it being used consistently across all populations. That is the only point.

PROF. CAPRON: Okay. The senator from Massachusetts would like to yield back the time that he yielded before.

MR. HOLTZMAN: Thank you, Mr. Chairman.

But with a different question. For those of you who are familiar with the literature in this discussion of the therapeutic misconception and putting aside the concomitant benefit, if it is

objectively the case -- say I have HIV and I am in an environment in which I am going to get no care and I will die, all right, or if I am refractory to all known therapies for a certain cancer, am I laboring under a therapeutic misconception if I go into a trial with an experimental drug in the hope of being cured when it is objectively the case the alternative is to die?

PROF. CAPRON: I think that if we are getting to some of the issues that we are getting to, we should have that as our -- one of the topics for our discussion after the break and I want to find out if there is before that break, which is now 20 minutes past its time, any further questions specifically where we need answers from our two experts today.

Arturo, who has not had a question, a brief one, and then, Bernie, a brief one.

DR. BRITO: Just a brief comment on this conversation here between Alta and our guest. One of the things that concerned me with reading your article, while very informative and it really -- one

of the things that struck me most is the pluralism that exists in Uganda, much like our own country, and I was struck by that. But yet the national -- this national committee that was set up seemed to me to have a very Western influence in its thinking and it did not by any means necessarily reflect the culture of the Ugandan people, is what -- except for the written informed consent issue. Okay.

And when I am hearing this discussion I think it is a reflection of the Western influence on this commission and how this commission truly -- does not truly represent all the Ugandan people or most of the Ugandan people.

And where that leads me to for both of you actually is how do we go about selecting appropriate community leaders or representatives when -- without imposing our own values on people that are most vulnerable in research?

It is just something that, you know, with all the reading and this is my biggest concern is because I am not sure this commission was a national

commission the way they were selected and the way that they go on to make recommendations about who should represent local communities. I am not sure they can see it from the other end, from the people that are most vulnerable and not be influenced by Western thinking.

I will just -- and I know that you hinted at some of this -- but, for instance, in the South Bronx, the decision to include minority women in there came about because of a lot of criticism earlier on about not including minority women so it is something that has taken ten or fifteen years to come about in HIV trials and both trials and also now clinical intervention.

PROF. CAPRON: Any comments from the panel about that? You were both nodding your heads as he was speaking. I gather you have agreement with the gist.

DR. LOUE: I think in terms of being influenced by Western thinking that is certainly true. Uganda's primary -- at least to the best of my

knowledge -- primary exposure, for instance, to principles of bioethics has been as a result of the HIV epidemic and various other diseases in Uganda that have really triggered foreign sponsored research.

To that extent Uganda has had to consider issues involving bioethics if only because it was demanded by the foreign sponsors of that research, which necessarily introduces a Western element.

I do not think the fact that that has happened necessarily means that Uganda is not also taking into account its own context.

So, for instance, when you look at the National Consensus Conference a number of the participants in that conference represented religious groups that, for instance, the -- that represented traditional African religions, represented the Islamic society. There were a number of pharmacists who -- not who were trained in Western pharmacy but who are traditional pharmacists under Ugandan law so that there was that perspective introduced.

I would agree that it is still problematic

that there has been no voice in the process that would be comparable, for instance, to the voice of an injection drug user from the South Bronx. That has not happened in Uganda and how to make that happen I am not sure.

But in terms of, I think, reflecting different perspectives even within Ugandan culture on maybe a macro basis, I think the organizers of the conference worked incredibly hard to try and have those different segments represented. So I mean there were women. There were men. There were people from various tribes. There were people from various religions, from various professional disciplines, from traditional society, from more Western oriented society. I think everyone thought that it was important to include human rights organization representatives who had direct experience with people who had been tortured.

DR. BRITO: Thank you.

MR. AVRETT: I would just answer that by saying it is -- in -- the -- in the question of how

you get a pluralism of representation and how do you select people from a lot of different perspectives, that is a very -- it is a good question. I think people present themselves and they self-select and they come up and present their own issues and their responsibility is to provide as many opportunities for people to present their issues, whether it is the informed consent process or just a long-term presence in the community -- community forums, CAF's, and so forth.

And in AIDS activism in the United States it has obviously been a cacophonous fractious bunch of activists who have come up from a lot of different angles to express needs and issues about research but that is the deal and, hopefully, you get a large number of perspectives coming up and deal with them in a whole bunch of different structures.

PROF. CAPRON: Bernie and Diane have each asked our leave for a brief question with brief responses.

Bernie?

DR. LO: Dr. Loue, you have had a number of questions that are sort of looking at the flaws in what you have been able to do and sort of pointing out that based on what we would like to see in this country, which we have taken a long time to get to and some that just have not gotten to sort of, gee, how come you have not done it already.

I would like to ask the reverse question, which is I would be really happy if most of the countries in the world had some process in place like your's, which is a first step, admittedly imperfect, admittedly not the final answer, but how many other countries like Uganda where research is being done are actually doing something on a national level to try and address the issues the way your commission did. Is this a totally atypical experience or do you know of other countries that are trying to do something like that where -- that we could also look at?

DR. LOUE: I would have to say that my knowledge in this area is quite imperfect and I am actually in the process of trying to look at processes

in other countries. My understanding is that several other African nations have been starting this process, although it is not clear to me how far along they have gotten.

Romania -- I do quite a bit of work in Romania -- is actually in the process now of looking at the establishment of bioethical guidelines. Romania, I am sure as all of you know, has a long history of repression under Cherchesku and bioethics and genetics and a number of other scientific endeavors were completely eliminated during that regime so they are now in a process of trying to formulate guidelines, although they are nowhere near as far along as Uganda is.

PROF. CAPRON: Any comments, Sam?

Okay.

Diane?

DR. SCOTT-JONES: I have a question about what advice the two of you would give us regarding what exactly we are comparing when we make international comparisons and I am thinking especially

of the role of poverty within a society, a lack of education and ethnic divisiveness within a society. When I read your paragraphs about the Ugandan cultural context, some of the sentences struck me as being remarkably similar to the United States of America.

For example, families requiring two or three income producing activities to survive economically. Members of a research committee composed primarily of members of one ethnic background and the majority of research participants of another ethnic background. Those things are true here in the United States and I think when we are undertaking these international comparisons we are holding up a view of a segment of the United States of America and we are turning our eyes away from segments of the United States population that are in dire straits as well.

I am wondering whether you could help us in how we should frame these international comparisons so we do not forget about our own dire poverty and ethnic divisiveness here.

MR. AVRETT: Well, I am not sure that I have

a really good answer to that but I do agree that you can talk about vulnerability of populations in a way that crosses different -- I think crosses different communities and different countries. And vulnerability because of poverty, vulnerability because of power structures, vulnerability because of stigmatization, and I think that is one way of getting at the commonality of what is happening in the United States and internationally.

PROF. CAPRON: I want to thank you both for your participation. You clearly stimulated a great deal of thinking in the commission and your work will, I hope, reverberate for the good in our final reports on this.

I want to tell people in the public that if you have not yet signed up and wish to speak at the 11:30 scheduled public comment period, I encourage you to sign up at the desk.

We will now take a 15 minute break and convene again at 11:00.

(Whereupon, a brief break was taken.)

PROF. CAPRON: So as not to have to interrupt commissioner's discussion we will go to public comment now and then Alice Page will present the additional material she mentioned and we will have discussion of it.

Eric will introduce the people on the list who have signed up to testify.

PUBLIC COMMENT

DR. MESLIN: Two people have signed up and we are grateful that you are able to start just a couple of minutes early so that it does not disrupt the commission's work.

The first person is Dr. Adnan Hyder. For the record, Dr. Hyder is also a consultant to NBAC's International Project, who has been mentioned to commissioners before. He is from Johns Hopkins University but my understanding is that Dr. Hyder here is speaking not in his capacity as a consultant to NBAC but as an international researcher.

Just to remind you, Dr. Hyder, it is a five-minute presentation. Thank you.

DR. HYDER: Thank you very much. My name is Adnan Hyder. I come from Pakistan. I am a physician. I am a public health researcher. I have been involved in public health programs, both in terms of health care delivery and research for about ten years. I am currently based on Johns Hopkins University. It is a great pleasure to be here and thank you very much for the opportunity.

My comments reflect some of my thinking after listening to the morning discussions which have been very stimulating, indeed, and I would like to make four short comments.

The first one refers to the context of research. I think that the ethics of research need to be looked at within the culture of research that exists in countries and the culture of research is often nonexistent in the formal Western way that it is recognized in many countries.

If there is an attempt to change that culture or influence that culture then culture change requires two things. One, an ownership and, therefore that

needs to be recognized. It requires ownership of the local people, of the nationals within that country. And, secondly, time so that it cannot occur in one year maybe or six months but may require a longer process. And I think that these two conditions need to be recognized in any discussion that is occurring with respect to changing the culture within which ethical research is conducted.

My second comment refers to investments on research because after all research is driven by and often paid for by investments in research, both by private and public sectors.

A comment made earlier on today said that local health priorities need to drive research. Well, that is an ideal but, ladies and gentlemen, may I tell you that of the $60 billion dollars spent on research annually in the world less than 10 percent, less than 10 percent, can be judged to be of eventual benefit to developing countries so that 90 percent of research will take a long time before it becomes translated into benefits received by developing countries and

that is important as well to consider in some of our discussions.

My third comment refers to testimonies from people in the developing world. I have tremendous respect for our colleagues from the developed world, my own colleagues here working in other countries, but I think that we can represent ourselves. I think we have a voice, we need to be heard, and I think we are able to reflect our views and, therefore, I would urge the commission to create opportunities for researchers from these countries to come here and testify before you as well.

My fourth comment refers to this notion of community participation, community activism, because I think that there is no poverty of activism in our countries. Rather there is an activism of poverty and this activism of poverty has changed governments and created revolutions. Why can't it deal with ethics of research? So I do take disdain at the thought that there is no activism in uneducated or illiterate people. I have worked with people in the Himalayan

mountains and village organizations, and women's organizations, and community organizations, or organizations that have changed the face of those communities. Not we, including myself, the educated elite, the five percent, coming in and teaching them something.

The question is exactly what was placed on the table, how do you mobilize them? But not mobilize them as in transporting your ideas on them but mobilizing them as in helping them thinking through their problems so that they come up with their solutions and there is a difference. And I think theories of development and work in primary health care over the past 20 years will give you some insight into how to do this in a better environment.

Lastly, again thanking the commission, I would like to say that this area that the commission has taken up is of critical importance, and I think it is very important that the commission should see this as a need for the entire global community and not just as a need of the commission itself. You do not want

ethics in countries because NBAC says it should do so. You want ethics in countries because it is valued and judged to be appropriate for the work that is done.

Thank you very much.

PROF. CAPRON: Thank you, Adnan.

Ms. Poland?

Are there any questions for Dr. Hyder?

Ms. Poland?

MS. POLAND: Good morning. My name is Susan Poland. I have been working with the Kennedy Institute of Ethics at Georgetown University since 1979. Some of you have seen me here before and may have read some things I have written about national bioethics commissions in other countries.

I am commenting on things I have heard today about looking for grassroots input at an international level into this commission's work and I hope I have something of a solution when you realize the problem that we have over with the National Reference Center for Bioethics Literature and the International -- the Information Retrieval Project, which you would know as

Bioethics Line.

Bioethics Line by its initial grant is restricted to English language articles only and over the years -- I have been working with them from '79 -- we have changed our input methods from keypunch machines, IMB mainframes, PO1 programming language, and dial-up modems to where we are now on Internet Grateful (sic) Med throughout the web and everything else. So both NLM and we are trying to make an outreach to people globally through 800 numbers and everything else but our clay, if you consider us potters and people making artifacts, our clay remains the same, English language documents.

Unfortunately, that has been a limitation when we serve you. That has been a limitation to anyone throughout the whole earth gathering information off Bioethics Line and it may be a programming language thing but we are now restricted by our grant.

It would be -- personally I have an Israeli Supreme Court decision, which is wonderful, even

though they have all the regional reporters from the U.S., they took a decision on a Tay Sachs child, looked at paternalism and looked at autonomy, and came out for paternalism, and if you know anything about Israel it is a religious based state for their law. It is very different.

When I was over there this summer I found out, indeed, none of their court decisions are published in English. You have to get them translated. We do not have funds for translation. However, under your Executive Order under Section 6C NBAC is authorized to develop reports and other materials. The expertise present with augmenting that the Secretary of HHS may contract for services of nongovernmental consultants to prepare other materials for consideration by NBAC. Also you may go to the heads of executive departments and agencies such as the CIA, the Voice of America, Library of Congress and all the foreign research reading rooms, to the extent permitted by law provide NBAC with such information as may be required for purposes of carrying out

functions.

The library is not necessarily an international institution although we have many people come from around the world to do research here. Our languages are limited to our own abilities in basically modern European languages, Spanish, Italian, French, and likewise.

What I am asking you is to consider either funding or contacting an infrastructure where you have this Executive Order where you can develop people that can translate or even if you just develop a bunch of documents that do get translated into English, pass them on to us, and we will make sure that the international community gets access to them.

You are in a position where you can hang out a shingle on the web in other languages, having worked with Diversity in Arlington County, it is very important to try to reach people in a language they understand and you provide the translation because they do not necessarily have it.

As you see with Loue you have people that are

working at basic levels that are never going to get to the part of the research, they are just looking for -- as the Central European woman says, "I want to make sure my third child has the same genetic disease because I have not got the resources to prepare two different meals for these kids that have this digestive problem." It is kind of the reverse of what we think of genetic counseling but that is where they are at in some countries.

And that is basically all I have to say is if I can help you develop that infrastructure or anything that would be great.

Thank you.

PROF. CAPRON: Any comments?

Professor Charo?

PROF. CHARO: Well, actually it was a comment -- it was a question for the previous speaker but I kind of got lost in the rush.

PROF. CAPRON: Okay.

PROF. CHARO: Is it permitted?

PROF. CAPRON: Dr. Hyder, would you like to

come back? Professor Charo has a question and there may be others as well.

PROF. CHARO: Sorry about that, Alex.

PROF. CAPRON: No, no, that is quite all right.

PROF. CHARO: Sorry. It took a second to kind of get it all processed.

I wanted to ask you to expand a little bit on your, I think, concerns about the role of this commission in the exportation of certain kinds of ethical morals. My understanding of our role here is to decide what kinds of standards must be applied to research in other countries in order to permit funding -- federally funded U.S. researchers to participate. It was not to actually dictate what the rules have to be in those countries but I do appreciate the fact that the functional effect could be virtually identical. That is this can export our standards because of the need to do this kind of collaborative research.

The exportation of standards through a kind

of do it our way or we will not play with you mentality is typical in the economic arena in which trade rules are structured so that countries may not play with us unless they abide by our patent laws, abide by our antitrust laws, a variety of kinds of concerns.

But in those settings one of the critiques -- one of the criticisms of our position is that those are rules that have been set up to protect our own interests and that we are then forcing other countries to play on -- play by our rules to continue protecting our own interests.

Whereas here the kind of de facto, although not de jure, exportation of our ethical standards is not for the benefit of our own economic interests at all, in fact it might be to the detriment of our own economic interests, does that affect the strength of your criticism about the role of this commission in exporting these standards or is it still so profoundly troubling that regardless of the kind of underlying motivation or effects we should be wary of it?

DR. HYDER: I think the source of the trouble lies in the process that is undertaken rather than the eventual outcome. I think the outcome is also important but the process is clearly very, very important. This whole issue about universality of some of the principles and some of the rules and regulations -- I think the -- if the process is that here is a particular model that needs to be studied, needs to be absorbed by representatives of national communities that are doing research on subjects and so on, and then processed into -- with alternatives available so that that is not the only model available to such communities then that may result in a format where there is an intrinsic thought process and ownership of that process coming up with rules and regulations that they define to be their's rather than a modification of those that were delivered to them.

It is a participatory approach. It will take time. It is often called idealistic but it has been done in other sectors. And the concern is that although the mandate of the commission and the mandate

of this particular project is very clear, however in the process of doing this work, in the process of looking at testimonies from different investigators who have been involved in international research, what you find is that there are those transportation without the process occurring all the time so that if on the request of certain investigators or certain funding agencies IRB's are created, a certain de facto process occurs, consents are given, and the next time new investigators from a different funding agency comes, unless he or she demands the particular formation there is no permanence in those. There is no sustainability in those efforts.

And I think if this process is looked upon from the viewpoint of how can it be sustained and it is not just a response to one country, one funding source, one organization then I think there is more hope than it being stimulated as a unilateral exercise.

I think for the purposes of the commission and the mandate of the commission it is clearly

important. You need to make sure that U.S. researchers abide by certain ethical rules and regulations when they go out and do research. I think that is very clear. It is the flip side that I am more concerned about. And you are right, the process will occur. I mean, it triggers -- it triggers a set of activities.

PROF. CAPRON: If I might follow-up on that. I should note that we have only begun to dig into the background for this report and today we are dealing supposedly primarily with the consent issues. There is no way of cabineting those issues. They spill over and certainly the point you are exploring with Dr. Charo and that both of our witnesses talked about today is something that we will also be getting to when we talk about chapter five of the report where we are talking more about some of the structural things.

Your comment -- your response just now seemed to me to go 180 degrees away from something that I had taken from the earlier -- and let me -- which is -- but I think it is also equally valid.

It seemed to me that part of the disagreement we were hearing between Mr. Avrett and Dr. Loue was between the emphasis that she was making on the difficulty of having an IRB that has representatives of a community where the IRB would be, in effect, meeting at the medical school which might be logistically inaccessible to many people who would be research participants and, therefore, their voice could not come in. And he was talking about the ways in which you could have community advisory boards and the like which supposedly would not have to go anywhere. They could meet in the community.

And the question then comes up of how do you link the advice from the community and how does it shape the research so that you are not as concerned by the fact that there is not a community member from that community on the IRB and your remark, as I say, by focusing back on the IRB says, "Yes, but don't you want to have some permanent, some ongoing structure of an IRB so that you do not have to reinvent it every time a new research project comes in. I think these

are issues that we will have to address.

I did not hear quite as much conflict between our two earlier speakers as some people were hearing because it seemed to me that they were talking about slightly different things and the feasibility or difficulty would vary about whether you are talking about an in place community group or an IRB with a community representation and that there may be different avenues to the same endpoint.

Are there other questions either for Mr. Hyder or Ms. Poland now?

I should also comment vis-a-vis her remarks -- thank you very much -- her remarks that I think we will be hearing some reports later on, not at this meeting, but later about efforts that are underway to promote the linkage, and I forget the computer term for the way this is done but where one can jump from one source to another and that there are -- for example, with the French National Consultative Bioethics Committee, some resources in French which may be available so that someone either at our web

site or at the Kennedy Institute library web site could have access to French language or there may be other resources that are available where you can, if not get them directly, get them indirectly by that kind of hyperlinking.

So I hope that we will also have it -- hear more about that at a later time.

With that the public comment period then is over. We have no further indication that there are people who wanted to sign up to speak and I turn now to Alice Page, who will bring up the other two topics that are ones which we need to discussion and perhaps take action on.

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

DISCUSSION CONTINUES ON OVERVIEW OF WORK TO DATE

MS. PAGE: Thank you.

The first of these items relates to the study of research participants and specifically whether NBAC should seek the views of individuals who have either participated in research or who are likely to participate in research in the future.

This was an issue that was discussed briefly at the last meeting and I understand it had been raised at higher meetings as well. Commissioners have expressed concerns about it and other members who have spoken at the meetings have as well.

The project, as you all know, thus far is examining through empirical studies the views of researchers, both U.S. researchers and researchers from other countries who engage in international collaborative research.

The project has not, however, undertaken to study in any way the views and experiences of individuals who are or have been the subjects of research.

The purpose of the project is to examine the ethical, legal and policy issues that arise when the U.S. funds or conducts research in other countries and certainly there are elements of a study of human subjects or research participants that would have a central and very important bearing on our project and so whether the project should undertake to contract or

conduct a study of human subjects is an issue that all of you need to consider.

The first question for you to think about is whether for purposes of this project it matters if the studies that we are -- from which we are drawing data are sponsored by the U.S. and the reason I say that is that Ruth Macklin has recently become aware of three individuals who either are in the process of conducting studies of human subjects or who have conducted them in developing countries, namely Chile, Brazil and Trinidad, relative to conform -- to informed consent.

Now the data from these studies could be utilized if it was determined that it was not necessary that it come from a U.S. conducted or sponsored study but if that is not an option and you decide that we need to undertake a study of research participants there are three possible ways to do it.

The first is to undertake a large scale study of human subjects and we have been contacted by Nancy Kass, who has made a suggestion as to someone with

whom we could contract for such a study. The main impediment to such a study really is time.

The current deadline for completing the entire international project is May or June of next year and if we undertake such a study we are not going to be able to meet that deadline. Cost obviously is also an issue but time is really our biggest problem.

There is also the difficulty in identifying research participants for such a study and particularly with a large scale it makes it even more difficult.

The second alternative is that we could continue to analyze the published literature that pertains to research participants. As I said, we are doing this and this would involve continuing to comprehensively review the empirical and other research that has been conducted on this topic by others and then summarizing it for our purposes.

Third, we could conduct or contract for a snapshots type of study which would basically entail a small convenient sample of subjects that have been

made available to us through contacts.

There are obviously design problems with this in terms of things like the number of subjects and subject selection so that could be criticized for that reason. However, it is an alternative that would require less resources and time than a large scale study.

We would propose to send to all of you a memorandum outlining the advantages and disadvantages of each alternative prior to the decision being made in terms of what, if anything, should be done but for now we just would like to get your views about whether this should be done and what sort of strategies should be followed if it should be done.

PROF. CAPRON: Okay.

Larry?

DR. MIIKE: I guess the question for me is what do we expect to get out of it and it seems to me that no matter what we do we are not going to get anything very definite. What we will get out of it is what are the issues that people are worried about, and

I think that one can get that out of -- we -- because every time I listen to witnesses come up who read papers the same kinds of issues come up and I do not think -- they may have individual variations among different countries but it is the same kinds of issues that we have faced over the past couple of decades, I believe.

So it seems to me that the -- that in this particular area it is sharpening the focus of a lot of the issues that arise and then it is up to us to try to decide how we establish a process to address that, not solve it but how to address that.

PROF. CAPRON: Alice has put several issues before us and I wonder if there would not be consensus regarding the first one she raised. Is there any reason that any commissioner would have for our restricting our examination of data here to studies that are sponsored by the United States? Is there any reason not to look, for example, at these studies in Trinidad and Chile and Brazil?

PROF. CHARO: For me it is not -- just

putting aside whether we are going to do it, assuming we did it, it is not whether or not it is U.S. sponsored. It is actually understanding what were the kind of ethical standards of things in implementation that were being deployed in that research to see whether or not anything we learned from that would be generalizable to our understanding of our own regulations have probably been working in our context so I do not know how to answer that without knowing, for example, if those studies involve informed consent and what that meant, and whether it was signed, and the kinds of things that we have circling around here.

PROF. CAPRON: My sense was that those studies that were mentioned are similar in a way to that second category that you mentioned, Alice, where you said we are looking at the literature and trying to tease out of it data on what subjects think about consent and risks and so forth. And that I would certainly agree with Alta that each of those studies -- when you are reading any particular piece you have to ask the question she is asking but the fact that it

is not U.S. sponsored does not --

PROF. CHARO: Is not a crucial point.

PROF. CAPRON: -- is not germane.

If we then lump those studies, which are ongoing and which I gather from your description of them would have results in a timely fashion for our point of view, the kind of meta-analysis, an attempt not to do the whole study but to say putting everything together what is known, are there any factors beyond, as Larry said, we have already heard from so many witnesses, and that we know from the history of research in this country are the kinds of issues that come up, and not trying to make any empirical generalizations from that most people are concerned about X. I mean we cannot say most because it is an opportunistic sample base.

But what do -- what do we learn so that we are not, in fact, or perceived to be ignoring the subject side of thing and only caring about the researcher side? I mean, that would seem to me to be a basis for faulting our eventual report if we did not

do something in this direction.

On the other hand, do any of us think that we should be pressing ahead and having Nancy Kass or someone else that she suggests trying to do a study which would have a large enough N?

The major difficulty here, it would seem to me, would be that I cannot imagine doing it in Brazil and not also doing it in Uganda and Thailand and Tibet and/or Nepal. I mean, what -- if we think that the very thing that we are looking at are the diversity of views you would have to look at representative samples in so many places. Otherwise we would have informed ourselves about, well, what one particular community thinks above and beyond what we are already familiar with.

So that seems a worthwhile avenue of research for the Fogarty Center over a five-year period or something but between now and next May it seems unlikely to work for us.

Tom and then Bernie?

DR. MURRAY: Thank you, Alex, and thank you,

Alice.

It seems to me there are three -- crudely, there are three purposes for doing a study. One would be to test a hypothesis. We do not have a hypothesis so that is out.

The second would be to develop valid descriptive inferences so that you could say X -- as Alice was describing -- X percent of people come from a social class different from the investigator. That could be the sort of description one might want to see or come from a -- the lower -- you know, if 80 percent of subjects came from the lowest 20 percent of the social stratification in a country that would be an index of something.

That would take the sort -- and particularly if you are going to make cross-national comparisons -- that would take the sort of multi-year effort that Alex was just describing so I suspect that is off. We do not have the time and we probably -- we certainly do not have the time and we probably do not have the money to do that.

Which leaves the third possibility which is a kind of in-gathering. It is descriptive only in the loose sense that these are the sorts of things one can find out if one looks systematically without making -- without giving you the appropriate statistical basis for making any inferences about precise numbers or percentages or the like.

And I take it that is roughly the third of the alternatives you were describing. It seems to me we are not doing one, we probably cannot do two competently, which I think this is rather like going to the -- you know, the sales office and -- you know, we have got lots of houses to show you but what we found is there is only one you can afford and this is it. I suspect that is where we are.

PROF. CAPRON: Or only one will be built by the time your family is ready to use it.

DR. MURRAY: Yes.

PROF. CAPRON: I have Bernie, Steve and Trish.

DR. LO: Well, I think it is important to --

as Larry suggested -- to think about what are we hoping to get out of the data we collect? What are our goals? What are our objectives? And I guess I have a much more modest perspective than the kind of definitive broad scale sort of comparative epidemiological approach that someone suggested.

I guess what concerns me is that we have heard from both American students of foreign research and indirectly from foreign researchers themselves that some of the issues we take for granted here are questionable or problematic or contested in their cultures and we focused on consent today.

And, you know, there are specific issues that have come up having to do with you cannot tell people their diagnosis, you cannot tell them that you ar really uncertain as to what is effective or not, they really do not have a choice because they are constrained by the realities and they do not have access to care.

We have heard all of that from the point of view of researchers and the people who have studied

the research.

I would be very interested in hearing something from people who might be subjects, how do they feel about entering a research project where they agree but they think they are coerced. They have no choice. Either they have to do it or realistically, you know, it is such a good deal for them in the sense that Alta was discussing.

I would like to get a sense of how they think about those issues so it is a much more qualitative approach than this notion of doing definitive studies.

So I think, you know, we are going to be constrained by both time and resources but, you know, we should not let our quest for perfection get in the way of doing something good and I think just as there was some purpose, albeit, you know, maybe not as good as we thought of having the focus groups when we were doing the stored biological materials and learning that people said, you know, I had no clue when I signed that but you know it does not matter. I would have wanted to donate. That was not scientific.

It was, you know, God knows how flawed. It was helpful for its qualitative impact of understanding the way people approach these issues.

And I think that is what I would hope to get out of finding out what potential subjects of research or actual subjects of research, how they address some of the issues that have been raised in these other contexts. And if it is a convenient sample and spotty, it may not generalize but we just have to -- like with any other data we have, we have to be aware of its limitations and its lack of generalizability.

PROF. CAPRON: Steve?

MR. HOLTZMAN: Let me for the moment try to distinguish the what from the how so let me assume for a moment we know what the what is we would like to get from these research subjects and just address the how.

What is it that would prevent us, and I am sure there is something in the regulations that would prevent us from going to people who have ongoing studies with federal money and they are interacting with these subjects and saying could you please get

the following information from those subjects and what would prevent us from going to private sponsored industry who is doing these things and asking on a pro bono basis that they do the same thing?

PROF. CAPRON: Okay. You want an answer to that?

PROF. CHARO: Do you want an answer?

(Laughter.)

PROF. CHARO: If he wants, I can give him an answer to that.

PROF. CAPRON: There is no answer.

PROF. CHARO: You can do it but it is -- there are regulatory implications, you are right.

MR. HOLTZMAN: Not with the latter.

PROF. CHARO: Well, it depends.

PROF. CAPRON: Maybe, probably.

PROF. CHARO: On the former because these studies have already been cleared through an IRB, they will just have to get clearance for this add on, but you will have to get clearance, if we formally sponsor it we will have to go through IRBs ourselves which

will take so long that the study will be over by the time we finish.

MR. HOLTZMAN: We do not have to sponsor anything.

PROF. CHARO: If we do not sponsor it then it is done purely within the local -- we just simply tell people we would be very interested in this information, anybody who wants to voluntarily add it on, they go through their own IRB and the corresponding IRB in the other country, and it goes much more quickly.

If you do it in the private sector you can before you have everything, as we know, unless you are working with a researcher who is at an institution that has pledged to have even privately funded research, right, covered by these rules so you have to check who is actually collaborating with your private company.

PROF. CAPRON: Okay. That is -- we will call that the third option that Alice described. That is the snapshot option and the question is who is holding

the camera.

(Laughter.)

PROF. CAPRON: Trish?

PROF. BACKLAR: I just want to make sure that my voice is heard in this just as I do want to hear the voices of these people because I think it is, as I said before, a fatal flaw to leave them out. I very much like Bernie's suggestion of the opinion study or the opinion survey. And if we could piggy back it might be a way to do it but I do not -- I think we have to find some way to do it. I do not think we can ignore it.

PROF. CAPRON: David?

DR. COX: So I, too, like Bernie's suggestion and I would like to couple it with Steve's. The only coda I would put to Bernie's is that I think qualitative studies are actually research. I do not know if you said that they are not research but I think that they can be very --

DR. LO: If I did it, strike that.

DR. COX: -- research.

PROF. BACKLAR: He did not.

DR. COX: What Dr. Lo meant to say --

PROF. CAPRON: He just lost half of his funding actually.

(Laughter.)

DR. LO: And half my friends.

(Laughter.)

DR. COX: This actually goes hand in hand with some of the comments from the public testimony. We are between a rock and a hard place here because of the fact that we are not really setting up any permanence in these different countries and for the fact that you are going to get all sorts of differences between the different countries.

The only hope that we have is to find the common threads between all the different countries so every -- you know, any person with half a brain is going to know there is going to be millions of differences. Are there any similarities in the context of Americans walking in and doing research?

It is the similarities that could be useful

to these different countries and they are certainly going to be useful to us as a commission so it actually gives us some rationale for doing what we are doing.

So is it possible to do one of these qualitative things? The answer is yes but not, okay, unless we use a practical approach for gathering the data like Steve suggested. So I am very in favor of first getting it, hearing from the people in the different countries, looking -- using qualitative -- established qualitative research methods to come up with what the commonalities are.

We have to then pose some questions. We have to have some ideas to start with but find those commonalities and then take advantage of practical approaches for gathering the data. I think in real time -- I mean, I am not the one that is doing this but I think in real time that that is realistic.

PROF. CAPRON: Tom?

Let me just tell you who I have. I have Diane, Eric, Alta and Larry on the list.

DR. MURRAY: Just first of all I want to note for the record that it was the molecular biologist who told the social scientist -- to defend qualitative research of the social scientist. I think that is worth noting.

DR. COX: I have a student getting a Ph.D. doing qualitative research.

DR. MURRAY: All right.

DR. COX: So even though I may be the molecular biologist.

DR. MURRAY: All right.

I have heard a number of good ideas. Steve's idea that we -- if when we know what we want to ask, we can, in fact, ask private industry to give us what answers they can provide, subject to the limitations Alta just put up.

We can, in fact -- again, when we know what we want to ask -- locate a convenience, so-called convenient sample and ask some questions and gather -- get some numbers. But people have been talking about qualitative research and I wondered if they meant the

last kind, this third type, which I think might actually be quite useful for our purposes, and that is some short term ethnographic studies done in a few of these settings, a few different national settings where we actually hear the voices of these subjects precisely because that is the data where culturally attuned anthropologists, for example, go in and spend time in the research, spend time with the subjects, find out why they participate, what their concerns are, how they understand what is going on.

And I do not know that -- to me when somebody talks about a convenient sample that is not what we mean by it but I think that last kind, the ethnographic work might be, in fact, very interesting and valuable to us.

PROF. CAPRON: Diane?

DR. SCOTT-JONES: I think if we undertake the kinds of work that Tom has just described and others have mentioned it would be important also to listen to the voices of participants in studies here in the United States. Otherwise, I think we might have an

implicit comparison of an idealized American research participant and I think we would learn a lot if we did not do that but actually had data from United States research participants.

PROF. BACKLAR: We have that from the ACHRE trial.

DR. DUMAS: I cannot hear you.

PROF. CAPRON: From the ACHRE report we have that. They did a large more formalized study.

Alta?

PROF. CHARO: Well, first, I am not sure that the ACHRE report is a complete substitute because it was interviewing people, many of whom were subjects at a time that the current protections did not exist and so it would not necessarily be representative of people's attitudes about participating under the current regime and so, in fact, I strongly endorse Diane's suggestion especially because a few studies we have indicate that most U.S. participants, not most, many U.S. participants do not fully appreciate that they are in research, do not fully appreciate the

nature of randomization, et cetera, et cetera, so we may see some real commonalities.

PROF. BACKLAR: But a --

PROF. CAPRON: Could we -- I will get -- I will let you continue.

PROF. BACKLAR: I just want to say that actually ACHRE actually did a trial of about 150 people. Does somebody have the stats on this, people who had been recently in research?

PROF. CHARO: Okay. Well, if that is the case then I will take a closer look to make sure it is adequate and I withdraw the comment.

Thanks.

More to the point what I wanted to say is first in response to Larry's question of what we are trying to get out of this, I want to echo what I think I heard Alex say which is that there is a political as well as substantive value in hearing voices of subjects because it enhances the -- I think the likelihood that the report is on the mark. It also enhances its credibility no matter whether it is close

to the mark or far from it. It enhances its credibility in important ways.

Because of the limitations we are suffering under, though, I wonder if there is yet another thing we can do. I recall the extremely valuable and effective interventions by families who had somebody in psychiatric research at one of the very early meetings and the kind of reverberations of that testimony throughout years of discussion before we issued the report on impaired decision making capacity in research.

Washington, which is the location for the next few meetings, is a city that is incredibly rich in emigrants, recent emigrants from Africa, from South Asia and from a variety of other places, and it makes me wonder if we could take advantage of that.

In the paper that Norm Fost and Dick Love wrote about the Vietnam breast cancer trials, they note that they had two different kinds of focus groups and one of the focus groups consisted of people who were Vietnam emigrants living in the region who were

asked to kind of speculate as to how they would have reacted if they were still in Vietnam. And although this is not the same thing as doing qualitative or quantitative research with methodological rigor, it makes me wonder if, as a way to avoid OMB, avoid IRBs and avoid critiques about the rigor, if we say we are not doing research, what we are going to do is we are going to advertise very heavily in the local community newspapers, religious institutions and cultural institutions, advertise for people to please come and testify as members of the public about this topic and see if we can attract any number of people to simply come and chat with us, and we will take away from that whatever we can take away from it. Not to say that that is a substitute for things like the add on studies, just as a thing to do in addition to anything else we think about.

PROF. CAPRON: Larry?

DR. MIIKE: A couple of things. One is that having participated in the focus groups around the biological study, you can plan it for X number of

months, you can triple the time it actually takes and we are maybe what, five months away from completing the international report so I think that anything that involves activities other than say a literature search and an analysis of already published literature is going to take an inordinate amount of time, let alone the time it then takes to analyze it and publish it.

So I would recommend that while staff and the commissioners mull about the ideas going around the table that we at least have the staff take a look at what has been published. I recall the kinds of studies that one of the panel had talked about in specific countries that had elements of community participation and that to the extent possible we will do a literature search looking at those specific issues so that we can have something that is drawn out of what has been actually studied and published already. Otherwise we may -- we may end up with nothing.

I also understand the political context in it but that is -- that to me is a given. My question is

whether we need to undertake it just to try to allay the political side of it all and so I would rather that we do something that is do-able and we can still talk about things that I think will take a whole lot of time.

It seems the simplest thing to do is to take a look at what we already know in different countries and take a qualitative look at that and see what kinds of things emerge from it.

PROF. CAPRON: I think Eric Meslin wants to help us wind this up and then we have Jim, Eric Cassell, and another comment from Trish.

DR. MESLIN: This will be very quick. Some of these things are not mutually exclusive. We are already undertaking the lit review. You have in your briefing books a letter from Public Citizen written by Peter Lurie and Sid Wolfe describing their voluntary interest in mobilizing their own groups of individuals. So we hope that they will in their voluntary and altruistic role make a number of folks available to come and speak with us a la some of the

things that Alta had just said.

Secondly, the ideas of whether or not -- I tried to get at Steve's question of the what and I just put this on the table for you. It would seem to me, and staff has had some discussion about this, that the only justification for going to subjects would be to ask the same types of general questions that are being asked of researchers.

This study began not with the question who is being harmed and how but the somewhat more general question of what are the ethical issues that arise when the United States conducts or funds research in other countries. It was a general question that has two pieces to it. One, are there regulatory or other infrastructural or procedural matters that when one exports our rules elsewhere one finds difficulty in interpretation, in implementation that we are unaware of.

And the second but by no means less important is what are some of the operational problems that attend to exporting some of these requirements? Like

informed consent and IRB review and confidentiality concerns and the like.

So based on some of the consultants' reports, Nancy Kass, Patty Marshall and others, we have been getting responses to those questions from researchers so it would not be unreasonable to be posing the same types of questions to potential subjects.

PROF. CAPRON: Jim?

DR. CHILDRESS: I share the sentiment that we really need to do what we can to get appropriate input here but I guess I am puzzled given the kinds of constraints that have been mentioned as to what we might do in a way that would really be illuminating for our work.

I think at a minimum, though, as Eric mentioned, these are not mutually exclusive possibilities and we ought to perhaps pursue as many as we could, the -- Alta's suggestion of a public hearing that might involve recent emigrants I think is something that could be pursued, and expressing an appreciation for Public Citizen's interest in this,

there is still an issue of sort of representativeness then because we -- each group that proposes to bring someone in will obviously have a certain kind of agenda that -- and that could obviously then limit the kind of input we receive so we need to make that as broad as possible.

But then in relation to Tom's proposal I guess a question of could we actually undertake in such a brief period a kind of appropriate ethnographic study that would get the information, and I would be curious whether you think that with your social science background something is actually do-able in this period of time. That would be -- it seems to me the ideal if we could get that. I think I --

DR. MURRAY: Can I answer?

DR. CHILDRESS: Is it do-able?

DR. MURRAY: As someone who has never done ethnographic research, sure.

(Laughter.)

PROF. CAPRON: I had thought that perhaps Diane would -- do you have any comment on that?

DR. SCOTT-JONES: To do a genuine ethnographic study you really need to live in this setting for a while and we could not do it for that reason but you could do qualitative work that would not be genuinely ethnographic but you could not by any means do an ethnographic study.

PROF. CAPRON: So it would neither be ethnographic nor quantitative but it would be --

DR. SCOTT-JONES: Qualitative.

DR. MURRAY: There are people who already know the cultures. You know, it would take some creativity to locate the right people but people, including some that we have had contact with like Patricia Marshall and some others, who have already done extensive work in particular communities could go in and probably pick up some very useful information. It would not be the sort of thorough documentation of an entire culture but I think anthropologists, my impression, are increasingly comfortable with the sort of tasks that we would set before them if we think that is a suitable task.

PROF. CAPRON: Eric Cassell?

DR. CASSELL: Well, I would like to go to Kuala Lumpur for about a week and come back and tell you what the local customs are.

(Laughter.)

DR. CASSELL: But I think one of the issues we have to see is what is the question we are trying to answer. What has been brought up by us today is something that said, oh, look at that, the issue is not informed consent. Oh, that is really interesting because that really changes the ball game.

The issue is not should we have informed consent. The issue is what is the issue. What does it mean? What does it mean to protect human subjects in Uganda or da, da, da? And for that, yes, we need to hear from people just as we heard today that was so useful but I think it is like when you want to know about what it is like to have kidney disease. You really should not ask too many people with kidney disease because they do not really know. They know themselves but they do not know how to generalize from

it.

There are a lot of people who know a lot about this and there is the literature search. I would like to hear more of this kind and I would also like us to define further what we mean if we have got a chance of getting a report out by May, which I might say seems to be less and less possible.

However, we could get a report out by May that says what the problem really is and that in itself would shift the conversation from its rather superficial level as it exists now towards one that requires a good answer.

PROF. CAPRON: Trish, David, and then we really need to wind this to some sort of conclusions.

PROF. BACKLAR: I want to know if we -- why we could not change the deadline on this report? That is the first question.

PROF. CAPRON: Oh, we will.

(Laughter.)

PROF. CAPRON: Is that enough of an answer?

PROF. BACKLAR: Yes.

(Laughter.)

PROF. BACKLAR: I think it is important that we all be flexible. That is really what I am asking. And do we really -- and the next question then is do we really consider this -- if you consider this important enough, are we willing to do that? And do we consider this important enough? It is interesting. I am not certain.

And then the one thing I did want to answer to Larry and that is I think that we are not doing this just because it is political. I think it would be wrong not to hear from people who are stakeholders in this.

DR. MIIKE: But we are differing in what we mean by hearing from people. I am not saying we are not hearing from people. I am saying about what -- what exactly -- what actual process we undertake to hear from people. That is where we are differing.

PROF. CAPRON: Maybe -- let me try expressing what I understand to be the alternatives but first let's get some clarity. Are we all concerned that

there be some information available to us about views of people who are not researchers but who are research subjects in studies that have been or might be done in those populations abroad? Are we all agreed that that is something that we would like to be able to say was an input to this report?

DR. CASSELL: Directly from the subject or from people --

PROF. CAPRON: No, no.

DR. CASSELL: -- who know about the subject?

PROF. CAPRON: Information about their views.

DR. CASSELL: Yes.

PROF. CAPRON: Okay. So then we -- that does not totally answer the what question because information about what views, is it their view about the sense that they are in an involuntary situation where the alternatives are both bad ones? Is it their view about whether they want to have full diagnosis and full information about what the -- what research means even if that is not the standard in their country previously? Is it their view about risks and

benefits, sort of the standard American disclosures? That I think remains -- and I doubt that we are going to nail that down today. For that we really do have to take Alice up on her suggestion that they come back to us with a memorandum describing it.

So the real question then is we have -- we have hard about three or four different means and Diane has underlined to us that we might want to keep in mind the value of having some comparative information with what is true of U.S. research participants as well so that we not react to something thinking it is so different when maybe it is quite similar.

But we have heard the possibility of finding in the existing literature not only, as I understand it, of studies that were done of this issue as such but information which is provided in description about the way in which an AIDS research project was done. Did the researchers report back on community consultation what emerged from that community consultation? In other words, what people were

saying? That is one source.

The second would be looking directly at studies such as the ongoing ones of these issues of consent and the like where people are studying what research subjects think about the consent process.

The third would be once we know what we want to know, asking for volunteers, which include both Public Citizen and so forth and researchers who are already conducting research in the field of a biological sort, a medical sort, and asking them could they get approval from their IRB's to ask their subjects in focus groups or individually or whatever a few more questions that have to do with the research process instead of whatever is being studied. This would be on a voluntary basis and the results would not purport to be statistically significant in any way but they would be -- I guess we are calling those qualitative -- qualitative information.

And the fourth would be that we would undertake one or more formal research projects sponsored by us in which information, again perhaps

qualitative but perhaps if the studies were large enough, quantitative data would be produced on this same set of issues. Is that a fair description of those four categories? Does anybody want to add a category?

PROF. CHARO: Just the public testimony idea.

PROF. CAPRON: Excuse me. And that somewhere up towards the early end of that is drawing on resources that are readily available, whether Alta's suggestion that we find people locally or whatever but we find people who could speak as individuals and they would not purport to testify about everybody's view but if they are thought to be knowledgeable about their own culture, at least somewhat representative of what they, as a representative of that culture think in the context of the questions that we are asking.

Is that --

PROF. CHARO: Yes.

PROF. CAPRON: That is the objective there.

Tom, is there an additional one?

DR. MURRAY: I think that is an excellent

list. Your last category, I think, lumped together two different things.

PROF. CAPRON: Okay.

DR. MURRAY: One is the convenient sample research that Alice was proposing. The second is I did not mean full ethnographies. I meant using ethnographic methods to go in and really get thick descriptions of how people on the ground experienced their participation in those trials. That is all.

PROF. CAPRON: Okay. And you were using that in the context, again, of researchers who are already familiar with settings and are already either there or --

DR. MURRAY: Preferably, yes.

PROF. CAPRON: Yes. So that it is not a question of trying to do all that in a compressed time frame.

DR. MURRAY: Not helicoptering in, doing an ethnography and leaving but rather people who understand the culture and are trusted.

PROF. CAPRON: Rhetaugh?

DR. DUMAS: I am back to Eric's question about the question, what is the basic question. It seems to me if we are interested in the ethics of research in the international arena -- my concern is whether those interests are different from those that we have here domestically.

I think this borders on what Diane has said and this continues to bother me. It seems to me that we are dealing with issues of principle and where there are issues of principle I do not know that they should vary. If they are issues having to do with how to operationalize them then I think we need to have information about the culture, the people and what have you.

I believe that there is some merit in separating and distinguishing those two. I do not know that we have a different set of ethical ideas or principles for the international arena. I do not think so. But I think that what we are dealing with is that the influence of culture and tradition will alter or dictate how these principles become

operationally.

PROF. CAPRON: Okay. I mean, I think that in terms of the writing of the report you are absolutely right and the question is does that mean that there is nothing we really want to find out from this process because we are either dealing with it on a principle basis or the application to a very particular environment, and we are not going to make statements --

DR. DUMAS: We are not going to make applications to --

PROF. CAPRON: That is right, exactly.

DR. DUMAS: -- so we cannot get to be -- we cannot get that specific.

PROF. CAPRON: And I suppose the question I have heard from other people is, is there a middle ground where there are categories of concerns that are either missed by the present regulations or topics that -- where they show that the nonfit between the regulations is assumed and the needs of the local community are going to be very severe.

Alta?

PROF. CHARO: Yes. It is specifically to that question of whether or not there are topics that are not currently covered.

One of the reasons I am interested in pursuing this, albeit in a limited fashion because I would love to see it not derail the report as a whole is I think because my interest in this area may be a little bit different than the ones that have been the focus of much of the literature.

I find myself far less concerned with the details of the consent process and far more concerned with the details of distributive justice following the conclusion of the research. I am much less concerned about finding out if subjects during the course of research know that they are in research and much more interested in finding out whether people would be outraged if they were to understand that none of this work could ever benefit them or their children under most foreseeable economic circumstances.

To figure out whether in a transnational

setting where you have got players of the vastly different socioeconomic resources, which I think is just a different beast than some other research settings, whether certain things become relevant to people's decisions to participate such as the extent to which is something that I might have access to personally, that people in my locale or my country or even my kind of, you know, transnational region might have access to, whether this is something that is primarily going to be marketed back in a rich country that they could not do it themselves there.

I mean, these are things that might turn out to be relevant to people as individuals and I find that important for two things -- for two reasons. First, because I think that genuinely helps us to understand what it means to further people's autonomy to the extent that we think that is of value that needs to be exported even if it does not have to be exported in the form of signed consent forms.

The second is because I think one of the reasons we are concerned about this area is not

entirely about the exploitation of individual subjects who may very well get an individualized benefit by participation. It is that the research enterprise depends upon public trust and public support in a very profound way and that a few errors that result in cynicism and anger in a couple of highly publicized trials can poison the atmosphere for decades with regard to corroborative collaborative research.

I think some of the old birth control pill trials in Puerto Rico are still having reverberations in the women's health movement and in the degree to which there is confidence in the medical establishment's research in a variety of reproductive areas for women and it is just one of several object lessons.

So that I guess my concern is really about the degree to which we are adequately assessing people's concerns about the politics of doing the research in these countries as opposed to the kind of micro ethics of am I being adequately protected.

PROF. CAPRON: Okay. Bernie?

DR. LO: I know we have spent a lot of time on this already and we need to move on but it seems to me we really are struggling with trying to define what are we hoping to get out of amassing this information. We sort of all think it is good but what exactly are we going to get out of it.

I think it is worth trying to clarify because the methods, it seems to me, will depend not just on what our resources are but are they suited for the goals and objectives we are trying to achieve.

I guess just again to take another cut at it, it seems to me one thing that I would like very much is to get the perspective of people, of potential participants, what are the ethical issues as they see it. Have we missed anything? Alta's question. And then are we way off on evaluating what is important and what is not? If we start to hear that people say, you know, you are not paying attention to this but we think it is really important, we have to factor that in. Or conversely, you guys are paying all attention to consent, we do not care about consent, we will just

sign up. That would be important for us to understand so we do not sort of go, you know, stumbling into holes in the dark.

The other thing I think is we are going to make some recommendations. We have seen them already in the preliminary drafts. Some of the things in our briefing books as to how you might address in some situations the dilemmas that come up, you know, this 24-hour waiting period -- 48-hour waiting period so you could get -- talk about it with your family if it is the tradition you do not agree just for yourself. What do the people who might actually be involved think about it? Are those viable options? Do they make sense or is it something a bunch of people at the Holiday Inn dreamed up reading the literature that is just not going to work and, therefore, make us look ridiculous if we propose it?

So I think that is where I would really like to kind of get some more direct voices from people, you know, speaking for themselves. You know, again we all understand how things are not representative and

they may not be generalizable and people come with biases and axes to grind but again we faced that when we heard testimony in our research with disorders -- mental disorders that may affect decision making.

We heard people who had an axe to grind, who were biased, who had a point of view, and some of whom were very persuasive, and I think we heard a lot of other things that were, you know, out in left field. But to get to the good material we have to be willing to put up with some things that we say, well, you know, I cannot really use that in our thinking.

PROF. CAPRON: Larry, and I have a couple of other people but I do want us to try to focus on a decision now.

DR. MIIKE: First, I just want to comment. Rhetaugh's question to me was something we are going to discuss this afternoon rather than right now.

I think that this -- the issue about research participants is getting to have a life of its own within this discussion here and it sounds like some people would rather have that as a separate report, as

a focus of a report.

I just want to reiterate what Eric had reminded us about what this charge is and it seems to me that what we are -- what I would be interested in is that we go in with our guidelines and standards for international research under certain premises and that is what you want to compare about what the understanding is of the research participants in other countries about whether there is a disjoint there or not.

For that reason I think that the suggestion that Alta made about maybe publicizing in the local communities will not fly because we cannot -- I am not prepared to sit here and listen to someone tell me about their culture without the context about what that has to do with our study. I mean, it has to be framed in a way that they have some understanding beforehand about this is how research is viewed for the United States when they are done in another country and these are the premises that would go in, and then I would like to hear an answer from that but

if all I hear from that is the particular cultural context of where they come from, it is of no use to me.

So I just want to say that the what is we are going in and saying this is the way that research is now currently conducted in other countries and the current policy of our research enterprise, our government sponsored research enterprise.

What is the disjoint, if any, and I know there are, from the research participant standpoint in these countries? Not on an individual basis but something we can generalize, and to me it means that we have to be much more focused, and when we look at these different four categories that Alex had enumerated in which we want to answer that question.

PROF. CAPRON: Just to try to bring us to a conclusion, Tom very usefully earlier said that it seemed to him that it was off the table to talk about NBAC sponsored research of a -- in a number of international settings which would be quantitative and completed between now and whatever. I mean, that was

the analogy to the house will not be ready by the time we need to move in.

If that is a wide view and at the other end of the spectrum we have already head that the staff is doing the literature search and I would take it that, with some confidence, that they have heard enough from everyone here that that is an activity that deserves probably even greater resources in terms of right now making sure they have got enough people working on it and that they are casting their eye widely enough in what the literature is.

So we really are coming down to do we have any reason to reject the staff exploring what volunteers would be able to get us? That is to say the researchers, the local resources, Public Citizen or other groups, any of the AIDS groups that have experience both nationally to fit Diane's concerns and internationally about subject -- knowledge of what subjects care about.

Do we have any reason to tell them not to begin a process and come back to us and tell us what

resources they are able to develop that way?

Okay. So I guess the real question that remains is if we want to have anything beyond that what is it? Can we be more precise? Because it seems to me that in terms of getting these snapshots of things we are asking for -- what we could have at the next meeting, it seems to me, would be a focused memo, and perhaps before the next meeting through e-mail, a focused memo of the different kinds of concerns that people have raised here, topically what do they expect to have come out of this, and always against the background that Rhetaugh and Eric and Larry have asked, which is in a way, what do we expect to do with the information.

Would we be expecting to say that a regulation should be changed because of it or merely in implementing a regulation here are some considerations that are not self-evident, some of which we may have gathered from the researchers, some of which we may have gathered through this process of the research subjects.

If we have examples of ways in which people have dealt with those problems that, too, but otherwise -- in other words, we are enriching the set of concerns that would be put on the table. For example -- I am sorry that Alta has left. I cannot imagine our ending up saying something that if it turned out that people -- that we happen to ask through these adventitious studies -- were not concerned or very few of them were concerned about whether or not the drugs would be available afterwards that we would think that that information is not properly part of the consent process, and could be left off the table.

I mean, if it is known in advance, it should go before the National Health Ministry, it should go before the IRB, and it should go before the subjects that we are developing a drug here which probably will not be used in your country for at least ten years even if it proves to be good. Do you still want to participate? Some people may say yes and some say no, some IRBs may say you can go ahead in those

circumstances, and some may say no, some health ministries may say you can go ahead in that circumstance.

Others will say we do not want that drug -- that study conducted here unless we can reach a deal with you, drug company, in advance that we can get the drugs very cheaply if they prove -- but I cannot imagine our saying on the basis of any evidence we get that that should not be talked about by people.

Ergo I do not see that we are going to lead to a change but I would like to have the staff put forward for us all the topics with your input to them in the next few weeks, all the topics that we could think of where we might want information and at least see what the likelihood is that we are going to be able to develop information on those points through the kind of processes that we have -- that I have just outlined.

So I do not hear a lot of disagreement in other words about the processes.

DR. CASSELL: No.

PROF. CAPRON: I know we are all groping and the real question is what do we think is going to be done with the information and we probably cannot tell ourselves that fully yet.

DR. CASSELL: I think I just want to add to that. I do not disagree with that. I want to add to that that the -- I am interested in hearing more Dr. Loue's in different places and I am interested in hearing people who attempted to solve the problem. That I have not heard anything about yet.

There are people who are genuinely interested in protecting the subjects in their country from risk in research. How do they go about it? Never mind conforming to our regulations because if that is any -- all anybody in the world is trying to do then we have a bigger problem than we thought.

PROF. CAPRON: Okay. I think that the staff should be aware of that in terms of the witnesses that they are planning to line up and some of the people that they have mentioned I know from my personal experience with them will be able to give us

information on that.

Steve and Trish were on the list before and then we are really going to stop. If I have stated the consensus well enough that no one wants to strongly object to that, I think we have given the staff all the guidance we can for this point.

MR. HOLTZMAN: What I find myself sitting here struggling with is that thinking about the heterogeneity of human subjects research in different contexts and just looking at my own company where we are doing very early stage genetic research in asthma in China, we are doing studies of bipolar disorders in Latin America where we are confronting issues such as when subjects of that research eventually die, and they are, how do we go about getting autopsies of brains, doing Phase III clinical trials in the U.S. and Europe of anticancer drugs, and certain biological material research in Scandinavia. All right.

And when Eric asks the question what do you run into in terms of implementing the regs in those places I can give very definitive answers of how one

runs into problems trying to conform to the letter but also the spirit of the regs and what it requires of you.

But then when I look at the -- beyond that and one were to ask if you were to go to those subjects what questions would you want to ask them. What is -- what would be important in the different contexts? I think of things like Alta's -- of what does distributive justice require of you?

Well, if you are doing a study in rural China where it is so basic that if it is ever going to mean anything in the way of a drug that is 15 to 20 years out, a promise of that drug seems pretty irrelevant as opposed to what else could you do there and then in terms of education or provision of medical materials today, et cetera, et cetera.

So that I -- how do we get it beyond Eric's question. What is the question that we could do with some level of generality that cuts across all of that heterogeneity? I do not have an answer to that but that is what I am struggling with.

PROF. CAPRON: Okay. Trish, the final word?

PROF. BACKLAR: Oh, I am going to let Bernie have the final word because I will come back at this afterwards.

PROF. CAPRON: Okay.

DR. LO: I just want to briefly say I think, Alex, you gave a very nice summary. I would just add in to keep in mind Steve's earlier suggestion that we look into the possibility of using -- people doing -- researchers doing ongoing projects in other countries to piggyback on some of these questions although there are existing subjects.

PROF. CAPRON: Yes, that I thought -- that was in the volunteer category. In other words, we would ask them if they would be willing. We are not sponsoring that research.

DR. LO: Right.

PROF. CAPRON: Because then we get into OMB problems.

We stand adjourned until 1:35.

(Whereupon, a luncheon recess was taken at

12:27 p.m.)

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

DR. SHAPIRO: All right. Thank you very much. I want to once again apologize to my fellow commissioners for not being here this morning but there was a special dividend and that is, as I understand, our Professor Capron led a very interesting and useful discussion.

Alex, thank you very much for doing that. I very much appreciate it.

We have a number of things to cover this afternoon but before we begin our formal agenda, Robert Eiss is here from the Fogarty Center. They have obviously interests in the international area and -- Bob, if you could just come to the chair here.

I thought it might be useful if he spent a few moments telling you about an upcoming conference which the Fogarty Center will be sponsoring soon and anything associated with that he would like to mention.

Thank you very much for being here.

DR. EISS: Thank you, Mr. Chairman. I am

delighted to be up here to talk about two of the Fogarty activities that might support the work of this commission.

In November, November 8th through 10th, the Fogarty Center is sponsoring an international forum to look at distributive justice issues in Western sponsored research that takes place in low and middle income nations and we have been very privileged to have both Ruth Macklin and Alta Charo as part of our cyber steering committee to prepare this meeting.

Half of the representation of the meeting will involve scientists or other health professionals from low and middle income nations and we also will have several community participants, individuals who are involved as public participants on institutional review boards in Gambia, Trinidad and elsewhere.

The meeting really does have two purposes. The first is acculturation. That is we are bringing together Western sponsors, including NIH, the Wellcome Trust, the British MRC, French NSRM (?), and scientists who host Western sponsors investigations in

developing nations to discuss mutual ethical expectations and obligations.

The second is this meeting is about reducing principles to practice, specifically what types of benefit sharing agreements could possibly be negotiated and what are the attributes to just sort of define what is a reasonable compensation to a study population after the trial.

In part, we are addressing the prima facia obligations in the CIOMS guideline to provide reasonable access to study populations or broader relevant groups to successfully tested products.

Because there will be community participation in these meetings I think some of our discussions will likely be of use to the commission and we would welcome -- we -- Eric and Alice both are able to come to this meeting and we would more broadly welcome commission participation in the meeting.

One of the outcomes, apart from being able perhaps to develop a template of what would be a benefit share agreement that could be negotiated

through a stage process with low and middle income nations.

One of the purposes will also be to define what should be the attributes of aspects of a training in research program that the Fogarty International Center will sponsor and we are, in fact, giving over the third day to a series of presentations by academic officials in low and middle income nations to note to us what they feel their training and infrastructural needs are.

The practical outcome will be what the NIH calls an RFA, a request for applications, for research in training program to help build the practice of ethical theory and practice in countries that the NIH is more and more working in. One of the possible outcomes of that RFA will be research to try to better develop an ethnography of ethical practice in a medical context in low and middle income countries.

So I note these two activities and would welcome the involvement of the commission and suggestions on how these efforts could converge with

some of your data collection efforts. I would say just in conclusion that there has been discussion this morning of the need to gain the perspectives of participants or their advocates in trials in low and middle income nations.

We have been able to identify a few of these for our meeting in November and I know the time frame is quite short, quite abbreviated, but we would certainly be willing to sponsor individuals who the commission could bring to our attention who you feel might be involved in this meeting.

Thank you.

DR. SHAPIRO: Thank you very much. I very much appreciate hearing about the meeting. It certainly has a lot of direct relevance to some of the things that we are doing now and I am very pleased to hear that at least some of our commissioners are involved and others may attend.

Did I understand you correctly to say that if there were an NBAC commissioner who were interested in this that you would welcome their attendance?

DR. EISS: That is correct.

DR. SHAPIRO: At that meeting.

So perhaps, Eric, we could ask staff just to get an e-mail to all commissioners just outlining the date, the agenda so far as it is known at this time, and because I think that would be very useful. It is very -- I did not know about this meeting and it sounds very, very helpful. I am very pleased that the Fogarty Center is taking this initiative.

Are there any questions from members of the commission in this regard?

Alex?

PROF. CAPRON: I was not clear how soon your own work products will be coming out of that. Do you expect something in writing as a result?

DR. EISS: Yes. What we will prepare is a summary of discussions to try to capture the discussion of the meeting, which I should think optimistically speaking would be available within two to three weeks of the meeting, and then following the meeting what we will do is we will develop a working

group of some of our sister research institutes at the NIH and we will develop an RFA which will be advertised early in the calendar year and awarded before the end of the fiscal year, before the end of September.

I also neglected to note that this meeting is being organized in collaboration with the World Health Organization, which is the co-organizer of the meeting. The steering committee or rather the steering committee involved several international organizations, including the Commission of the European Union, the Council of Europe, the Nuffield Council, the Organization of African Unity, and I think I might be missing two or three.

PROF. CHARO: The Wellcome Trust.

DR. EISS: The Wellcome Trust as well was involved in the meeting but we consider this a multilateral initiative. We have been the catalyst because we -- to be quite candid, we have -- we are providing the early sponsorship but our expectation is that or our aspiration is that this forum is not a one

time event.

It will result in a series of annual fora where there would be a balance of representation from Western sponsors in low and middle income nations and there would be a consortia of sponsoring organizations which would include European, Asian, African, Latin American and U.S. institutions so that is our aspiration and I think we are reaching that gradually.

DR. SHAPIRO: Thank you.

Any other questions any members of the commission have?

Well, thank you very much.

DR. EISS: Thank you.

DR. SHAPIRO: Thank you for being here and thank you for that invitation. I hope that some members of the commission will be able to take advantage of it.

DR. EISS: Great. Thank you.

DR. SHAPIRO: Thank you.

I want to just mention -- make one comment and then suggest a change in our agenda, a modest

change in our agenda.

First of all, you will recall from some of the materials you received there was some discussion last time regarding standard of care and what that means and how that relates to what we are doing. That is an issue which we certainly -- we will have to deal with. It is a question of using language that is -- that means what we hope it means and so on but I would propose that we really not deal with that today and we wait until we get to it more naturally in the report as it unfolds. So I do not want to go back to that today.

It is not because I have either forgotten or think it is not an important issue but I want to go back to it when we have something in front of us which -- into which that can be incorporated in a useful manner. So even though that is discussed in one of the memos that we have we will come back to that at some future meeting.

The change that I want to propose in the agenda is -- I know that Lori Andrews is here and she

is going to be talking to us about some issues of the reproductive technology area and how NBAC might think about this and so on. One of our -- as we go we were thinking about our priority setting process and thinking of various possibilities.

I would propose that we ask Professor Andrews to really come forward and deal with that right now and then we can spend whatever time we need on the proposed draft findings and recommendations regarding informed consent. I do not want to interrupt that discussion since it is really extremely important.

So, Lori, if you are agreeable and if -- is there any objections first of all?

If not, Lori, if you are agreeable, why don't you come forward, sit down right here, and let's begin that aspect of our agenda.

PRIORITY SETTING FOR FUTURE PROJECTS

REPRODUCTIVE TECHNOLOGIES

DR. ANDREWS: Okay. In a Canadian business journal last summer an article started out saying, "The year is 2010 and little Jimmy is being teased in

the playground. 'Your mother is a dead fetus and your father is a mouse,' taunt the school children."

And the article went on to state that British researchers were exploring the possibility of using eggs from aborted female fetuses to serve as donor eggs for women who are infertile. It also reported on some Australian research where they were creating genetically altered mice to act as surrogate testicles for the production of human sperm. And, in part, because of those developments the Minister of Health in Canada is in the process of proposing a bill -- he just reiterated last week his intention to put a bill before the Parliament which would create a federal agency to deal with reproductive technologies and also have some limitations on what can be done. So in that sense it would be like the British model of a Human Embryology and Fertilization Authority.

This process took a long time in Canada. They have had since a decade ago various commissions looking at this using a variety of innovative methods. They instituted a toll free number so citizens could

detail their own experiences with reproductive technologies and express their opinions. They got tens of thousands of calls on that number.

They commissioned studies from disciplines such as psychology and anthropology on the social impacts of infertility, assisted reproduction, human embryo research, and they came to a consensus that Canadian values were in favor of noncomodification and nonobjectification as well as protection of the vulnerable.

So they have come up with this series of suggestions that come from those principles such as bans on human cloning, genetic enhancement and sex selection for nonmedical purposes.

Well, I do not think we can so easily in the United States come to shared cultural assessments around reproduction and, in fact, for me the most notable aspect of this field has been how it has developed strikingly differently from other medical services. Prolife sentiment has prevented any federal research funds from being used in procedures involving

embryos so there have been no federal research money going into reproductive technologies.

Consequently researchers are not getting their proposals for experimental techniques for couples before institutional review boards. That mechanism that protects people in other medical settings is not so prevalent here. In fact, according to Mark Sauer, an in vitro fertilization doctor, IRB review of reproductive technology proposals is so rare as to be "remarkable."

In one instance, in fact, an infertility doctor sought IRB approval but he had already started advertising the procedure in the Washington Post before he even went to the IRB and the IRB chairman said one feeling was that if we approve the study at least we can monitor his actions and collect meaningful data about safety and efficacy so it went forward and did not have the sort of teeth of a review that one would expect.

Another problem has been that unlike new drugs or medical equipment this has not been an area

that has been regulated by the Food and Drug Administration because it involves services rather than technologies under the FDA mandate and it also differs from other medical procedures because insurance rarely covers it.

Thirteen states have very minimal laws that, for example, in Hawaii allow couples one attempt at in vitro fertilization.

But what has happened is that it has created an issue because you do not have health insurers, you know, looking over the shoulders of physicians in this area, having their own assessments about what is safe and efficacious or reasonable to do but in addition you -- because there is no insurance you have clinics in this vast competition for patients and doing things like trying to compete on the basis of offering the newest technology so bringing experimental procedures in as a marketing device.

You also have some implanting as many as ten embryos or using infertility drugs indiscriminately to increase the number of babies created so that they can

inflate their success rates. Additionally there have been some clinics that have reported as pregnancies small hormonal shifts in the woman which would not be otherwise reported as pregnancies by physicians because it is at such an early stage that many of these are reabsorbed by the woman's body.

Additionally, I see a problem because medical practice litigation, which might work in other areas of medicine with novel techniques does not work as well in this field. Even in vitro fertilization, which now has been done for the past 21 years, has a success rate of only around 25 percent and so when couples go in even if something massively negligent is done wrong, you know, the clinic is missing one step in the process, the couple generally thinks they are in the 75 percent that just it would not have worked for. Unlike faulty heart surgery, say they do not get worse in their own health and so that signalling method about when malpractice litigation might be appropriate is -- you know, is not in place.

In addition, risk to children may not be

discernible for many years past the time when statute of limitations would run and it is interesting to note that even though there have been over 300,000 births through in vitro fertilization around the world, only one of those children, a woman, has gone on to have her own child. So we are even at the very basic stages about getting data about reproductive capabilities of these children.

So from my vantage point what we have seen are experimental techniques rapidly being introduced into the more than 300 high tech fertility clinics in the United States without sufficient prior animal experimentation or randomized clinical trials or rigorous data collection that would occur in other areas of medical experimentation.

In fact, in vitro fertilization itself was applied to women years before it was applied to baboons, chimpanzees or rhesus monkeys, which led one embryologist to opine that it seemed as if women had served as the model for nonhuman primates.

I think there are problems with this

approach. Couples often do not realize how experimental the procedures are that they are being offered. In addition, there are incidents where an individual's reproductive tissue is taken for research without their knowledge and consent. In fact, going back through three decades there is evidence of that.

One of the researchers attempting to develop *in vitro* fertilization would jokingly talk to colleagues about how he poached eggs. He pierced patients' ovaries and aspirated eggs when they were undergoing pelvic surgery for other reasons without their knowledge and consent. He claimed that this did not harm the patient in any way because they would have undergone the surgery anyway but, of course, an unauthorized procedure is a legal and ethical harm in itself.

More recently a California couple learned that without their consent their embryo had been sent to the University of Wisconsin's Zoology lab for research and in an East Coast hospital recently doctors proposed a protocol where they would take

sperm for research purposes from men undergoing vasectomies without their knowledge.

Now despite the fact that many experimental procedures are being done in fertility clinics we had astonishingly little data about the risk of these fertility treatments primarily because reproductive technologies are unregulated and we do not have any mechanism really for follow-up. Other countries have put registries in place, for example, to track the outcome of children born through in vitro fertilization and its adjuncts and compared that to children born through more traditional procreation.

So some of the concerns in that area have come about because of the high use of infertility drugs. There are 1.3 million prescriptions for fertility drugs written every year leading to many multiple births and, as I mentioned, some clinics still put back seven to ten embryos. Obviously there are major health risks to women and children in this approach.

For example, while only eight percent of

single births are premature that rises to 92 percent for twins and, in fact, the infant mortality rate for triplets -- I am sorry, 92 percent for triplets and the infant mortality rate for triplets is six percent in the first year of life.

It concerns me because I review informed consent forms from some clinics and many of them use forms that list totally remote possibilities. What would happen to an embryo if there were an earthquake, an act of God, labor strike or war? This is right off of one form. But not the real and statistically much more probable risk of multiples. Some clinics never mention the fact that one in three ivf births is a multiple and I certainly have not seen the sort of follow-up data in there to say what is the health outcome for children.

So multiples are an issue. I think there is an also an issue around ICSI, intercytoplasmic sperm injection, which began to be used in 1993 for men with a low sperm count where you can actually use a single sperm and inject it directly in the woman's egg.

In Australia and Belgium, unlike the United States, the government keeps track of how many children conceived through reproductive technologies have genetic abnormalities and last year they noticed that children created by ICSI were twice as likely to have major chromosomal abnormalities as were children created naturally.

A Lancet editorial criticized the use of ICSI on people before it had been adequately researched in animals. Other areas of concern just to highlight because of potential risk to the children are the use of frozen eggs. In 1996 an Australian doctor produced the first known birth using eggs that had been frozen. We routinely freeze sperm or embryos but there has been difficulty with achieving pregnancies from frozen eggs.

In August 1997 the first American baby was born with a frozen egg and just two months later South Korean researchers published a study in Fertility and Sterility suggesting eggs frozen at the early stage of development and then thawed had an increased incidence

of chromosomal abnormalities compared to eggs which had not been frozen.

And yet I went on line yesterday and, you know, checked and there are at least five clinics that are competing in the United States by advertising the use of, you know, frozen eggs. Some are now offering women the chance to freeze snippets of their ovaries before they go through menopause and have the potential to have children then later on. The first successful implantation has occurred where they put the ovarian tissue back in and the woman has started producing eggs again.

So should NBAC take this one, which I guess is why I am here, I think many of the topics you are considering have great merit. I think the gene patent issue is important. Looking at the impact of the Bayh-Dole Act needs to be critically assessed as well. The practice of pharmaceutical companies giving large payment for the recruitment of research subjects deserve special scrutiny so you have, you know, a variety of equally worthy issues and I thought what I

would do is just briefly tick down where this would fit in your mandate.

In terms of reach it is important. 600,000 Americans have already tried assisted reproductive technology so it is a large group being affected. They are vulnerable. There is some psychological research suggesting the level of depression among infertile couples is similar to that of desperate cancer patients. So just because they are physically "healthy" does not mean they are not vulnerable.

In terms of abuses there have been many. Consequently it meets the criteria of having urgency as a public health and public policy issue.

I think it also meets the criteria of the lack of another entity to be able to deliberate appropriately on this issue. We are the only technologically advanced nation that is not analyzing these issues on a national nonpartisan basis and there is currently no other body likely to do the sort of assessment that is necessary.

I mean, I want to point out this is not like

the situation of embryo stem cells where NIH itself is itching to do the work and we will come up with some, you know, regulatory structure and an alternative deliberative body.

In fact, in this field most of the researchers at NIH who are interested in these issues from Joe Schulman to Gary Hodgen left NIH when they were forbidden to do in vitro fertilization at its adjunct so NIH is not the alternative deliberative body here.

Nor is the FDA particularly well suited to regulate in this area. At the 1998 annual meeting of the American Bar Association an FDA representative suggested they were moving in the direction of regulating cloning and human reproductive technologies and took a lot of flack from lawyers in attendance who raised concerns that the FDA was overstepping its bounds since it is supposed to steer clear of regulating the practice of medicine and surgery. And much of reproductive technologies does involve services rather than drugs and devices.

I have since had the opportunity to meet with the FDA about its proposed tissue regulations, which would cover a narrower aspect of this donated gametes and I think that proposal falls short even within that small area because it uses a framework that is similar to drug regulation. It looks at the safety of the procedures from the standpoint of the recipient.

For example, it protects recipients of donated gametes through infectious disease screening but it does nothing to protect the donors from coercion or in the case of egg donation from dangerous drugs or procedures. So, you know, taking this drug approach, we are worried about who is ingesting it, we do not know where it comes from, and it is very different here.

So some of the studies NBAC could undertake that would help in policy development in this area have been suggested by Andrea Kalfoglou and they would address things like the extent to which couples even realize they are participating in experimental procedures to create children, the type of research in

which excess embryos are subjected to, and how couples feel about it, whether donors are informed that their gametes might be used for research, and whether the type of research matters to them, what amount of compensation to donors is coercive, the extent to which institutional review boards are reviewing ART research, the extent to which the ban on federal funding on embryo research has had an impact on the quality of these services, and whether the FDA should regulate certain aspects of assisted reproduction.

I think all those sorts of things fall within your mandate and I hope this brief overview has helped you get a glimmering of the field and I would like to open it to any questions.

DR. SHAPIRO: Thank you very much. Let's see if there are commissioners that have questions and we will ask Andrea after if she has something which she would like to add also.

Alex?

PROF. CAPRON: Lori, one of the questions that came up at our last meeting as we were discussing

this was whether it would be a topic for a federal commission given our mandate which mostly focused on federal agencies where this is an area which is principally being a matter of state law, the practice of medicine and the formation of families and so forth. And the analogy that I was drawn to was the works of the President's Commission on the determination of death, which was also a matter of state law.

As we entered that field one of the reasons that there had not been effective and universal legislation on the subject was that the American Bar Association had one proposal, the American Medical Association had one proposal, the National Conference of Commissioners on Uniform State Laws had another proposal, and the one that was most widely adopted was one that Leon Kass and I had put forward in 1972.

And we were able to facilitate a coming together of those three groups with the President's Commission and, of course, the result was the Uniform Determination of Death Act and the report that went

with it and then it became the most widely adopted statute and so forth.

In this area the National Conference of Commissioners has put forward several bills as I recall. The last time I checked the principle one -- other than the Uniform Parentage Act, which goes way back and, you know, I think was originally the Uniform Paternity Act before it was the Uniform Parentage Act, but the most relevant one which is the Uniform Children of the New Assisted Reproduction or some such name like that was not widely adopted.

What is your sense about the potential that if we do not address the subject it will be addressed by other law reform bodies? You mentioned the inability of the NIH and FDA and so forth at the federal level. What about these bodies that deal with state law?

DR. ANDREWS: They mainly are focusing on the paternity issue and it sort of does not make sense the fact that a child of a surrogate mother belongs to the contracting couple in California but, you know, if the

child is born in North Dakota or Utah it is the surrogate mother and her husband's child, but I do not really see that would be your focus anyway.

I do not -- I am very familiar with the ABA's effort. There is a group within the Family Law Section which sponsored, you know, a wonderful bringing together of the FDA and the American Society of Reproductive Medicine, and all the interest groups around a proposed model law of their own but it really focuses more on what happens once you have actually got things in clinical practice and beyond.

Issues like not only parenthood but the type of psychological counseling that might be required and whether you should harvest sperm from men who have died. Nobody is getting at these issues about the review of things that are novel experimental procedures and nobody is dealing with issues of should we draw the line and have things in or out.

So I do not think that anybody else is going to do it and unlike the position you were in, I think the position more that NBAC would be in here would be

to look at what other countries had done because there is a total -- a vacuum here.

I think that -- I also think that unlike when the original bill was passed -- there is a bill that suggested in vitro fertilization clinics have to report their success rates to the Centers for Disease Control. Now there is no penalty on it and one of the largest clinics does not report at all and has a great video they can send you about why they think they should not report and things like that. But -- so there is no teeth in that but when that was passed the sense was that there was just a legal preemption problem and I think that even in the material I prepared for the commission around the cloning issue there is much more precedent to do something now at a national level and have it upheld within the commerce clause.

DR. SHAPIRO: Thank you.

Alta?

PROF. CHARO: First, and with apologies to the commission, I have to say since, Lori, you

mentioned my institution and put it on the public record, I feel compelled to just add two facts.

First, we had no idea that consent had not been obtained and we were investigated and that was --

DR. ANDREWS: I did not suggest that you --

PROF. CHARO: It could easily --

DR. ANDREWS: I said it got sent. I did not say --

PROF. CHARO: The second is that it was not actually embryos that were sent. They were eggs that failed to fertilize. But, anyway, just because it was on the public record I just wanted to straighten that out.

I guess my question is very much in line with what Alex was asking because this has been a subject of chatter on the e-mail among the commissioners, which is exactly what role we could play here that would be constructive.

As you pointed out, much of the situation here revolves around the interaction of the free market and the provision of medical services as

opposed to the approval of drugs and the approval of devices. To the extent that medical services are ever regulated in the United States, it is directly regulated as opposed to indirectly through the influence of insurance and medical malpractice. It is almost entirely on the state level and even there it is fairly uncommon to have direct regulation of whether or not particular medical services can be provided and exactly how.

DR. ANDREWS: But then think of the organ transplant area. There has been national guidance, you know.

PROF. CHARO: Yes, there has but it revolves around the actual organs as opposed to revolving around the decision to do transplants. In other words, the UNOS regs do not talk to what kinds of people should be put on the transplant waiting lists. They talk about what to do with a scarce resource. If a resource were not scarce I doubt that they would have any impact at all on the way those waiting lists are constructed.

So is this a topic that is best addressed on its own or is it a topic that is best addressed as one aspect of a larger debate about the regulation of medical services and whether that is wise in a kind of free market health care economy where other medical services also have been diffused without direct regulation and I think about -- I am thinking now specifically about things like some cosmetic services like liposuction and a whole variety of plastic surgeries, genetic testing, which has diffused as a service as opposed to -- because we do not yet have laboratories being approved for these things and we do not have test kits --

DR. ANDREWS: The marketing.

PROF. CHARO: -- test kits going through device regulations. Those are now still being handled simply as a marketing issue. And I ask this in a very serious vein because this is such a hot button topic. One that tempts people quickly to want to make judgment calls about things on which there is profound division of opinion such as what kind of people should

become mothers and fathers, how many people should be considered mothers and fathers, how many people should be involved in the process, the extent to which an absent or deceased parent is relevant to these questions, that I fear the more fundamental question about the regulation of medical services would get obscured by those hot button issues and we might struggle to a sensible resolution of whether or not we want to begin regulating medical practice in the U.S. like we have not done so far.

DR. ANDREWS: Well, we do regulate medical research in the U.S. at least federally funded and so, you know, in that sense there is a gap. We are treating this different. It is not like, you know, we are going to start regulating medical services.

I mean, there are two ways to go. I mean, clearly if you did it as a separate issue you would have more things on the table and I think Andrea's paper illustrates that because you might nudge your way a little bit into some of the clinical things or what you are calling services, you know, is it

appropriate to be implanting more than three embryos, for example. I mean that is one scenario.

I mean another scenario, though, is to do it as part of a larger review of what is going on with human research and IRB's generally and ask questions about when you have an increasing amount of research across the board being funded through nonfederal sources, in this because of kind of federal application but in other areas because the private sector is moving in and spearheading a lot of the research. Do we need a different model? Do we have to think about institutional review boards in the same way even if tomorrow every IVF clinic set up their own IRB would I be satisfied? You know, what happens when you have privately funded research with this high commercial potential? And where then are the gaps between the kind of FDA approval and things that look increasingly like drug? You know, a sperm donation as an alternative to an infertility drug but that may not quite fit.

I think that the Federal Government is trying

to do pieces of it. You know, the FDA with its little slice, and they are trying to meet with other people at HHS and elsewhere but they do not really have, you know, a kind of umbrella in which they can, you know, do it in a comprehensive way and so perhaps having some guidance or some principles would be useful there.

DR. SHAPIRO: Okay. I have quite a few commissioners who want to speak and a finite amount of time I want to spend on this, this afternoon, but I have so far David, Tom, Steve and Larry.

David?

DR. COX: So I will try and do this rapidly. I agree with what you said, Alta, in terms of the charged part of this but I was struck by Lori, which I actually believe but I never had collected them, which is -- and I find this ironic because you will see we had this discussion earlier this morning about other countries about the idea of when you are doing research and when you are getting medical care.

I think that is in the context of the human

subjects protections so I do not think it is just in the context of reproductive rights so we do not have to sort of have that be the deflector but this concept of when something is -- and I hate to bring this up, Harold -- standard of care and when it is, in fact, medical research.

DR. SHAPIRO: I was only talking about international.

DR. COX: I think it strikes me that that is sort of fundamentally what you are talking about so is that fair?

DR. ANDREWS: Yes. And, in part, each new technology that has been introduced -- it is -- not all the clinics have told people -- for example, there has only been birth in the world of this or that has really never tried in people before and things like that. So the basic idea that something is experimental is not necessarily described to people uniformly. Some clinics do a good job, others, you know, do not.

DR. COX: So I think there is a broader --

personally I think there is a broader mandate to deal with this issue and certainly reproductive technology is one that would spearhead it but that it is not just the reproductive technologies that needs this to give some guidelines on this point, I believe.

DR. SHAPIRO: Tom?

DR. MURRAY: First of all, Lori, I have to say I regret your presentation today. It sets so high a standard that few people are going to be able to match it and it just raises the bar for all of us so other than that it was terrific.

I agree with you, Lori, that this would be an appropriate subject for the commission and for many of the reasons that you stated.

I want to respond to Alta's assertion that perhaps we should instead focus on the "more fundamental" question of regulating medical services. It is a broader question. I would hardly say it is more fundamental than how we make families and how we create children.

DR. ANDREWS: Creation of families.

DR. MURRAY: For one thing, gametes and embryos are not services. They are human tissues, early forms of human life, and in my own view and I have said this in my -- some of my writings -- is that there has been entirely too much of a focus on the putative parents. It is inappropriate that we look at the role of the adults involved in this process but there has been hardly any attention paid to the children that are created by the process.

Shifting that focus or, I would argue, sort of correcting the disproportionate focus on the adults and highlighting once again the children created would be a service.

DR. ANDREWS: And that is not common to other medical areas nor is, you know, the fundamental aspect of it that you talk about, which might raise some constitutional concerns and how the government could regulate. So a study that talked about sort of standards of care and privately funded research and did not go into the extra dimension at least of the family nature and the resulting children would be

remiss then.

DR. MURRAY: I think so.

DR. SHAPIRO: Thank you.

Steve?

MR. HOLTZMAN: Thank you, also.

The line of questioning and discussion that was initiated by Alta goes to this distinction we have in the United States between practice of medicine versus research, say drug research. You have cited the fact that in most of the other industrialized nations when it comes to reproductive practice of medicine, if you will, okay, or experimental procedures there are review bodies so it is held differently.

Do they have equally this tradition of practice of medicine not being subject outside of the reproductive area or, in fact, do they regulate that differently?

DR. ANDREWS: I mean, no. I mean, you are absolutely right in your implication. You know, once you have a national health care system, you as the

government can say, "Well, we are going to do X or we are going to do Y." It does not -- many of these efforts, though, like the British effort actually came through the physicians themselves.

It came first as a voluntary licensing authority because there is a way in which some of the providers do not necessarily personally want to feel that they should have to provide everything that couples might want, sex selection, genetic enhancement, you know, they are looking for some larger social guidance about what is appropriate or not and so part of it has come up in that way but it is a different context.

DR. SHAPIRO: Thank you. Larry?

DR. MIIKE: I would like to raise a different way of addressing this problem. I think it is an important issue that the commission should address but I think what is limiting our discussion and some people's reservations about it is that we seem to want to be heading in the inevitable conclusion that some regulatory mechanism needs to be put in place. That

does not necessarily have to be the topic of our -- of a report on this subject.

It seems to me that even though we do focus on fairly comprehensive studies in our report, it is a useful exercise or at least a useful product to have an issue paper to scale down the scope of such a study just -- we are not going to do all this in one big step so it seems to me one way of doing it is to raise the consciousness around the policy makers on this issue, identify the critical areas that seem to be disjointed from other areas of medical research and medical practice in the United States, and as well as the -- and the way that -- right now it seems to be no obvious body that the United States can turn to towards if we move to our regulatory system or something like that that is in there.

So it seems that is an alternative at least to me about how one might address this issue.

DR. ANDREWS: I think you know a lot of coverage that I see of this in the press, <u>in vitro</u> doctors, they will say, "Well, we are regulated just

like every other area of medicine." I mean, in one article they said, "The FDA regulates us." I got a call from the FDA that afternoon, you know, saying, "Could you see us about this?"

DR. SHAPIRO: Alex?

PROF. CAPRON: I may be way off on this but my sense of the posture of this issue in front of us now is that we are holding auditions for candidate reports and part of --

DR. ANDREWS: I would have brought my tap dancing shoes but you heard I said I like gene patenting, I like Bayh-Dole, you know.

(Laughter.)

PROF. CAPRON: And part of that is that we will have only a few spots to fill and I would feel uncomfortable now, although there is going to be some urgency that we get some of the reports going, of making a commitment for one topic when we have not heard about the others.

On the other hand, it seems to me that we may hear some reports of topics which on balance the

commission thinks it is very unlikely we are going to pursue and we do not really think the staff should be spending more time on it.

I would put forward as a response to what we have heard today -- because I do not think we should spend too much time on this today -- that the reproductive technology, particularly the issues of the regulation of research or the absence of a lot of the regulations of research and the practice that uses research techniques is a topic which deserves to be in our -- on our final list and that -- in other words, it does not fall off the table now.

I think on the other hand -- and I am not prepared to go further today and so I would suggest if that were the consensus of people that we ask staff to continue to work with Andrea's outline. Page five of which was missing, as you may have noticed, which is why I asked if it got distributed this morning in its full. We ended up getting the whole package all over again but this time it did not have page five of Andrea's report. And, you know, and have this topic

a little further ready based upon today's discussion without having to spend more -- a lot more time today talking about it.

DR. SHAPIRO: Let me ask a -- we will come back to this issue of just how we organize ourselves and make these priority decisions. I agree with your notion that now is not the time to drop this and I had not anticipated making that decision today.

Let me just ask a question. You mentioned that -- unlike in this country and other countries that have licensing authorities or other ways of regulating or watching -- monitoring what goes on in this area, could you say anything about what they are learning? Is there something that they are learning that has been important in this field?

DR. ANDREWS: Well, I mean they have -- you know, I mean, in a country like Great Britain where they have a limit of three to four embryos that can be reimplanted, I mean they are not having the same problem with multiple births that we are having, you know, here and also, you know -- I do not know. I

mean, since it has been so-ill studied I do not know the quality of care comparison. If you go in and you make sure people have -- are meeting certain lab standards.

I mean, certainly we seem to have had a number of issues in the United States with mix-ups where couples got, you know, somebody else's embryo implanted and so forth, you know, but it is hard to say how much -- having audits of your records or having to meet a certain standard in advance contributed to that.

So those comparisons are not available.

DR. SHAPIRO: As far as you know, therefore, in these other countries people are not following, for example, the children?

DR. ANDREWS: Well, in Australia and Belgium -- I mean, there are registries, apart from -- which you could have even if you did not have a licensing authority. You could collect follow-up data and that has not been done to a great extent here. There are only one or two NIH grants that I have been aware of

that, you know, followed up the children in any way.

DR. SHAPIRO: You had an interesting statistic -- at least I found it interesting -- noticing -- which suggested that maybe the class of people, infertile couples, is a vulnerable population because using the rate of depression as one possible measure equals those who have cancer, which might be another vulnerable population. Have people who have been focusing on that followed through in the sense -- in the following sense: Some part of those -- some number of those couples actually go ahead and try IVF or some other kind of assisted reproductive technologies? Others do not. They abandon the project or they go to adoption of one kind or another. Has anyone followed these two separate rivers of people who have made those kinds of different decisions as to how that impacted them at all as far as you know?

DR. ANDREWS: Not that I am aware of but there are a tremendous amount of psychological studies following up couples going through the infertility

process so I would be surprised.

DR. SHAPIRO: Right.

DR. ANDREWS: I mean, I -- I know of ones that, you know, compare people who adopt to people who then despite their diagnosis give birth to children in the normal way but I do not specifically know of any off the top of my head and I will be glad to look and send things on if I find them of the IVF, the high tech versus low-tech.

I think one of the issues is -- when I first came to this area I thought that many, many people were interested in this approach, even things like surrogate motherhood, to be able to have a genetic or other biological bond, the tie. And when I interviewed 80 couples who were going through surrogate motherhood, surprisingly most of them said, "You know, we would have adopted but we were told we were too old or there is a seven-year wait in our state and this way we can get a baby in a year."

And so genetics was actually less important, adoption was more difficult at least of an infant and

so that may be why there are not those comparisons. I mean, it gets muddy if the same people who would have adopted end up in one of the other categories.

DR. SHAPIRO: Let me ask one final question in this regard and that is a question of access to ART or any of these assisted reproductive technologies. There is the issue that you mentioned with respect to whether insurance companies cover it at all and, if so, for how many cycles and so on and so forth.

But are there other issues that you have found over time such as perhaps clinics who did not want to provide service, for example, to gay or lesbian couples or other couples they considered somehow less worthy than --

DR. ANDREWS: Well, certainly with artificial insemination clinics there have been many who have turned away lesbian women. There was a lawsuit against Wayne State University on the grounds of right to privacy and equal protection where they did change their rules to allow unmarried women to have access but they were a state facility. That would not apply

to private facilities.

I mean -- so there are -- there are differences and, you know, access issues are very clear if you walk into any of these in vitro clinics where they have pictures of the babies up there. All -- you know, they are far and away, you know, white babies. So the financial costs are prohibited for a large segment of the population.

DR. SHAPIRO: Thank you.

Two more questions and then we are going to have to move on.

Alta, and then Bernie.

PROF. CHARO: This is an area where even more than in most the task of separating debates about views on morality and debates about appropriate policy responses is difficult because it is easier to slide from one thing to another in one's discussion.

Indeed, I am not sure but I think I felt this happening already here in the exchanges about what could be done by virtue of a federal report and the kind of consensus building or guidance it could offer.

At times it seemed like the discussion was about guidance for regulatory interventions and at times it seemed like the guidance had to do with things that come closer to notions of morality, although I might be reading too much into what I am hearing.

If this commission were to, in fact, take on the task of looking at the adequacy of protections for research subjects as a general matter, which would include protection for research subjects in the purely private context and, therefore, would encompass those situations where infertile people are being used in research.

And if the commission were to consider the issue of regulation of medical services, what is left that is unique to ART that is not just a -- not just an artifact of those more, I would call it, general as opposed to fundamental so we do not have to disagree about language here, more general dilemmas about the way in which we regulate health care in the United States?

What is left with ART that you think would be

useful for a federal body to do and specifically what is left that you think of in terms of a federal body that is going to now try and forge consensus on specifically moral -- kind of moral debates about appropriate roles within families and family formation versus consensus over specifically regulatory issues that might deal with things that have more of a kind of physical safety aspect to them?

DR. ANDREWS: I mean, I think, I can understand trepidation about something that gets into the who should have access issue and, you know, are we going to start licensing parents in some sense as one philosopher has proposed. But, I mean, I think there are just really basic issues about no matter who comes through the door of that infertility clinic, you know, are there basic, you know, human rights being violated? Are there unsafe practices that would echo what you had before?

But I think this dimension that Tom Murray talked about, you got, you know, a third-party and interest there, you know, we have got the potential

child and you have got, you know, embryos where there is social divisiveness about how you treat them, you know, are use for at least, you know, some footnotes or some, you know, telegraphic material within a larger context that that says, you know, here are some things that really multiply the issues in a way.

DR. SHAPIRO: Bernie?

DR. LO: I wanted to follow-up on Alex's metaphor about auditioning and I guess I wanted to ask your opinion on what do you think our likely audience was going to be and how -- what the ticket sales were going to be in the sense that --

DR. ANDREWS: I think the movie rights are high but --

(Laughter.)

DR. LO: Yes, we are going to be looking at a lot of different topics competing for a relatively limited amount of time and attention. And I wanted to ask your thoughts on how ripe is this topic for an NBAC report and what is the likely sort of impact of a report we could do? I have no doubt that it is an

interesting topic. It could use some good thought. We could probably produce a really nice report but what is the likelihood that either the public is going to say, "Wow, this is really going to help us think through these tough issues that we have been really muddled on up to now." Or that state or federal legislators or regulatory agencies are going to say, "Terrific, we have just been waiting for, you know, recommendations one through seventeen."

Can you give us any sense of how likely you think it is going to make a difference that we do a report on this?

DR. ANDREWS: Well, I did not actually realize I would be here today defending this client of mine called assisted reproductive technologies in this beauty contest. You know, I would start with it from a different perspective.

I would say, you know, there are 70,000 children in the United States, at least, being born each year through these techniques. There are only about half that amount available for traditional

adoption. We have lots of principles, lots of policies, lots of legislation on what you do in adoption and what is fair and appropriate and so forth.

You know, we only have three states that have comprehensively tried to address reproductive technologies. I do think you have at least some audience in the state legislatures. I think there is a gap. There is a vacuum. Someone should do it.

But I cannot analyze for you how it stacks up against other really important things like gene patenting, like, you know, looking up to see what the impact on -- and university researchers is of, you know, commercialization in the genetics field. I mean that -- that you will have to do.

I am just, you know, pointing out a large number of adults are affected, a large number of children are affected, and there is a gap. There are abuses, you know. So perhaps addressing this as part of a larger -- a small part of -- as part of a larger project might be appropriate, you know, to fill that.

You are going to run into problems with getting policy implemented in this area just because everybody has a notion about how children should come into the world so it is not easy.

DR. SHAPIRO: Thank you.

Andrea, the last word before we move on. Thank you very much for your memo.

DR. KALFOGLOU: I just wanted to address both Alta and Bernard's comments.

The first one -- I will start with, with Dr. Lo's comments, one of the reasons that this topic is particularly ripe right now is that the ASRM, the Professional Association for Reproductive Technology, has been trying to deal with this issue of giving themselves legitimacy for the last ten years or so. They tried to do it independently and it did not work. And they are actually -- I have heard from inside the Ethics Committee there that they are hoping that NBAC is going to fill the void that exists because the SRM cannot -- does not have the mechanism to fund a licensing board or a private IRB that would deal with

the research related to ART.

And for Dr. Charo, your question was about what makes ART unique. The page that was missing, page five, discusses the issue of comodification and I think that is one of the areas that makes ART unique. This is -- we have decided in this country that we will not traffic in organs. Yet we see this huge commercialization of human gametes and embryos that is unlike any other transactions taking place for human tissues and that is completely outside any type of regulatory environment so that is another thing that makes ART unique.

DR. SHAPIRO: Okay. Thank you very much.

We will be returning to -- Lori, thank you very much for coming today. We really appreciate it very much.

Trish?

PROF. BACKLAR: Did I understand from what you just said about ASRM that that would be similar, Lori -- Lori? What was just said about ARSM would be similar to what happened in Britain with the

physicians wanting to license themselves and I think that is really important to know if this group of people would like --

DR. KALFOGLOU: A segment of that group.

PROF. BACKLAR: Okay.

(Laughter.)

PROF. CAPRON: The other question is if we are going to study ART should we hear from Dr. Kaplan, I suppose.

DR. SHAPIRO: We can take that issue up also at another time.

Let's now return to part of the subject -- is Alice here? Okay.

Then maybe I will turn to Eric then to get us started here.

I thought it would be helpful if we went to the informed consent proposed findings and recommendations document, which is provided in tab 2 something. There is 2A, B, C, D. I have forgotten which --

PROF. CAPRON: D.

DR. SHAPIRO: 2D. Thank you very much. Which contains both findings, recommendations and so on. I think it would be helpful if we worked our way through those just to see what the reaction of commissioners are, which ones seem -- we are not voting on this in any substantive sense right now but just to see what your actions are because that may help us just as we try to plan as we move ahead.

So does everyone got a copy of that -- those documents? They begin with informed consent, proposed findings and recommendations, finding one, et cetera, et cetera.

Okay. Eric, let me turn to you to get our discussion started.

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

DISCUSSION OF PROPOSED DRAFT FINDINGS AND RECOMMENDATIONS INFORMED CONSENT

DR. MESLIN: Alice has joined us so I will just indicate that the proposal that you have before you is principally for your consideration and there is really two tabs, both the findings and recommendations

in 2D and a short background paper that Ruth and Alice prepared that provide at least an initial justification for what those findings and recommendations would be.

It goes without saying but I will say it anyway that commissioners had requested this as a useful mechanism for getting started on this topic. Staff is fully aware that you may accept some of these, reject some of these, and change your mind a number of times over the next few months. We are well prepared for that. At least those of us who have been here a while are well prepared for that. The new people will have to get used to that. But I think it would be just easiest to go through it from top to bottom.

Alice is here.

Do you want to add anything else to the background?

MS. PAGE: Well, I just wanted to mention a word about finding and recommendation number eight. It is drawn from subpart B of 45 CFR 46, which

requires that the father of a fetus give informed consent for research involving a pregnant woman, and there are certain exceptions to that as well.

But I recently had a discussion with someone in OPRR that told me that there is currently pending a proposed revision that was published initially in May of 1998 to change that consent requirement when the fetus is in utero and I was unable to get a copy of the final revision because it is considered confidential but apparently it is working its way through clearance in HHS and they are expecting Dr. Varmus to sign the revision this week.

It will then go to the Secretary for signature and then to OMB for review.

The individual that I spoke with thinks that the revision will be adopted and that -- but that it will take a number of months for that to happen so we will just sort of continue to keep you apprized of that -- the status of that proposal as we find out more about it ourselves.

There just were a couple of other things that

I wanted to bring to your attention. Obviously what we are looking for is what you think may be missing from this list in addition to discussion of what is there.

Second of all, there is a need to think about linkages between this information and future chapters particularly relative to matters that may be -- that may need to be disclosed to subjects.

A couple of things that we had thought about -- for example, is there an obligation to disclose to subjects that there are subjects in a same or similar trial in another country who may be treated differently? In other words, they may be given a different intervention or more follow-up care. Is that something that may need to be disclosed.

Another disclosure question that pertains to chapter three has to do with the stopping rules and that is whether if in a trial in one particular country stops, is there an obligation to disclose to subjects in another country in a same or similar trial that the trial in the other country has stopped?

So those are just a couple of things that we need you to think about as well as looking at these particular findings.

DR. SHAPIRO: Okay. Thank you very much. Let's just begin by working our way through this topic and see which findings and/or recommendations are of particular interest to which the commissioners may have some response. Let's just begin by going to finding one and, of course, there is a series of findings here. I do not want to restrict us to go to line by line through this but under -- let's just deal with the issues under -- the findings under item one.

Larry?

DR. MIIKE: Just a background comment. I know we are going to go through these very specific things but the end result is and what I am more interested in is how are we going to implement this in a different country? Are we going -- and I think that is listed about -- we have about three or four choices in the summation of the actual report itself.

So I guess this is not the appropriate time

to say it but I just -- I think that I can contemplate going through each of these one by one but I want to know how we are going to implement them in the different countries. Are we going to go have standards and assume that they are followed? Are we going to follow each one of these in another country to make sure that each one of these -- in every clinical trial or otherwise that each one of these activities are followed?

PROF. CAPRON: Since IRB's do not monitor research at domestic institutions --

DR. MIIKE: Yes.

PROF. CAPRON: -- according to the Office of the Inspector General, it would be extraordinary to expect that.

I wonder if we are not -- we have all of these going back to that initial dilemma as posed to us when we had the FDA people here about a year-and-a-half ago, two years ago, I do not know, two years ago -- and when I say here, I mean generically whatever hotel we were in that day. And that was that there

are at substantive and procedural levels certain things stated by the federal regulations which are difficult for foreign researchers to comply with according to the researchers or American researchers when they are doing research abroad.

There are also certain points where there seems to be attention to ethical issues which are not addressed but perhaps should be addressed and so I thought we were not going to be getting into the question of the -- particularly the monitoring or whatever but we were going to always be asking as recommendation number one does, although maybe it is not phrased in a way that brings that out where it says, "Researchers may not deviate." It would be a way of saying the FDA and the Common Rule ought not to allow deviation from a substantive ethical standard of informed consent.

DR. MIIKE: But, Alex, I only raise the issue because in the very end of the brief description of the whole report itself --

PROF. CAPRON: Yes.

DR. MIIKE: -- those issues are raised specifically.

DR. SHAPIRO: Okay. Those are issues we do have to confront but I would still like to suggest that we consider these section by section and see if there is some reaction to their findings that you find do not make sense to you or do not add up or are not to the point and then, of course, in each case the particular recommendations that follow from that, how you feel about that. So let's address those under item one.

Alta?

PROF. CHARO: Focusing on 1A. I guess I am going to begin with a question if I may, Alice. Finding 1A lists the basic elements of informed consent pretty much --

DR. MESLIN: Excuse me, Alta, can you go closer to your microphone?

PROF. CHARO: Sure.

DR. MESLIN: Thanks.

PROF. CHARO: Finding 1A lists the basic

elements of informed consent pretty much as one finds them in the federal regulations. I was not sure if this finding was supposed to basically recite what currently is the understanding or if it is reciting what the understanding ought to be.

DR. PAGE: All of these are reciting what Ruth and I felt should -- what ought to be. Not --

PROF. CHARO: Okay.

DR. PAGE: -- and we just have drawn from certain things that are already in existence.

PROF. CHARO: Great. Then in that case what I would want to put on the table for discussion among us would be the possibility that in these particular situations of transnational collaboration with countries of differing resource basis that we consider whether informed consent requires telling people something about the likely uses of the research and whether or not it could ever inure to the benefit of themselves, their children and people in their own country, and discuss later whether or not we think that is a new kind of thing that people routinely need

to know before they can give consent.

DR. SHAPIRO: That is an interesting proposition. Before -- Bernie is also on the list but does anyone want to respond to this? I do not mean against it or for it but just respond to your own feelings about it because I think that is a very important issue.

PROF. CAPRON: I would second it.

PROF. BACKLAR: I would, too.

DR. SHAPIRO: Larry?

DR. MIIKE: It depends on how one implements that because she had some fairly absolute statements in there.

DR. CASSELL: Yes.

PROF. CAPRON: But it depends on the difference between clinical trials where a drug or device is being tested versus somebody doing something which is not connected to that where how will basic knowledge about an infection be used. Probably the researcher could only give a sketchy answer about that and is likely to be wrong about a lot of things which

eventuate but certainly where a drug is going to be developed and would be potentially subject to approval based upon data gathered here the question is a very immediate one and you had talked about that earlier this morning.

DR. MIIKE: But the way I read that is it may be approved but whether that actual patient ever has a reasonable chance of getting it is a totally separate question. And then, of course, I am still keeping in mind what we require telling our domestic research subjects.

PROF. CHARO: If I can clarify, let me just -- it really does echo, doesn't it? Let me just give a couple of examples of the kinds of things I have in mind. I do not expect this can be resolved nor do I think the details could ever be worked out in these ten minutes.

Example: It is extremely difficult to test an AIDS vaccine in the United States. We do not have a high enough prevalence rate in any particular population that does not have alternative means of

protection that would reduce the rate of transmission within that population, right, to the point where the statistical demands of the study would require vastly too many people or vastly too many years.

So to do AIDS vaccine trials one might want to go to a country where there are very few opportunities for prevention where there is a fairly high prevalence rate where transmission seems to be still very high and yet no to a near certainty that if the vaccine does develop out of that research it will be financially outside the reach of that country and its primary market will be in Europe, North America and Australia.

Example number two: There is research -- for example, the research that was done in Vietnam that was discussed in that paper that is included -- and by the way just by way of open -- it seems like Wisconsin keeps coming up, that paper discusses a very controversial protocol. I was not on the IRB at the time it was approved but I did have some peripheral involvement and there was a lot of debate.

That protocol involved testing a procedure that could not have been done in the United States because it would have been considered malpractice. That is to do breast cancer surgeries, lumpectomies, mastectomies, followed either by no adjuvant therapy or by an oophorectomy, the removal of the ovaries as opposed to the other kinds of secondary therapies you can use. You could not do it in the U.S. It would have been malpractice because it fell below the best standard of care that we know of as of now or as of now at the time that this was being debated and so the only way to find out about this was to go to another country where the standard of care was different and "lower."

All right. Now that is a particularly interesting study because if, in fact, it turned out that oophorectomy was a great thing to do it was something that would be used probably by Vietnamese women but also it would be used by women around the rest of the world.

If you were to look at the numbers of women

who would benefit from this finding the majority would not be in Vietnam because in Vietnam most people with breast cancer were not getting any kind of surgery, period, let alone this particular form of surgery.

So you have got examples of research where there is no likelihood of any benefit flowing back to the people in that country. You have got others where the benefit may flow back to some people but it is primarily being done there because it has got a beneficial possibility in another set of countries where you could not do it because it is considered inadequate medicine for the moment and one could continue going through different iterations of these kinds of examples.

It is that where I thought it might make sense to begin to look more closely at these variations in who is bearing the risks, who is getting the benefits, and also why some people are unable to get the benefits and the extent to which it is an artifact of pricing systems that are protected by international trade rules governing intellectual

property versus things that have to do with the logistics of the country, roads, numbers of doctors, et cetera, that are really beyond immediate change by virtue of a policy statement from a government or a multilateral arrangement.

DR. SHAPIRO: Steve, did you want to address this particular issue?

MR. HOLTZMAN: I just had some of the same questions that Larry had about people in glass houses and do we include disclosures that if you are among the 40 million Americans who do not have health care coverage you are not likely to benefit and also thinking about questions about in typical FDA trials Phase I's are in normal healthy volunteers to test the safety.

So there is no concept there in general that you are likely to ever have any need for the drug. And so then also then lastly tying in the disclosure you are talking to -- there to how does that work against or for the therapeutic misconception.

DR. SHAPIRO: Eric?

DR. MESLIN: I want to know what we are talking about. I mean, I have lost it somehow. I cannot find out what the issue is. I am looking at this set of documents that is so at odds with the testimony we just heard in the earlier part of the day about trials in countries like Uganda that now I am really intrigued to find out what is the issue that brings this Homeric statute right in front of us with no relationship to reality.

DR. SHAPIRO: Well, I can try -- I hope I can try to help out in this respect although I do not aspire to Homer's capacity here.

This -- finding 1A, which I think is what Alta was addressing if I am correct, are trying to lay out what we feel ought to be the basic elements of informed consent, whether they are practice or not. It is an "ought" not a description of what goes on.

As I understand items one through eight that is what you -- Ruth and Alice have attempted to put down and Alta has suggested that in dealing with these "oughts" there is yet another "ought" that ought to --

that should go in here. I do not want to use "ought" twice here. Namely it has to do with whether it is appropriate to inform -- as part of the informed consent process -- to inform potential research subjects regarding the likelihood that they --

DR. CASSELL: Will benefit.

DR. SHAPIRO: -- might benefit as opposed to benefits flowing elsewhere. Now it is not a description of what goes on so it is not dealing with the issue that you are but that is how I understood Alta's question and I think this is an interesting issue and we ought to -- we will take some other comments but we ought to pass this on to Ruth and Alice and see how they want to deal with it. We do not have to decide fundamentally whether it ought to be now -- right now.

Bernie has had his hand up.

Is this the same issue, Bernie, or something different?

DR. LO: It is different so if you want just to Alta's --

DR. SHAPIRO: Okay. If anyone wants -- let's have the last -- excuse me, Eric. I have not answered you.

DR. CASSELL: Well, just one step further. Would you think, Alta, that this is an "ought" that applied in the United States?

PROF. CHARO: Yes.

DR. CASSELL: The people who are -- that people know that this is something from which they might benefit?

PROF. CHARO: I was not saying their personal benefit. I was saying benefit to themselves or people in their own countries so it was much broader than that but regardless in answer to your question, well, yes, we did the same thing in the HBM report. In the HBM report we said there were certain things in informed consent that are not present in this list that is reflective of current regs and it included things like the effect on people in my perceived community, whether it is ethnic or racial or geographic or religious, whatever, and that is very

much of a piece with what I am suggesting here, which is that we have had a fairly physical risk focused notion of informed consent and that why people enter trials or refuse to enter trials may transcend questions of self-protection against physical risk and may have to do with their evaluation of whether they want to make a sacrifice or not in the name of science under these circumstances.

DR. MIIKE: Alta, doesn't three really -- is stated broadly enough that it will address your concern?

PROF. CAPRON: No.

PROF. CHARO: And I really did not mean to make this a moment at which everybody has to fight it out to a vote. I just wanted to put it on the table for discussion.

DR. SHAPIRO: We are not going to do that.

PROF. CAPRON: Right.

DR. SHAPIRO: We are not going to do that. This is mainly information to our colleagues who are working on this in some --

DR. CASSELL: I just want to go one more step with it.

DR. SHAPIRO: The last step, Eric, for this one.

DR. CASSELL: For this step. That is a shift in system level. The rest of this stuff is very much directed at the individual signing the consent and the individual participating, and I think that is fine. The minute you make the change in system level and say that that applies, I can sacrifice myself to the group, then you introduce a possibility that the group's decision, in part, has something to do with me because I have something to do with the group and the group has something to do with me. And that is a problem because later on we say that -- we bring up issues in which we will permit that.

So I want us to be very clear that when we meant this we have moved away from an individual unless the individual identifies so closely with the group that the sacrifice is really a personal sacrifice to themselves.

PROF. CHARO: I really think I am being unclear here, Eric, because I never wanted to suggest that people would be then drafted into research. I am saying only that if I am deciding whether to enter a research trial it would matter to me to find out that the results of that research was going to be used to benefit only the people who live some place that represents a culture that I despise. I might choose not to enter the research trial.

DR. CASSELL: That is nice.

PROF. CHARO: Right? It has nothing to do with forcing my decisions.

(Laughter.)

DR. SHAPIRO: No, I do not think you despise anyone, Alta, so you better --

(Laughter.)

PROF. CHARO: There is a short list.

DR. SHAPIRO: There is?

(Laughter.)

DR. SHAPIRO: You will come back to that later.

I think, Alex, you have one other comment? This is the last comment on this issue because I want to get on and get some initial responses to some of the other material and I want to turn to Bernie next.

PROF. CAPRON: Two comments. One is to respond to Larry's remark. The present requirements of the regulations, which are reflected here, include point number three, which says something which is quite germane but not the same.

PROF. CHARO: That is right.

PROF. CAPRON: The description of any benefits to the subject or Eric or to others which may reasonably be expected from the research. I think that is conventionally understood to mean from the research in the sense of participating in the research and I think what Alta has said is that we ought to be clear about the products of the research as well. Now if you read it more broadly then what she is saying is already encompassed.

The second point to respond, which I think is also that point of discussion she just had with Eric -

- do you have to leave, Eric?

DR. SHAPIRO: We will let you know what happens.

PROF. CAPRON: The -- when Alta was out of the room earlier having made her earlier intervention on this subject, I suggested that this topic would be one which would probably get examined for many of these kinds of studies at two points prior to the research subject. It is very likely that a Minister of Health or someone at that level in the country in negotiating an initial agreement that this would go on would have on the table this issue. Now he or she might be able or might not be able to extract something from the drug companies about making the products available at a reasonable price.

Then the IRB might looking at research saying given the amount of risk that is involved, we feel it is only acceptable if that research is carried on with some pay back to our population who are the potential subjects.

I think what -- and I do not think that any

of us would raise the questions that have been raised, well, what do we mean, how predictable does it have to be -- well, that would be subject to the circumstances of the particular research. In very basic research the answer would be no, this is just for science, highly applied clinical trials is something else.

And I -- the reason I seconded Alta's point is it seems to me I -- that we would individually, if we were in the circumstances that are described here, say that is something that we would like to know as a research participant as well.

We have also heard this morning, and this is why I do not think what we heard this morning is inconsistent -- I do not know if it was Eric who said that -- with everything we heard this morning that people have other reasons for participating in research even if they know that after the research is over the drug product is not going to get to their country for five years or ten years and then at a price that maybe only the elite can afford, which is in the immediate sense they are going to get much

better care of all the range of other medical problems they have by being a research participant and so someone might say, "I am glad to know that but it does not change my view that I want to be in research or I want my child to be in research," or whatever.

I would, therefore, hope that the staff in working this through tries to look for some language and that they explore whatever documentation is available about the history of the language in point number three. And if the history indicates that the benefit to be derived, particularly the benefit to others, from the research incorporates this then we are moving to the level of commentary that we believe that in implementing this that point should be explicitly part of the consent process.

DR. MIIKE: Excuse me, can I respond just briefly?

What you have just described tells me that even if I were to agree, placing it in this section is the wrong place because if you are saying that the IRB's or the Ministry of Health, et cetera, would most

likely be cognizant of these kinds of issues, that is the level at which such a review for those kinds of discussions with the clinical sponsors should take place. Not to the level of the informed consent of the individual.

PROF. CAPRON: Well, Larry, there are many things where an IRB or somebody higher up in an institution will say we cannot do this research at this institution. We are not willing to put people to a certain level of risk even if you might recruit some people who are willing to do it.

There are other times when they say there is a balance. The balance is favorable enough for the IRB to approve the project but we will recognize that individuals who would be "eligible" for the research are going to have very different opinions about whether or not they want to participate after they are told the relevant facts.

So you and I are only disagreeing or you and Alta are only disagreeing as to whether one of those relevant facts is whether the product of the research

if it is a clinical trial and a drug is coming out of it, whether that product of the research will become accessible. Am I doing by being in this research something on behalf of my group because if they find this out we will be able to get treatment which we all need, and we know that some people who are very sick think in those terms. They identify with a group. It might be a group of all other sufferers with their disease and they say --

DR. MIIKE: But I agree with you that we are in --

PROF. CAPRON: -- and --

DR. MIIKE: -- disagreement. I think it is an inappropriate place to put this.

PROF. CAPRON: Okay.

DR. SHAPIRO: I think --

PROF. CAPRON: I think we are not going to hammer --

DR. SHAPIRO: Right.

PROF. CAPRON: -- that out right now.

DR. SHAPIRO: Let me say I think we have

given you enough input on this issue and you and Ruth will think of this and I want to turn to some other aspects of this which I think Bernie has been waiting very patiently here.

DR. LO: In looking at Finding 1 and 1A and Recommendation 1 and 1A, I have been trying to think how that would actually apply in an actual scenario of a research project like the ones, say, we heard about this morning. I think the way they are stated -- I mean, I do not think we are going to disagree that -- with the way they are stated but I am not clear how we mean these actually to apply. And we make a distinction between substance and procedure which sounds very clean but on some of the tough issues we talked about this morning I am not sure what the implication is.

So just to really lay it out, one, do you have to tell the people in Vietnam they have breast cancer when you otherwise would not? Is that part of informed consent Finding 1A? Do you have to tell about equipoise in a culture where doctors are not

used to disclosing uncertainty and yet the whole ethical justification for a clinical trial is that it is a toss up between the two arms?

So under Recommendation 1A when we say researchers should develop culture appropriate ways, are we saying that you have to figure out some way to mention you have cancer, doctors really do not know what is best in a way that makes sense to them or are you allowing them to sort of duck it?

So I think -- and to have some examples of how that is done well, sort of best practices where it was alleged in the beginning that you never told people they had cancer but here is a way of disclosing it in a way that makes sense?

I want to raise the caveat that I do not think we should focus too much on -- so much on disclosure that we lose sight of what people understand. So if all we do is craft good ways to say it without having a sense that people really understand it and it makes a difference to their decision so I would like to see that addressed.

And finally the last point and sort of a recommendation sort of grouped on one is the notion of coercion that there are two different types of coercion that people were talking about this morning and I am not sure if the term is best applied to both but one is coercion in that someone other than yourself makes the decision. Your village chief or your husband or your father says, "You are going to be in the study."

There is another kind of coercion we talk about which is my life is so bad that signing up for this trial is a good thing for me no matter what the physical risk because of the attention, the medical care, the free lunch, whatever it is, is worth it.

And I guess the two issues are, one, for that second type of coercion from inadequate access to care, is that then part of the informed consent process and if it, in fact, is materially true that I will be better off in some limited way by being part of this study should that be part of the risks and benefits of being in the trial and if we say that is

that, in fact, an undue inducement?

So I think there is that tension that always needs to get worked out between being very explicit and sort of pretending an undue inducement and again how that gets worked out, I think, is going to be key and I think to make this really come alive it is going to be essential to get some examples of how these kinds of very specific dilemmas and others got worked out in ways that we think are appropriate, noteworthy, praiseworthy, as sort of an inspiration for others to try the same thing.

I think otherwise we just say you should do this, this and that. It is going to sound like, you know, there are these guys at the Holiday Inn again sort of going off, you know, pontificating.

DR. SHAPIRO: Alta, and then Eric?

PROF. CHARO: Speaking directly to your point, you know, I think that the attempt to separate coercion into these two forms, right, this kind of personal reduction of my voluntary range of choices versus the more impersonal background dilemma problem

is like your first point, one in which it seems like there are clear categories but they are not totally separable.

Example: What would you say -- Steve has left. He would be the one who knows. Which is the company that manufactures AZT? I forgot.

DR. SHAPIRO: Burroughs Wellcome.

PROF. CHARO: Burroughs Wellcome. Okay.

Imagine that they wanted to do a trial in South Africa on AZT protocols that do not take as much AZT as is now considered standard of care because it is so expensive in South Africa to use AZT so it would actually make sense to come up with a protocol that does not require such a long course. Does it make a difference that the reason why it is expensive in South Africa and, therefore, is a background condition that creates this kind of opportunity for undue inducement stems directly from their pricing practices and directly from the litigation which was only recently dropped in which they tried to fight efforts by the government to find a way around those high

prices?

I mean, the degree to which the background conditions that create these opportunities for inducement are very much the result of deliberate conscious policies by business and governmental entities, I think, cannot be left out of the equation. I think it is crucial to the evaluation of the degree to which we ignore that as a kind of ethically significant factor versus taking it into account, and that will vary from situation to situation, country to country, drug to drug.

DR. LO: So, I mean, I think this comes up both in the risk/benefits and justice issues but --

PROF. CHARO: Right.

DR. LO: -- here specifically what do you tell the subjects in helping to make this decision or her decision to be in the trial?

PROF. CHARO: I am not sure. I was only reacting to your -- when you tried to kind of separate out these two forms of coercion in order to help us clarify our thinking there, which I actually agree

with in general. I just wanted to point out that they are not as entirely separable as one might think. The same actors that create the background conditions are the ones who are offering the inducements.

DR. SHAPIRO: Eric?

DR. CASSELL: Well, I have the same problem with this step by step as I did before. This is a wonderful document to spell out in the United States what we mean by informed consent in educated populations for research sophisticated and it has -- from what I could hear this morning, it does not accomplish what we want to accomplish. It does not protect subjects because it does not apply to them. It cannot be applied in a meaningful way and consequently to spell this out this way is a much later step than how are subjects to be protected in the absence of the ability to, for example, do what Alta just talked about or in the absence of the ability to -- of the possibility of explaining what is the matter with them and what it means to them or in the absence of the -- any benefit to them, direct

benefit to them from the research aside from the free lunches, a coarse way to put it but that is what we meant.

So I think it is a later step and that what I heard this morning suggests to me that we are not hearing that. That this, in fact, is a way of saying, listen, there is no deviation from a good informed consent policy which this certainly is, what all this is about, and yet what we hear this morning says there better be or nobody is going to get protected in certain countries where research is being done, and I do not know what is the protection to be but I do know that if we have to rethink it, if this is where we -- if this is where we are now in the United States and in international research the standard of care and research does not make this possible and, therefore, it ends up a mockery. I mean, people can import it and go through it but it would not mean anything and then the net result is that human subjects are not protected.

DR. SHAPIRO: Alex?

DR. CASSELL: I have said it now, Harold, and I will not do it again.

DR. SHAPIRO: I understand what you said.

PROF. CAPRON: Again, Eric, I did not hear the same thing this morning that you did.

Point number eight under the list of basic elements of consent is the one that I believe addresses the issue that Bernie is raising and the core of that, I believe, as a principle is that it is wrong to coerce by threatening to withdraw or make unavailable something which a person would otherwise get, and the examples we hear about people getting health care in circumstances where there is very little care for the general members of the population are in compliance with the language here and out of compliance with the spirit.

The spirit is that the researcher should not be able to exploit a person's need to threaten them if they do not cooperate in becoming a research subject.

And the example that -- Alta sort of created an example, I think we have a real life example in the

reaction to the Willowbrook study. For those of you who remember that, you can correct me if I am wrong, but the way the Willowbrook institution was run, there were two entities. There was the general population and there was the research population.

In the research population it was possible by the expenditure of resources to keep the kids from getting hepatitis simply by their presence in the institution and the reason it was necessary to do that was that they were being given various treatments and vaccines were being tried out and so forth, and it was necessary that that be done -- that their exposure be a controlled exposure but for the general population hepatitis was rampant and, therefore, parents with mentally retarded children who would be eligible for Willowbrook wanted their children to be in the circumstance where they would not get the disease just because it was endemic and, of course, were disappointed by the institution's statement that there was nothing they could do and it was automatically endemic for such populations.

And so they would agree to enroll their child through the research wing of the institution and I think as Willowbrook -- as that experiment was stopped and changes were made at Willowbrook it was out of a sense that that was a wrongful exploitation of their necessitousness and I think that is what point eighth points to.

So the question then is a larger one. First, do we adhere to this generally in the United States now? Is that broader interpretation given it or is it the narrow interpretation which is, well, if you are entitled to a benefit, if you are now getting some treatment, we will not alter that simply because you refuse to be a research subject, which is just flat out blatant coercion. Or is it this -- is it a broader sense?

And then if we try to apply that or the bodies that would be applying it, not us, but if that were to be applied in that broader sense in countries in which ordinary care is unavailable and the only way to get ordinary care -- and this is not the free

lunch, this is basic medical care, is to get into this protocol because as long as you are in the protocol they want you to be at a healthy level and if you get some other infection or something that is unrelated to it you are going to get treated and, you know, you are going to get advice about your rickets and what you should be doing about this and that is all the things that would make up normal medical care.

The result of that would be that no one in that society could be at that point a participant in research and maybe that is a perfectly good conclusion to come to but we should be clear that it seems to me that that is what is at stake. So it is not -- here it is not a matter of drafting in some new regulation. It is understanding what the import of this is and, as I think we are going to find repeatedly, looking abroad is going to also hold up a mirror to what happens in this country and we will probably be looking for -- I mean, Willowbrook is now 30 years old.

PROF. CHARO: Alex, the interpretation has

been clear in the U.S. That phrase "entitled" is always interpreted as "legally entitled" and what the discussion has moved to is whether or not morally entitled should also be on the table. And it is exactly why it begins to open up debates about human rights and the nature of, you know, an argument for a human right to basic health care. So I think it is pretty clear how it has been used.

PROF. CAPRON: Fine. But --

PROF. CHARO: Not how it ought to be used but how it has been used.

PROF. CAPRON: What we are doing, as Harold found himself saying before, was ought, ought, ought, and I think we are going to need to address that and our addressing it we are going to have to ask do we mean this as a situation in which a researcher is coming into another country with all the additional burdens that go with that cross cultural or would we say, well, that actually is a standard on a moral level that applies in the United States.

PROF. CHARO: I agree.

DR. SHAPIRO: It is my own feeling, also, that it is the right time for us to be thinking about this and trying to think it through despite the difficulties you point to, Eric, which are very real and which we will have to deal with as we go along because if we do not have this straight in our minds it is hard to know how we are going to deal with it. At least for me it is hard to know how to deal with it so I think it is time to at least give some feedback to the staff and others who are working on this things that we are interested in and let's see if we can articulate these in ways that are helpful.

Trish?

PROF. BACKLAR: I am sorry. I just have been discussing this with Bernie because there is something here that I do not understand why we are arguing about this point and I just wanted to give a little --

DR. MESLIN: Trish, will you move the mike?

DR. SHAPIRO: This is a rock band here so you have to use the microphone.

(Laughter.)

PROF. BACKLAR: A what?

DR. SHAPIRO: A rock band.

PROF. BACKLAR: Oh, okay.

In this country if I recruit a mentally ill subject into a trial I say to them if you do not want to be in the trial do not worry, you will not lose your care from your community mental health center but if we are doing this in a country like as was described to us today, if we say this to people it is meaningless.

PROF. CHARO: That is right.

PROF. BACKLAR: So what is it that we are trying to ensure if we say this to them? I do not understand what you are trying to argue about. Maybe I have missed the point.

PROF. CAPRON: I think the point -- as I took it, the point is does the concept of being subjected to a penalty which, therefore, coerces you into doing something include the penalty of not getting something which you desperately need and which is available if you will just sign right here, ma'am, and that is

normal medical care, normal by our standards, a higher standard than is available to the person. You are not legally entitled to it and, as Alta says, it is a question are you morally entitled when it will be provided to everyone who signs but -- and to put it the other way, obviously if you drop out of the study you lose it and at that point it is very easy to imagine it being a penalty but, you know, there is all this economic literature about how people sometimes evaluate penalties and incentives differently but in theory at least we ought morally to look at them as being very similar. It really does not make a lot of difference if I say to you here is $10 you can have if you do it versus you have got $10 and you have got to give it to me. In these circumstances we are talking about people who do not have the $10 --

PROF. BACKLAR: Right.

PROF. CAPRON: -- to start off with but they can get it if they will just sign up for the research.

PROF. BACKLAR: But if you say to them, if you -- when you are in this research if you decide you

do not want to go on with it do not worry, you will not lose your benefits. There are no benefits out there. Are you, in effect, saying as a part of this trial even if you are not in the trial we will continue to care for you?

PROF. CAPRON: No. You would not continue to care for them except as is relevant to following up anything you have done on them. I mean, if you have given them a vaccine and you were worried and they, you know --

PROF. BACKLAR: I have got -- in other words, you are offering them nothing but the trial and you are not saying otherwise what you would be entitled here. They are not entitled to anything.

PROF. CAPRON: That is right. That is right. And the question is, is that a circumstance in which it is still all right or is it so inherently coercive? I mean, it is obviously all right for someone to set up a medical office there and offer whatever level -- low level of care he or she can offer given the circumstances but is it -- is it wrong for someone

else to offer a very high level of care but only to the people who join the study which they lose as soon as they --

PROF. BACKLAR: And then we get --

PROF. CAPRON: And it is over as soon as they withdraw.

PROF. BACKLAR: And then one more thing, though, then we get back to the same issue and that is if people are going into a trial that has something to do with their own disease it is vastly different than they are going into a trial that does not have something to do with their own disease.

In other words, they are more likely to come in. What happens to people that you are going to use in which they are not going to get any benefits at all? It is so -- this -- all this discussion is so context dependent, it is extremely difficult to discuss in the abstract.

DR. SHAPIRO: Well, I think it is difficult and is subject to all these difficulties people have pointed out. I guess we have different perspectives

on this. There are different contexts in every country in every trial and if we really get down at that level we are going to find ourselves in an impossible situation. We somehow have to create a framework that sort of makes sense to us understanding that its application is going to require lots of different challenges and issues that go along and at least they will have some guidelines if we can ever agree to anything to think about and to focus on whether -- and they will have to modify them on a case by case basis. That is what review can do.

We cannot resolve all these contextual issues because they are so different and there are so many of them but let me go on. There is a lot of others who want to speak and I want to give them a chance.

Arturo?

DR. BRITO: This issue -- Randy's recommendation, although it talks about being culturally appropriate in different places, I found them to be a little bit culturally insensitive. I want to go to recommendation two to come back to this

issue.

In recommendation two at the end of it is, however, no case may permission from the community leader or counselor replace requirement of individual informed consent.

Well, this may be -- this may be a situation, this abstract idea here may be a situation where it may be more prudent to have the community leader to determine the decision for his or her community because if you have a group of individuals in a certain community and you are going to offer them a research study and you are going to offer a transitory increased standard of care and then you put it -- make individuals make that decision then I think that is more coercive than you have got a community leader that is not coerced to do this.

I think the issue here is that what you are doing is having a transitory increase in the standard of care and I think here it is like a different level and we have to rely maybe more on the community leader which a lot of cultures already rely on anyhow for

their opinion about involvement so I am not sure the statement about no -- in no case may permission from a community leader or council replace the requirement of individual informed consent.

So I do not know. I am just hearing this as -- this is going to somehow come up with -- I do not think we have spoken enough about the community leader and the influence he or she has in each individual community and that is the first point.

The second point is I want to touch on something that Bernie mentioned and all the things he said that I have not hear reemphasized and I think it is real important. When we are talking about being culturally appropriate, okay, and we are going through different levels, no where do I see anywhere where we assure that there is an understanding, not just a disclosure by the investigator or the research party but there is also an understanding on the part of the participant, whether it is the individual or the community themselves. So somewhere in there because I think that makes it more culturally appropriate and

enters as a level where there will be more protection for that specific culture.

DR. SHAPIRO: Okay. Larry, do you have something further on this?

DR. MIIKE: Your statement just prior to Arturo was basically what I wanted to say.

DR. SHAPIRO: Thank you.

Rhetaugh?

DR. DUMAS: You mean me?

It seems to me that our discussion kind of goes in circles. Earlier today I mentioned that I thought we needed a set of principles, ethical principles that would apply no matter where or what group and I still believe that and I think as you mentioned a minute ago, Harold, that there would be differences in the application and then we may need to give some guidelines for applying them.

When we get to the issue of culturally appropriate and sensitive and what have you I think that applies no matter what and it bothers me that we have to make that statement. You see I believe that

appropriate guidelines or an appropriate way of informing -- of getting informed consent is an appropriate way and that includes being culturally sensitive no matter what -- you know, what the culture is. So I think we get into trouble when we try to be too specific. I think we need to get very clear about what we believe the minimal or the desirable or desired standards that we want to achieve, and then any deviation comes in how to achieve them, not what should be achieved.

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

DR. COX: Yes. I am going to give a logical argument about why I am going berserk here. And the argument --

DR. SHAPIRO: Calm down.

DR. COX: So, first of all, Harold, I completely agree with you and Rhetaugh and others that have said we need a general set of principles. That is great. Those are basically the ethical principles that we want to live by, you know, in any context. All right. Here is the disconnect because we heard

earlier this morning in our other situations that there may be situations where their ethical principles and those cultural contexts do not match the ones that we say have to be made everywhere so what the hell do you then because that somebody has got to win. Right? And so we will just take up our ball and go home because then those people are not playing by what -- the way we are doing it.

This is a no win situation because if you say that the people would be better off if we just sort of caved in on our principles and like -- you know, it would make their lives better but then we cannot do that because then we are caving in on our principles.

So this is a real logical conundrum. I agree we need general principles. They are going to come up against, okay, somebody else's general principles and it is going to happen all the time. All right. And then there is a simple choice that if those are our principles then we are going to say as NBAC that we should not have federal funds doing research in that situation because it does not meet our principles and

I have got to say I, for one, am going to have a really hard time when we come to vote on that.

DR. SHAPIRO: Alex, Trish and Eric?

PROF. CAPRON: I have not heard any dissent from the principles as stated here. Most of our discussion has been about two extensions of those principles or elaborations of them. The one that Alta raised and then the concern that Bernie raised. But if you look at -- I take Finding 1A to be a statement, Rhetaugh -- Rhetaugh, I take Finding 1A to be a statement of principle.

DR. DUMAS: Yes.

PROF. CAPRON: It is at the level of principles.

DR. DUMAS: Yes.

PROF. CAPRON: The later conclusion is you have got -- is you can achieve these principles, these goals, these objectives through different means.

DR. DUMAS: Yes.

PROF. CAPRON: It is exactly what you are in favor of.

If someone has a particular thing here and they say, well, we know culturally it is impossible to do point five here then we ought to talk about it.

DR. DUMAS: I would not believe them. I would not believe it. I think it is a matter of --

PROF. CAPRON: But David has sort of suggested -- and Eric has suggested that somehow what we heard this morning contradicts this --

(Simultaneous discussion.)

DR. COX: That is precisely what I am saying.

DR. CASSELL: These are not basic principles. These are derivative principles. These are not fundamental or a fundamental principle of which this is -- these are derivative is respect for persons and if I am a person who has no ownership of my body because I am an Orthodox Jew or I am a Mormon then giving me the right to exercise control over my body does not respect me. It disrespects me because it does not apply in my culture and yet there is such a thing as respect for persons in my culture or Uganda or something. The question is what is it? And what

these are is a wonderful statement of 20th -- late 20th Century United States autonomy and all that kind of stuff but that is not a basic principle.

It is the respect for persons which has moved along in this Century that counts. So it is the moving forward of that in the research context recognizing that we are here because the application of this kind of thing failed. That is why we are here. It did not work and started a dispute and we are trying to resolve the dispute and I do not believe we will resolve the dispute by spelling out even more tightly whether, you know, this benefit is really a benefit to me or others or whatever it is.

We are at the wrong level at this point, I believe, and I will try shutting up after this, Harold.

DR. SHAPIRO: Okay.

DR. CASSELL: We are at the wrong level of generalizability.

DR. SHAPIRO: Alta, Trish, Eric.

Well, Eric, you have already talked.

(Laughter.)

PROF. CHARO: As if I have not.

You know, Eric, actually for a second there I thought you really had it and then I found as I listened to you I still -- I still found myself fighting what you were saying and going back to what David said about whether this is -- there -- the way it has currently been constructed is a no-win situation and we may have to look for new alternatives.

I appreciate your point that the notion of respect for persons is more abstract and more amenable to variation than the specific notion of informed consent or even autonomy as a middle statement, right.

The problem with the phrase "respect for persons" when used in that malleable fashion is that it has come to be associated with regimes in which respects for persons includes looking out for their best interest which means having them all have their various functions in the world. You were born a serf, you were born a knight, you were born a woman and,

therefore, a wife and a mother, and you were born a man and, therefore, a hunter, gatherer -- you know, a hunter.

I mean, the notion of respect for persons is so malleable that it has come to be associated with things that I cannot bring myself to accept as being consistent with my notion of respect for persons. So we move the discussion up to a level of abstraction now that is so high that it is inevitable people will come to grossly different conclusions about what the words mean and find themselves back nonetheless in the debate that David had focused on.

So I agree with you. It is no win. If we are going -- researchers from the U.S. can only work if they follow U.S. rules versus researchers from the U.S. can work so long as they follow our rules or their rules, and either way there is going to be a problem. We may have to think outside the box. There may have to be like for where there is an actual conflict maybe you refer to WHO or to UNESCO or the CIOMS, or some other body and say, well, but if they

say it is okay then this is an exceptional case. We may have to look for solutions outside of the kind of binary options we have been exploring but I do not know if I can go as far as you, Eric.

DR. CASSELL: I am not allowed to comment.

DR. SHAPIRO: Correct.

(Laughter.)

DR. CASSELL: You are all wrong but I am not allowed to comment.

PROF. CAPRON: The principle of beneficence.

DR. SHAPIRO: The interesting aspect of this interchange is the kind of dueling principles. You are each accusing the other of going to too high a level.

(Laughter.)

DR. SHAPIRO: It is all together difficult for this ceiling here.

Trish?

(Laughter.)

DR. SHAPIRO: Calm down. Blood pressure is not worth it.

PROF. BACKLAR: One of the things -- maybe a way to do this is to try to get it to be context dependent and to develop series of scenarios. We certainly -- we have some ideas of what it is to do research in various different countries. Some of the articles that we have received give us some idea. Some of the discussion that we had today. And it really might be enormously helpful if we had a set of different scenarios. We will not have everything but it certainly would make a big difference as we go through these abstractions to make it more concrete.

DR. SHAPIRO: Well, I think that goes back to a recommendation or at least a -- that Bernie made before that really we ought to give -- as to some of these some examples which would give us a better grasp of just what it is and I think that is a good idea actually. I think that that may help us in some ways and we have to also remember here that we are trying -- struggling to get a set of parameters here that might apply to U.S. researchers working elsewhere.

We are not trying to get a set of parameters

that work for everybody, everybody else, everywhere, in every possible situation and we have to face the fact, I think, that there is some things because of our commitments that U.S. sponsored research simply will not do even though it helps somebody and it is a good thing to do in some other context. There is just some things we will not do and that gives us the possibility, I believe, not to satisfy everybody or to do all the good that is possible to do in this world.

It will not reach that level but it might very well reach a level where we can feel well about what it is that U.S. researchers are involving themselves with. I think that is at least as I see it the picture.

Tom, and then we are going to break.

DR. MURRAY: There may be a distinction lurking here that -- at least I am using it to try to think through some of the problems. On the one hand some of these issues on informed consent -- we have the sort of argument can you translate (a) are there universal principles; (b) can you translate them; (c)

how much do you sort of give in to local cultural understandings of human nature or religious understandings of do I own my body. Those sorts of things.

Those are knotty problems at times but they are one category of sort of problems. It is essentially kind of a translation of moral ideas that have governed the research with human subjects.

There is a second category of problems that I think is -- are even tougher and I think Alta alluded to them earlier when you said what you really thought was of interest. And that has to do with the fact that we, being a wealthy country who occasionally sponsors and/or conducts research in less wealthy countries where we have a very different medical system than they have, issues that are relatively straight forward within one nation, what is the -- what would be the alternative standard of care, you know. Granted there are differences in the U.S. but at least we sort of -- we sort of know what people ought to be able to get in terms of health care. Very

different in another country.

I have talked to researchers who went to Uganda and some of the -- what would be standard of care here would simply be undeliverable there. Not just because the money did not exist, the infrastructure to deliver the treatment just did not exist. And that is a -- to me that is a different order of difficulty and we are not going to solve that one even if we agree completely on everything that is currently on these pages. Now they intersect at some points.

Finding 1A8 about the -- sort of what other -- what sort of treatment to which subjects would otherwise be entitled, et cetera. They intersect at certain points but I just -- I just find it useful to keep the two sets of problems to recognize that they are both difficult but they are somewhat different in their nature.

DR. SHAPIRO: Thank you very much.

Let me suggest that we take a ten-minute break now since we have been here for a couple of

hours. When we come back what I would like to do is focus on the recommendations just to see what your initial response to them is and we will try to see how many of them we can actually focus on because what we are trying to do is give some feedback to people who are working on this to develop this material somewhat further.

So let's try to reassemble here at 20 after 4:00.

(Whereupon, a break was taken.)

OT DR. SHAPIRO: I think you have at your place a memo -- e-mail, I guess, some e-mail material. This particular one is from Jean Silveri to Steve regarding a particular item having to do with, I think, gene patenting.

Is that right, Steve?

MR. HOLTZMAN: Yes.

DR. SHAPIRO: And Steve has to -- has an early plane and so he has asked if we could give him two minutes by which presumably means five minutes.

(Laughter.)

DR. SHAPIRO: To just bring this to your attention and then we will return to our topic. It is this e-mail, which I think we have passed around a copy to everybody.

MR. HOLTZMAN: So one of the subjects we are considering as a future priority is gene patenting and in connection therewith tomorrow morning Mark Sagoff is giving a presentation and I believe today were handed out a couple of articles which people will presumably read tonight by Dr. Sagoff.

I asked Eric if he could send them to me in advance and I read these articles and the gist of the articles has to do with why products of nature ought not be patentable subject matter. Okay. And he particularly cited a case of a court decision in 1928, General Electric versus DeForest where the court ruled that tungsten is a product of nature and is, therefore, not patentable.

And then he went on to cite the fact -- and this is a quote from his material that "the practice of the patent office changed dramatically after a 1980

decision, Diamond versus Chakrabarty," which was the fundamental case in genetic engineering.

That struck me as odd and it spurred me to write an e-mail to two people. One, Becky Eisenberg of the University of Michigan law school -- many of you know Becky -- saying, you know, it is worth thinking about. What is the argument here and, in fact, Eric passed on that e-mail to all of you hopefully -- if you have not received it I hope Eric can pass it out -- in which I basically asked Becky, you know, why is an isolated protein different than tungsten in this regard and the gist of Becky's e-mail is, you know, this doctrine of products of nature not being patentable is not really spot on here and she was in a rush so she did not get into detail though she did cite the cases of adrenalin and vitamin B-12 as things which have been the subjects of patents.

The second person to whom I sent the question was Jean Silveri in Millenniums intellectual property department, a patent lawyer there, and what I am handing out is her response today. And I also gave to

Eric the specific cases. There are two cases involving Merck which, if you are interested, you can get from Eric or he can e-mail it to you. But the gist of it comes down to -- and you can see it in the e-mail -- the following quote in those cases that says, "The patent act of 1952, as its predecessors, authorizes a patent for any new and useful composition of matter provided only that the conditions for patentability are met. There is nothing in the language of the act which precludes the issuance of a patent upon a 'product of nature' when it is a new and useful composition of matter."

I would just let you read the e-mail. The point I wanted to make with this was that as you listen to Dr. Sagoff's testimony where he poses a huge contrast between a 1928 and a historical tradition versus Diamond Chakrabarty with respect to genetic engineering that, in fact, there is a very learned discourse and tradition of case law throughout this century which he does not cite, which suggests that the decision in Chakrabarty, in fact, was not a

radical departure.

So that is the background. Was that two minutes or five minutes?

DR. SHAPIRO: It was a lot closer probably to two than five. I did not actually time it. But, thank you, it was very concise and thank you for bringing our attention to it. This is an issue we will return to tomorrow. Since there seems to be some controversy here over the interpretation of a legal tradition and various kinds of precedent I will turn to our two legal scholars here on this commission to help us in that discussion tomorrow morning.

Thank you very much and thank you -- Tom, do you have some --

DR. MURRAY: We have three legal scholars now. Three.

DR. SHAPIRO: Three. Excuse me. That is right. I apologize.

PROF. CHARO: Four.

DR. SHAPIRO: Who is the fourth? Oh, right. Our new member. Exactly.

DR. MURRAY: He is the third.

DR. SHAPIRO: Who is the fourth?

DR. MURRAY: Who is the fourth?

PROF. CHARO: Larry.

PROF. CAPRON: Larry has got a law degree.

DR. SHAPIRO: Larry.

DR. MURRAY: Larry.

DR. MIIKE: I just went to law school. That does not make it a lawyer.

(Laughter.)

DR. SHAPIRO: Thank you for that clarification.

PROF. CHARO: It does --

(Simultaneous discussion.)

DR. MURRAY: We mean that as a compliment.

DR. SHAPIRO: That is right. It is not what we teach at law schools. It is what they learn there.

(Laughter.)

DR. SHAPIRO: Thank you very much.

Let's return -- oh, let me just say two

further things by way of announcement because it came with the same set of handouts. In that same handout that e-mail came in there are two other things. One is the -- our charter, which has been now kind of reissued and will be on our web shortly. That is here and you can just peruse it at your pleasure.

There is also a copy of a notice in the Federal Register regarding nominations for membership in NBAC. I think you might want to take a look at that also when you have a moment. Those were three things handed out together.

Now let's return. I -- we are not going to have a long time here this evening because I think we have -- I would like to adjourn at 5:15 or 5:20 so we will just have -- we cannot complete our discussions in any way but I am wondering if we could in the few moments that we have left focus on the recommendations in this document that we have been looking at and not trying to decide whether we should adopt or not adopt these recommendations but just what reaction -- initial reactions you had to them and see if that

would be helpful for people who are really working acidulously on this.

Remembering all along that what we are trying to adopt here are rules and regulations that will apply to U.S. researchers. So as I said just before our discussion -- U.S. researchers, U.S. IRB's and those involved in this process -- and as I said before, these are not recommendations designed nor is our report designed to write down a series of things so that U.S. researchers could do all the things in all the places because that is -- what they do not only impacts something abroad but impacts who we are and what we are willing -- and how we -- what we think appropriate behavior is.

So I think it is useful to keep that in mind as we go forward but let's try to look at recommendations two, three, four just to get started here, two and three let's say, and see what initial reactions you had to them. There will be other findings that come along as we go through this. I do not want to focus too much on the findings given the

time we have available today. We can return to that at another time.

So let's just see what your reactions are, for example, to recommendation two, which Arturo already made a useful comment on earlier this afternoon.

Any reactions at all to recommendation two?

Yes, Diane?

DR. SCOTT-JONES: My reaction to recommendation two is similar to my reaction to some of the later recommendations, recommendation -- I think it is seven -- because it seems that the recommendation is trying to take both sides of a difficult issue by saying that -- you know, that permission can be sought from the community leader but permission from that community leader should not replace individual informed consent. Later there is a recommendation that asserts that procedures for recruiting women and obtaining their consent should be done in the same way as recruiting men but if the woman wishes to involve the spouse then it is okay to

do that.

It just seems that we are taking what is a controversial issue and just saying that we can go along with it. It is not really a strong and forceful statement about one or the other side and it seems to me that we should probably try to think through and make a statement that is clearer and more definitive than one that just seems to acknowledge that there are both sides and that we will just do that, acknowledge both sides of a difficult issue.

DR. SHAPIRO: Tom?

DR. MURRAY: I commend the sentiment behind Finding two and Recommendation two that we be respectful of local customs. As I read it -- I do not know that there is a way around this but as I read it, it would, for example, require a researcher say who wished to do a study even in the -- say it was the U.S., of a group in the U.S. in which the local custom or a group of some other country appointed a male member of the community as the chief decider and the research was directed at a health problem particular

to women in the community and the male member just said, "I do not approve it," and perhaps his reason for doing that was to continue the control and possibly the oppression of the women in that particular community.

We create here two conditions, both of which you must satisfy. Namely the leader must approve and then you must get individual informed consent. No one can quarrel with the later. I just am pointing out a potential implication of the former.

DR. SHAPIRO: Thank you. That was very helpful.

Arturo?

DR. BRITO: One comment I have about two is there is a little bit of overlap between recommendation two and nine and nine talks about that there is no coercion from community leaders for the individual subjects but what I do not see here in two or anywhere else is that there is no coercion of the community leader by the U.S. researcher, and I do not know if that needs to be placed in here because I

think that what we heard from previous meetings is there can be -- community leaders could be unduly coerced to get their communities involved in some research program and that might help somewhat later on with the individual coercion.

DR. SHAPIRO: Okay. Other --

PROF. CAPRON: Are you thinking of the incentives that we heard about?

DR. BRITO: Right.

PROF. CAPRON: I do not recall hearing about coercion.

DR. BRITO: Not coercion. The undue incentives.

PROF. CAPRON: Well, no, I am not disagreeing to the validity of the comment.

I am not sure, Tom, if we looked at this as a standard about the United States and a researcher for Uganda coming here could not get individual subjects to sign up until the leaders under our local custom who are the members of the IRB have approved the research. So in talking to people who do research

abroad about this kind of a thing who have had exactly the same kind of concern I have been told, well, realistically we cannot do the research there. I mean, it -- if we go in and tried to do it and had not consulted the tribal elders or whatever in a situation in which nothing goes on there without their say so it is an oxymoron. We have to consult them otherwise they will stop the research and no one will be willing to be in it.

DR. MURRAY: So it is really an argument for prudence and not an argument for methods?

PROF. CAPRON: No. Respect but it is respect which -- as to which the alternative -- there is not an alternative.

DR. CASSELL: That is right.

PROF. CAPRON: So better to act as though you are being principled when you cannot act otherwise.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Having been part of an organization which has faced this issue, sure there is the pragmatics of it but it also comes back to respect

for persons, right, and the notion of where is that person's -- those individuals' sense of self-identity in a community which involves leaders who have certain kinds of positions of power. So it is not purely pragmatic.

So I actually think that recommendation two works. The real issue that you then face is then reflected in nine, having -- if you are working in such a community when you do then seek the individual's consent what is the standard of true consent you are looking for there because I can tell you that -- you know, we have been in those communities where after you have consulted with the leader, effectively they send out a word. You will show up at thus and such a time and you will donate your blood.

Now you can go through -- you do go through the proforma exercise of talking to the people but there is no question but that they are going to do it. And I think this comes back to some of the questions that Eric and Alta were talking about. Well, are you

disrespectful? Or is that, in fact, okay? The people trust their leader.

And I think you can make distinctions and you should look at it because when -- if you envisage the case where the persons really have no choice, they have no sense of identity, they are truly not treated as persons, they are just showing up because they have to versus where they are happy to show up. Okay.

And I think one has to look at the particulars.

PROF. CAPRON: The hard case, Steve, would be the situation in which you ask yourself, I think, some of the questions that Bernie has asked about the effect of "informed consent" on local practice. If this were the U.S. and we were dealing with people who were going to be familial organ donors I think it is very customary in that circumstance for the physician to say we -- if you do not want to be tissue typed we will not tissue type you. If you feel that you have to be tissue typed but you really have major concerns about being a donor we will report you as being

ineligible as a donor. That is what -- that is -- the understanding there is by raising it that way with a person you are not going to upset them. You are going to make them feel that they can avoid all the opprobrium.

If you were in the circumstance here, the hard case would be someone familiar with that culture saying if you say to them that we will give you an out, we will put a little bandaid with a little cotton thing on your arm as though you gave blood but you did not, if you do not want to do it, if you want to contradict the order from -- is even raising that possibility something which would be offensive to the community in your doing it. That seems to me to be the kind of case which -- I do not know that we can resolve that but I think the point you raise is a good one. How do you get out of it? It is not as obvious to me how you get out of it.

And we say in number nine they should specify the steps that will be taken to ensure that privacy is maintained in recruitment and by privacy, I guess,

they also mean voluntary choice and, you know, I do not know what you do with the example. Maybe we should ask some of the researchers who come here that kind of a question.

MR. HOLTZMAN: If I --

DR. SHAPIRO: Go ahead, Steve.

MR. HOLTZMAN: Just because I am going to have to leave and because it is also then tying into seven, you know, seven effectively is a statement that says we endorse gender parity or gender equality, which we do. But realistically since we are not -- if it is a culture where the woman has to get the husband's approval and, therefore, we are going to say only if -- we will only do that if we are going to seek the wife's approval for the husband and that is not going to happen. You have just said you are not going to do research in that case. And one cannot help but wonder if what we are trying to do is change a major social problem in a particular culture with this very, very small stick called research (and it is not going to happen) and what you are going to do is

throw the baby out with the bath water.

DR. SHAPIRO: Just a minute. Hang on.

MR. HOLTZMAN: What the recommendation says, seven, is effectively use the same procedures for both. If the same procedures -- so, therefore, you can say the woman may be involved if and only if the spouse, and the husband, agrees. But if and only if the husband can be involved if and only if the woman agrees.

PROF. CAPRON: Which was the old standard for doing vasectomies and tubal ligations. You were supposed to mutually -- because reproduction was a possession of the couple. And that is long gone in this country.

DR. SHAPIRO: Arturo?

DR. BRITO: The issue I have with what you just said is something that -- general theme that I have been hearing here seems to be, including what is written here and what people are saying, is: Who are we to say in another culture that -- and I do not believe this. I will say this because Alta is sitting

right next to me but --

(Laughter.)

DR. BRITO: -- but here we are saying that there are not cultures --

PROF. CHARO: I know where he is going.

DR. BRITO: -- or situations where it is okay for someone else to make the decision for the woman or the child or what have you. I think we are confusing -- we are being very ethnocentric here and if you read Robert Levin's paper here it talks -- it really talks about this. So I think we have to get away from -- I thought recommendation seven -- I do not think it should be in there because there may be situations where the man has to make the decision. Okay. And I do not want to sound like I am being sexist here but what I am saying is -- because I do not believe this but I am saying is -- but in certain cultures I think we need to hear from those cultures, including the women from those cultures, why this is in some situations. As long as we are not taking away basic human rights, not American rights but basic human

rights, I think we have to be real careful how we start defining --

DR. SHAPIRO: Well, I think we do --

DR. BRITO: -- what social problems are.

DR. SHAPIRO: I know there are other people who put their hands up but I think there is something here that we should discuss and clarify amongst ourselves at the very least.

It is quite true that there are some things acceptable in culture A that would be unacceptable here. We all understand that. There are differences. Not that we are better than them or worse than them. It is just that we are different.

The question that has come up in cases like this international research area is what happens if we, who feel one way, are operating in another country or wish to operate in another country, and they feel differently. It is my own feeling that there will be cases where we cannot operate there even though what we do might help them from their perspective because it impacts who we are and that is very important to us

because it is not just doing good for us where we have to live with ourselves and with a certain set of commitments so we do not have to solve all these issues.

What we have to solve is what are the minimum standards that we have to go abroad with for which we can live with ourselves, not only fail not to harm abroad, which is of course important, but also satisfies us. Now if, for example, we have just been talking about this informed consent issue, I ask myself am I willing or should I -- do I believe we should be willing to go abroad and do -- employ -- enroll someone as a human subject without their permission even though in that culture their permission is irrelevant. Right? Somebody else decides for them. Some -- I do not know any particular place but just imagining a place.

Now just speaking only for myself now, I find that a very hard thing to accept. Not that they would do it. They are entitled to do whatever they would like to do. That is not for me to evaluate or say or

anything. But if I ask myself, ?am I willing to go abroad and do an experiment with someone, on a human subject, and not have something equivalent to or around or substantively alike?, and I do not know what the right language is -- well, I personally have some difficulty with that.

It is no lack of respect for who they are and what they are doing. And it is not because it may not support their views of autonomy and so on and so forth, whatever they may be. It is because of who we are and the question is to find out just how far we can go here. Some compromises and some changes are acceptable, others are not.

But what I hear keep coming up is what do you do if someone else is different than you and I say, "Well, you know, sometimes that means we cannot work together."

DR. DUMAS: Right.

DR. CASSELL: That is right.

DR. SHAPIRO: That is the solution at least the way I see it but obviously there is going to be a

variety of views here on this issue.

Bernie?

DR. LO: Yes. Harold, I think that is a really useful and constructive formulation because I think all too often what happens in these kinds of debates is you get into name calling and, you know, one side gets accused of being cultural imperialists and the other side gets accused of being Nazi's or something, and I think --

PROF. CAPRON: Or something.

(Laughter.)

DR. SHAPIRO: Just one of those little things.

DR. LO: One of those bad words.

PROF. CAPRON: Not these art critics or something as opposed to others.

(Laughter.)

DR. SHAPIRO: That is even worse.

DR. LO: And I think, you know, some of the -- you know, some of the work that -- I am talking about universal human rights -- also makes it ?let's

go to the mat? sort of issue and I think it makes it a lot less contentious if we back away and say that, you know, the real question is whether we can work together as an American federally funded researcher and the other party. And if we can sort of get away from this, you know, you are really wrong and I am really right issue and just say, well, we may just have to disagree not because I think you are right but I -- my own integrity does not allow me to sort of not do what I would do in this country.

I think it de-escalates sort of the conflict and I think it is worth our considering as commission whether that should be the approach we are taking as opposed to the let's really prove that we are right and they are wrong, and we need to extend our values to them because they are really universal, timeless values.

DR. SHAPIRO: Eric? You see, I did call on you again.

DR. CASSELL: Yes. In a low voice.

(Laughter.)

DR. CASSELL: We come from a culture that says the principles that are behind us reach back roughly 5,000 and maybe 2,500 years but two sets and in the last forty years these principles that we are looking at right in here have come into being, and now we are acting as those are the principles that cannot be ever bent or -- but there is another thing, Harold. Let's take the example you gave.

I cannot get permission from each individual in the culture or in the community we want to go do our research. The disease is common. For the period that I am in there I am going to make a difference in a lot of lives and I am also going to make a difference in the community, but I will do that because you cannot give me permission according to this set of rules because after all I have my principles.

And I find that there are principles that override those and that we ought to figure out a way at least a route -- it does not have to be final yet for us. I mean, we are talking about a real problem

so we have got to start the route towards a solution to the problem. That is all.

Isn't that nice and low key?

(Simultaneous discussion.)

DR. SHAPIRO: Well, I think -- I do not want to -- just then speaking for myself -- think that we have to necessarily be rigid or find no processes which might be able to resolve conflicts that arise in this case but I do think at the end of the day my judgment or somebody else's judgment of what is good for somebody else cannot always induce me to put aside commitments but I agree that, you know, one has to be --

DR. MURRAY: There is a clear analogy here with American companies doing business abroad where the claim is made that you cannot do business if you are not willing to engage in bribery and a lot of American companies have just said we are not going to do that and that will, in fact -- that may close down certain lines of business but it is the price we will pay.

PROF. CAPRON: I would suggest it is a little different because what we are talking about here, as I understand it, is a researcher and a research sponsor who would be comfortable doing the research under the circumstances.

DR. SHAPIRO: Right.

PROF. CAPRON: And the question is, those who control their ability to do that, either the FDA in its willingness to accept data and says data that we accept has to comply; or you have someone from a U.S. institution who has to go through her own IRB to get permission to be one of the researchers and they say, according to our rules no -- I understood the chairman to say to us, let's ask about each of these, tribal elders, husbands for wives, parents for children, and so forth.

Is this something which if it is a cultural difference we want to say is one of those things where the U.S. at the level of government approval of or local IRB approval under government rules will say you cannot cross this line.

Our involvement is such that even though a U.S. researcher and a U.S. drug company are willing to put money into it and want to see the research done on those items, they should not be allowed to. And obviously the drug companies can say, well, we will never get U.S. approval for this drug, we will get Ugandan approval for it, but if realistically they say we do not develop drugs that cannot go through FDA because in the long run we need to be able to market them here. Then it is the same thing. And I think that is a very useful way of focusing us on each kind of controversial point here but it is -- so it is not exactly like the companies because the company might be willing.

DR. SHAPIRO: Diane, Rhetaugh and David?

DR. SCOTT-JONES: I think it is very important for us to consider the issue of whether we should, in fact, be doing research in all developing countries if the standards are such that we encounter all the problems that we have just been discussing and maybe in those instances the most that can be done is

to work with medical researchers in those countries in different ways because I think a missing element in this discussion is what are the standards of the medical researchers in that country with whom presumably one would be working? How do they see these issues?

But it just seems to me that we cannot take both sides of an issue in going into developing countries and I think that is what we are trying to do in some of these recommendations. We are trying to acknowledge sides -- both sides of an issue when you cannot legitimately do that. You need to have a stand one way or the other that you stick to and you cannot go into another country and tell them that our way of seeing a controversial issue is better than theirs.

I think that we might need to work in different ways with developing countries than to go and implement a research project there.

DR. SHAPIRO: Rhetaugh?

DR. DUMAS: See, I think we have -- we get bogged down in some fixed notions. I think we can --

in some cases we can have it both ways. In the case of where there is an elder that the community looks to, to make certain decisions, it is fine if they want to have the elder sanction this project and make the decision. For the researcher that is fine but that does not take care of the issue of informed consent of the subject and I think we make a lot over this whole issue of informed consent.

If we go abroad now and waffle on that then I would have some serious problems but I do think that there are times when there are just certain things that we cannot afford to compromise and I think I personally feel that informed consent is one of those.

That does not mean that we will not accept somebody else agreeing that this is okay but it does not substitute for us for the subject.

DR. SHAPIRO: David?

DR. COX: So as usual, Harold, you have helped me out of my misery.

DR. SHAPIRO: I sort of think of myself as a doctor --

(Simultaneous discussion.)

DR. SHAPIRO: -- high blood pressure, all kinds of symptoms that are arising here at the table.

DR. COX: And it is because of the context. Okay. So -- and the -- so -- but actually I added a little bit to this so I will not put it all on you. The -- I said to myself why is it, you know, what is it that I am actually worried about here in terms of this international stuff. Right?

And so I do worry about improving the quality of people's lives in general and that is what I have been focusing a bit but, in fact, that is not what this is about. What this is about, why we are starting this in the first place, and for me it is because what is really unethical is for people who live in one culture, that is the U.S., to bypass our ethical rules to get something done by going some place else where the goal posts are different.

So that is what I want to prevent from happening. All right. Now how do we prevent that from happening? Well, we do not prevent that from

happening by looking at the other people's point of view. Right? Because that is exactly how our ethical principles are being violated. So we look at it from our point of view and that is where you really helped me.

So if you look at it from our point of view then you are saying it has nothing to do with respecting other people's culture or not. If you go and live in that culture then, I mean, you may, you know, personally feel that that is okay but what is not okay is to go against the ethics and the rules that we have for doing research in this country.

So then we make up that list of rules and people cannot go and do it if they violate those. Now that is what you said before. What I did not understand before, though, was this -- the context of why you are doing it because it is looking at it from our perspective. It has nothing to do looking at it from the people that are suffering in other perspectives. And that does not mean you cannot do other things to go and try and help those people

but you cannot do it with U.S. federal research money.

So I can come to grips with that and I can understand it. I do not necessarily like it but I mean I -- but -- so --

DR. SHAPIRO: We have time to think about these things.

Alta?

PROF. CHARO: I would like to add one more factor to your context the way you set this up, Harold, because it is not just about what American researchers can do when they are abroad, it is specifically about what can be done when researchers are funded by the Federal Government or --

DR. SHAPIRO: Yes, that is absolutely right.

PROF. CHARO: But I think that actually is a distinction. There is a difference between --

DR. SHAPIRO: No, I agree.

PROF. CHARO: -- regulating what private American citizens can decide to collaborate on in another country when it is consistent with local law and what is appropriate for the Federal Government to

do.

I think it actually raises the stakes in terms of the -- I do not know, the ethics of international relations perhaps as opposed to the bioethics of the situation in terms of the degree in which one allows oneself -- one -- you know, one being the Federal Government -- allows oneself to take advantage of socioeconomic differences in order to accomplish things that could not be accomplished otherwise.

I also wanted to just add as a note of interest here that although we are talking almost -- in fact, exclusively in the context of developing countries, as I understand it, these regulations are written without regard to what kind of country is the collaborative country and, therefore, these debates about the language apply equally well to collaborations with our European counterparts, South American -- you name it, every level of development in terms of their scientific base. And it may be that we need to be thinking about how well these words work in

the context of collaborations with people who do not have such a power imbalance.

And then a final note for those who are still uncomfortable with the idea of what seems to be here kind of cultural absolutism on what we will permit ourselves, I would only say that when people from other countries come to the United States, regardless of what their legal rights are in those countries, they gain certain rights because they are present here as tourists, as business visitors, for whatever reason. Once they are here they gain certain kinds of rights.

And so, for example, if somebody is visiting from Vietnam and gets ill, her treatment in the United States is going to include a right to make decisions on her own and a right not to have decisions made for her by somebody else regardless of what would have happened if it were still back in Vietnam.

I think that that is done not as a statement of disrespect for other cultures but, as you were saying, for a notion of what is necessary in order to

maintain the fabric of this society. And I think that is -- I think because we live very comfortably with that phenomenon, I do not think we should have so much discomfort at the idea that we self regulate what we will do abroad.

In a sense what we are doing is saying that the subjects in those trials will be treated as if they were tourists at an American laboratory and that they were undergoing that research in an American facility.

DR. SHAPIRO: Bernie?

DR. LO: I know the hour is getting late and we talked about this a lot today. I wanted to throw out some ideas that I think are missing in our current formulation of the problem.

We focused, I think, rightly so, on protection of subjects in international research and we probably had in mind the sort of exploitation cases where for malicious motives as a researcher I am going to do things to people in a developing country that I cannot do here because it is easier, cheaper, fewer

restrictions and such.

I think what makes these -- and it seems to me we are all having trouble with the idea that the bottom line may be we just sort of walk away and say I am sorry, we cannot do the research there, not that I do not like you and respect you but I cannot do it.

I think that what is missing is there are other very important ethical values at stake. One is to try and help other people who are in dire need and I think there is a lot of research that is done that is done by people, I think, who are genuinely trying to address what they think are the big health problems in the world and they say if you look at the AIDS epidemic here we are looking at sort of a very narrow set of issues and if I really want to make a difference and really want to help mankind and be a good scientist I should really go to where the suffering is.

And so trying to relieve suffering when you have the expertise and the American Government has the money is a good thing or can potentially be a good

thing and I think we need to acknowledge more in our report that a lot of these dilemmas are tough because American investigators and funders are genuinely trying to help in ways that would be regarded as beneficial by the host countries.

And the issue is do you sort of let these disagreements over research ethics reach the point where you say I am sorry, we just cannot do business when you know the implication is that the questions that need to be addressed make the public health better will not get addressed.

So I think there is a sense of loss that goes along with not doing the research. I think we have to acknowledge what we are losing and giving up because that is what makes it hard for researchers.

DR. SHAPIRO: Larry, you have a question?

DR. MIIKE: Yes. Well, first, something specific. I think that recommendations two and seven do not get to the issue. They just talk around it and the basic issue is individual consent. The way it is phrased is sort of confusing.

I am still undecided about an absolutist position such as you take, Harold, or a default position where these are recommendations that should be done but if there is enough justification for an exception to be made and some process be found in that.

I worry similar along the lines of what I think Eric and Bernie are saying, which is if we are talking about government research monies, I expect that NIH does research -- would sponsor research in other countries where it may be for diseases that we are not particularly interested in but it is of great importance to the country that they are doing it.

If we stick absolutely to these recommendations we may be shut out of doing those kinds of research so those are the kinds of things I worry about and I -- my initial inclination was that we say strongly what these recommendations are but they really are a default position and we leave a little wiggle room around for some specific exceptions, and how we define that I do not know yet.

DR. SHAPIRO: I think that is quite reasonable.

Okay. Rachel, you have been trying to speak for a while.

DR. LEVINSON: I guess this is relevant as an example to the point that both of you have just brought up, and that is -- and I was concerned when David seemed to say that we are addressing situations only in which a country -- we would be using research in another country in order to avoid the regulatory system here which would otherwise not permit it.

In an address to the U.N. General Assembly the President announced that he would like to try and work with pharmaceutical companies around the world and in this country and use government funds in order to develop vaccines that would be of use in the developing countries so the market would be those countries, not ultimately here necessarily.

It may be, in fact, that there are vaccines that are perfectly suitable given the infrastructure that is available in this country but not in other

countries where they do not have refrigeration or health care personnel available so that the government now is looking for ways to fund or find incentives for pharmaceutical companies, including those here, to get them to develop vaccines for diseases that are endemic in other countries.

So we would not want to foreclose that possibility.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I am still thinking about this issue of whether we should be doing the research at all in a specific country and it seems that maybe the disease that is under study is an important consideration given what Rachel has just said and what Larry said.

DR. CASSELL: Malaria.

DR. SCOTT-JONES: If the disease -- malaria is an easy example. Then the justification for doing the research there is very different than the justification for doing research on an issue or a disease that is more relevant to people in developed

countries who will ultimately be the main beneficiaries on it and I think that is all part of contextualizing the problem rather than seeing it as an abstract problem.

But some of the desire to help people in other countries can be accomplished outside the research process so simply the desire to help other countries is not a sufficient justification for doing the research there because you could help them by providing medical supplies when those are lacking.

It seems to me that you have to think about this in a more contextualized way at the same time that you are adhering to principles that you do not want to violate.

DR. SHAPIRO: Alex?

PROF. CAPRON: I think we are coming together around some notion -- and I think it would be very helpful if Alice and Ruth, around the kinds of things which are dealt with in a number of these recommendations, and they do not seem to be grouped in any way, but where the issue is someone else's

permission and then the remaining issue of consent would be able to put them in a way that we would ask are there some of those sorts of criteria which we would not contextualize away.

And so the fact that AIDS is endemic in a particular country would not make me comfortable saying that soldiers could be used as experimental subjects without their consent or something.

I mean, in other words, even there -- even if the soldiers in that country are routinely shot by their generals or marched off to useless wars or whatever and we sort of -- I mean in the country being a soldier is like a death sentence or something. I mean, in other words, there would be limits that we would say even for the great good of having the vaccine for their country we would not feel comfortable saying that the U.S. Government or the CDC should be a cosponsor of that research.

And that there are others which are in this context specific category and we could begin to differentiate them. I am not sure whether we are all

saying, for example, yet that informed consent is always a requirement at the end of the day and the real question is are any of these prior screening methods acceptable?

Is it all right to have the husband's consenting for wives -- not consenting but giving permission for their wife to be involved if that is a local custom? Is it more all right when it is malaria than when it is something that is basically an experiment of convenience where you are really developing a drug for the U.S. market and so forth?

I think it would be helpful if you could try, Alice and Ruth, to tease out some of these recommendations so we can see some of those and decide whether our recommendation really would be that some of these are contextually adjustable the way it does say already, for example, that the requirement for written signed consent ought to be something which is contextually adjustable and could be waived. And then we see if other things are in a category, no, context is not going to ever be enough to waive that

one.

That is just my suggestion of how we might move in our next iteration of recommendations.

DR. SHAPIRO: That sounds like a useful idea.

Eric?

DR. CASSELL: I think we are beginning to come together and I also found your layout of the problem helpful, Harold, because we could -- just like you said, this is something as long as it is sponsored by the United States Government, no matter what good it does, that is just the way it is. There are some things with which it will not work and this is one of them.

On the other hand, if we just stop there then we would be the ugly American in reverse. When this happened the first time, which was after the first World War when Americans were going and giving cross-cultural medical care in other -- you know -- neglect of any cultural -- got into all kinds of trouble. Then there followed after that an understanding that you just could not do that.

In the 1950's Cornell did a project at the Navajo Reservation in the mini-farms aspect of -- part of the Navajo Reservation and in that thing there was no requirement for consent. That was in the 1950's. And that was done by bringing the whole community together and meeting with the whole community and presenting what they were going to do and the whole thing so that the informed in that instance was not just the community leaders but of the entire community at the same time and working around that.

I am not suggesting that is the only way to do it but I am pointing out that, in fact, there are models for this so if we stopped and said the Federal Government says we will not do that, I think we would stop short even though it might be true. That is the way it is. But if we were able to move on and point out that there are other principles that require implementation in international research then we would be doing a favor beyond just that blanket prohibition.

DR. SHAPIRO: No, I certainly understand that and I did not mean to say something as absolutist as

it sounded apparently but I was trying to get a focus on a subject, which I think is going -- we are going to have to make decisions on that boundary because, yes, we should not be absolutely rigid but, yes, we should not do everything. And so where to find that is -- and I think Alex is actually helpful in this regard to see if there are issues here which are, as he very helpfully put it, context dependent on which we could feel comfortable and other issues which are not.

I do not know -- I mean, I think that is a very useful idea. I do not know what will happen when we actually try to fill out these boxes, whether we find anything -- one box remains empty and one does not. I do not know what will happen but it is, I think, a very useful idea.

Well, let me suggest that we have taken this as far as we are going to take it this afternoon. We will have more time tomorrow when we perhaps get back to this but we may not because we only have tomorrow morning and we will begin with a presentation on gene

patenting, which starts, I think, about 8:15. Is that right?

DR. MESLIN: 8:10.

DR. SHAPIRO: 8:10. And then we will come back to what is general priority setting but key in that area is that we hope that the President's science advisor will be here to talk to us about his views about things that the NBAC might do and things that they are, indeed, anxious for us to do, and that will have, of course, a major impact on -- at least in my own mind will have a major impact on what it is that -- how it is we carry our priority process forward.

So before absolutely adjourning, Eric, were there any announcements of any kind?

DR. MESLIN: No, fortunately.

DR. SHAPIRO: No announcements. WE are adjourned for this afternoon. Thank you very much.

(Whereupon, at 5:20 p.m., the proceedings were adjourned.)

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