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DAY ONE: Tuesday, May 19, 1998

Welcome and Overview of Agenda: Eric Meslin, Ph.D. . . . . 1

UNAIDS Washington Meeting Update: Alex M. Capron, LL.B. . . . . 3

Ethical Issues in International Research, Review of UNAIDS Activities: Ruth Macklin, Ph.D. . . 7

Basic Protections for Human Subjects in International research, The FDA Perspective:  
Stuart L. Nightingale, M.D., Food and Drug Administration . . . . . 18

Basic Protections for Human Subjects in International Research: Marjorie A. Speers, Ph.D.,  
Centers for Disease Control and Prevention (CDC) . . . . . 28

Public Testimony . . . . . 40  
Ms. Casagrande . . . . . 40  
Dr. Bauknight . . . . . 43

Panel Report Update: David Shore, M.D., National Institute of Mental Health. . . . . 46

Psychiatric Symptom Provoking Studies: Donald L. Rosenstein, M.D., National Institute of  
Mental Health . . . . . 57

Discussion of Staff Draft Report on Research Involving Persons with Mental Disorders Affecting  
Decision Making Capacity: James Childress, Ph.D., Jonathan Moreno, Ph.D., and  
Commissioners . . . . . 72

## **Welcome and Overview of Agenda: Eric Meslin, Ph.D.**

DR. MESLIN: [Opening remarks and administrative details] ... Dr. Childress and Dr. Cassell suggest that we have another look at the Belmont Report, not only because this document has had such an enduring legacy in bioethics and public policy in this country and elsewhere, but because there is an anniversary next year, 20 years since it was published by the Office for Protection from Research Risks following completion by the National Commission.

Dr. Childress and Dr. Cassell have been working on an idea which is not even a full proposal yet, but an idea for bringing that forward and Professor Capron was kind enough to offer some comments just as late as last evening.

There will be time during the course of the Commission meeting, more likely toward the end of the day today and toward the end of the day tomorrow, when Commissioners will have an opportunity to talk about these three projects in detail and to reflect on them. We're hoping that by presenting you with two memos on the day of your arrival, we will not discourage you from thinking about these items. I apologize that we couldn't get them to you sooner.

And the last item, really more of a housekeeping item, is to let both the public and Commissioners know that we have our dates and our locations set for the remaining meetings for this calendar year and materials are available outside the door. We'll be meeting on the 14th and 15th of July in Portland, Oregon, in the Oregon Ballroom, if you're interested in making your reservations; on September the 16th and 17th we'll be meeting again in the Washington, D.C. area, this time in Alexandria, Virginia; and then in November we will be meeting in Miami, Florida, on the 17th and 18th. Again, these materials are available on the desk outside.

We have also been circulating our draft plan for the meeting dates for 1999, and you have received materials from Henrietta Hyatt-Knorr asking for dates and availability. Once those are confirmed, we will also be discussing with Commissioners whether the cities from which they hail might be appropriate locations. But it's our intention to still mix our meeting locations so that there is adequate meeting time in the Washington, D.C. area, but also, in keeping with the National Commission, that we try and move about the country in an appropriate way.

So those are the items that I wanted to include in my Executive Director's Report. If there are any questions that the Commissioners have, I'd be pleased to address them now. And if there aren't, we'll be able to turn to our agenda.

Alta?

PROF. CHARO: A couple of questions on the status of things. What's the status of the Federal Agencies Report? I understand that you were discussing this in Washington on Friday and I was wondering if you would brief us as well on that.

DR. MESLIN: The staff has been working on a report that began some time ago, which was examining the extent to which Federal agencies were implementing the Common Rule. This report has been called the Federal Agencies Survey, for lack of a better expression. That staff report is close to being done from the data collection side. There are a couple more interviews to

do. But we expect that a draft version of the staff report will be available within the next month to six weeks.

It's our intention to distribute that report to Commissioners for their benefit. But more specifically, as I briefed the interagency committee last week, we are intending to share that report with the agencies themselves in a, hopefully, very collaborative and consultative way so that factual materials can be clarified and, more hopefully, any constructive suggestions for implementing what the report finds can be taken. The working idea, however, is that the report, which of course will be widely available once it's produced, might best be seen as an integration into the Comprehensive Human Subjects Project which, again, is the two-page memo in the folders that we've handed to you.

We expect that the staff draft will be available within the next month to six weeks. We are also developing a proposal for consulting with Federal agencies or perhaps having them come to a Commission meeting and sharing with us thoughts for how to implement some of the findings. But the status of the report is, even though I don't want to put a percentage on it, 97.3 percent done.

PROF. CHARO: And on the cloning report, is there a finalized version that is going to be released sometime?

DR. MESLIN: Yes. I don't know if Henrietta wants to speak to that, but the good news is we did the final edits and I believe—do you want to give a quick update on what our expected publication time is for that?

MS. HYATT-KNORR: I would think probably another three weeks.

PROF. CHARO: The last thing is just a question about the timing. In light of the expansion of the agenda on the international topics, do I still understand correctly that we're going to try to finish the existing workload before we take on any other projects?

DR. MESLIN: Yes.

PROF. CHARO: Okay. Thanks.

DR. MESLIN: Any other questions?

I neglected to mention, Commissioners may be aware of this, but some of our members are not here. Dr. Lo is unable to come, Professor Backlar is going to be available by telephone at 10:15, and Ms. Flynn will not be able to attend. Those three members are not in attendance but one of them will be joining us by conference call.

Professor Murray is en route. Which is ironic, given that this is his host city. But when he arrives, if you can wait for that moment, I will explain why he was late and I think you'll agree that it was a well-deserving reason to be late. The Chair will be arriving shortly, and Steve Holtzman is en route as far as we know, and Larry Miike is en route as far as we know. So we are going to begin with the complement that we have at about seven minutes after the hour.

Our agenda today and tomorrow consists of three parts. The first part is the Commission's continuing interest in international issues, and the second and third parts relate to

the reports as described.

I want to turn the meeting over now to Alex Capron, who attended a meeting a week ago, to describe some of the work of the UNAIDS consultation that occurred in Washington, D.C.

**UNAIDS Washington Meeting Update: Alex M. Capron, LL.B.**

PROF. CAPRON: Thank you, Eric. The reason I gather that Eric thought it was appropriate for the Commission to be involved with the UNAIDS activity is that the way in which we were first drawn into the topic of research was through the protests, as it were, the complaints that had been voiced about the AZT trials in Africa and Thailand. And the UNAIDS program decided to establish an ethics committee, which is chaired by Ruth Macklin, and to have a series of regional consultations leading up to a meeting in Geneva next month. The three regional consultations in Uganda, Brazil, and Thailand drew researchers, ethicists, physicians, and the public health officials from those areas of the world in which research is being carried out not only in the antiretroviral treatments, but, more particularly, in vaccine development.

The consultation held in Washington at the Pan American Health Organization last week differed somewhat. First, there were representatives from several of the other regions that had already had their consultations; and secondly, the focus it seemed to me was less on what is happening in North America, but rather on the interaction between the interests of the major sponsors, particularly the governmental as opposed to the drug company sponsors, and the regulations in the United States, the interaction between those and the research design of vaccine trials.

The topic was, therefore, particularly appropriate because the kinds of questions that we're asking in our own potential international agenda are very much the questions of what are the effects of the American regulatory framework, both within the Food and Drug Administration and in the Common Rule, on the ability to carry out and the suitability of research that is carried out abroad, and whether changes are needed either in that framework or in the Helsinki and Council for International Organizations of Medical Sciences (CIOMS) document. The one aspect that I think is only a partial response to our international agenda is that the focus is solely on AIDS. And when we get to the international agenda I, at least, will argue for the notion that we should use AIDS perhaps as a springboard but ought not to limit our examination to that one disease or to the attempts to find vaccines. I'm very much indebted in what I'm about to very briefly report about that meeting last week to Ruth Macklin, who took very extensive notes, which she has shared with me.

It seemed to me that in ethical terms, the central prerequisite for the vaccine trial is the notion that despite some counseling and encouragement to avoid infection, a certain percentage of the people who are vaccinated will nevertheless become exposed to the virus. If preventive measures other than the vaccine itself were totally effective, then it would not be possible actually to do a vaccine trial.

Now, some of the issues that arise have to do with at what stage in the trial process, whether at a preliminary stage when the dose being given is not necessarily aimed at achieving any immunity but rather looking for reaction and side effects, or later in a trial when a large number of

subjects are used with the hope of finding out whether the vaccine in fact will prevent the development of the disease.

I'll leave it to Ruth to describe more fully the technical questions with which she has become familiar about the vaccine. But one of the particular facets of the vaccine which raises its own set of ethical questions is that it is not a vaccine that will probably prevent infection. Instead, it is intended, if it worked, to hold the viral load at the same low level that antiretrovirals now hold the viral load, which prevent the development of the disease itself.

There were a number of issues; let me just mention two or three of them as examples of the problems that were discussed. One of the questions is something that is pervasive in research generally, and that is the question of when and where one draws the line on inducements to participate. This particular area is complicated by the question of what will be done for people who become infected in the process.

The major inducement that could be offered either to individuals or would, in effect, be offered to the host country and its public health organization or its governmental arrangements is the offer of treatment for people who have the infection, and, again, with the realization that some of the people who are vaccinated will nevertheless get infected and would be, therefore, at risk of developing the disease, and certainly anyone who did not receive the active vaccine would be at risk of getting infected.

The notion of having available a treatment for a person who becomes infected seems to be a moral imperative. But if, particularly among intravenous drug users, the probability of becoming infected for people in certain populations is enormously high at the outset, then you can see that a dilemma arises when the person is offered the prospect, which is not otherwise available to the person and may be just generally not very available in the country at all, to have free antiretroviral treatments for an indefinite period. Because if the person is otherwise thinking, well, everybody I know is coming down with this disease, it's likely that I will also, but the one thing that would be available to me is only available if I participate in the trial, does that mean that the trial should not be conducted under those circumstances?

In a certain way, that's the population that researchers would most like to address because of the high risk of exposure. In another way, the question is: can anyone freely consent under those circumstances?

So this question of providing the treatment is central. And it was interesting at the meeting to see that not only have the different regional consultations come to different conclusions about this, but the countries within the regions have reached different conclusions. For example, the regional consultation that was held in Brazil had concluded that the drug should be made available as part of the experimental design. And the Brazilian representative who was at the meeting explained how his government has, indeed, decided to make the drug available to all known cases of infections with HIV. Whereas the representative from Trinidad and Tobago, whose country had been represented at the Brazilian consultation, took the contrary view that it was simply too expensive and burdensome even to the individuals to expect that they would be on a course of antiretroviral treatment for the rest of their lives, and that this should not be part of the research design, and it should not be regarded as, in the language of the CIOMS document

and the Helsinki document, “a treatment that is reasonably available and therefore should be part of the research design.”

There were many areas of remaining disagreement as to whether or not the level of intervention provided to the subjects—for example, in the AZT trials in Africa involving pregnant women and maternal transmission of HIV— what was meant by the best proven treatment, whether that was a world standard or a host country standard. Barry Bloom, who was a participant in the meeting, was pushing for the notion of the highest attainable standard, which was interpreted by some as too burdensome because of the emphasis on the word “highest,” and by others as too low because they took the word “attainable” to mean practically attainable given the resources of the host country. So if there was consensus on any point, it was that it’s not likely that a few words by themselves are going to answer this and that one has to understand the principle or the objective to be gained and the wording comes later.

The final point that I’d like to draw from the meeting was the emphasis that was placed on the desirability of developing a mechanism which would not only facilitate communication between the sponsoring countries and the researchers from those countries, but also the researchers in the host country and the government of the host country on behalf of the potential participants. This emphasis on developing a practical, ongoing means of resolving disputes in the interpretation of these international guidelines struck me as an area where we could make further valuable contributions, even if the particular mechanisms would likely be in themselves international mechanisms.

DR. MESLIN: The Chairman has joined us, but I’ll allow him a chance to get seated.

Were there any questions or comments for Alex?

Jim?

DR. CHILDRESS: I’m very glad that you’re broadening the discussion beyond the AZT trials. I participated in a discussion in the Tropical Disease Division, and we’ve circulated the summary of some of the points that came out in that discussion involving people from around the world. I think some of the issues that come up, for example, in that area are quite different from the ones that arise in the AZT trials. So I’m glad that we’re going to cast a pretty broad net in order to be able to deal with the kinds of issues that may be quite different.

The main example of this in the discussion that came up was, in contrast to having an established drug therapy, you’ve got a reduced course that will work relatively well, perhaps as well. In this particular area of tropical disease research, most often there’s an effort to develop a pilot study that will suggest this thing might be effective and then try to entice a pharmaceutical company into developing it. That’s very different from having something available. So that’s just one example of some of the complexities that might arise in thinking about providing an access to what is developed. The issues would be different in that from the AZT area.

PROF. CAPRON: One of the issues that arose, which I think was probably a question at the tropical meeting and, if not, could be because it’s not at all particular either to vaccines or to AIDS, is the statement in the present CIOMS guidelines which caused a lot of consternation actually on the part of representatives of several of the developing nations that were there, and

that is the requirement that any drug or vaccine be tested in phase I and II in the sponsoring country first. There were two objections raised to this. One was that the whole notion of sequentialism here may not make sense and it might be important to test it, in part, because of variance in the biological processes that we're talking about that can occur: different strains of a virus or different manifestations of a disease in different countries.

But the other objection that was raised is what does this imply about the progress in addressing diseases which are perhaps of much greater concern to other parts of the world even if you could find sporadic cases of them in the United States? There are some things that you're not going to find in any endemic fashion in the United States that are major problems there. And, clearly, that kind of a barrier, if it was a U.S. or a European drug or vaccine sponsor, would prevent any progress.

My impression, having participated in the CIOMS process, was, as we've seen in the pre- and post-AIDS era, the emphasis of the CIOMS document, as recent as it is, is still very protectionistic and it grows out of the experience of drugs being developed for conditions that exist both in the Third World and in the United States, using Third World populations because they were more convenient and cheaper to use, not because one was addressing illnesses that are particular there. And some attention both to that concern and yet not overprotecting to the point where you prevent not just the development of the vaccine or drugs, but the development of the necessary infrastructure in that host country to become an active participant in the process is a real dilemma. And it isn't adequately addressed by any of the guidelines. We heard a little bit about the process of the Helsinki revisions, and I'm sure Ruth may have more to say about that a little bit later.

DR. SHAPIRO: Thank you. Are there any questions, comments?

Thank you very much. And, Alex, I apologize for coming late. I will catch up with you later on what was heard.

And let me apologize to the Commission members. My only quasi excuse is it took me longer to get from the airport to here than from Newark to the airport. So I apologize for coming somewhat late.

We have three really very important guests here today. I want to turn to them now and apologize to them, first of all, that we are running a little late. I hope we don't upset your own schedules.

Let me just turn to the first of them and welcome Professor Ruth Macklin here this morning. She's a distinguished professor of bioethics at Albert Einstein College of Medicine, a member of the Institute of Medicine, and Vice President of the International Association of Bioethics, if I have the association name correctly. Ruth, it's very nice to have you here again. Thank you very much. We look forward to your comments.

**Ethical Issues in International Research, Review of UNAIDS Activities: Ruth Macklin, Ph.D.**

DR. MACKLIN: Thank you and I'm pleased to be here again. I'm going to say less than I had planned to say. Alex and I discussed whether he should be presenting the summary of the Washington meeting, and since the summary of the Washington meeting actually included much of what I was going to say, I'm going to avoid redundancy.

Let me begin by saying a couple of the lessons that were learned from the AZT controversy that erupted which, in turn, almost directly led to this series of consultations that Alex described that UNAIDS conducted. One question, and Alex has already pointed to this, that emerged from the controversy is whether existing international guidelines are adequate to address the present and future conduct of international collaborative research.

As it became apparent, specific items in the current version of the Declaration of Helsinki, which is distributed by the World Health Organization to all its collaborating centers in any cosponsored research, and the CIOMS international guidelines, the ones frequently referred to as the Red Book, those guidelines may be open to different interpretations. The guidelines themselves may well be internally inconsistent, and careful examination, as Alex has reported, showed that some of these statements or guidelines may be in need of revision. Let me give as an illustration, in the AZT controversy, guidelines and principles from both of those documents that were cited both in support of and in criticism of the trials following the controversy over the placebo controlled AZT trials.

Let me give a couple of examples rather than speak generally so it will be clearer. I'm sorry, if you had a text, it would be easier. I'm quoting from guidelines which sometimes are in turgid prose. Here's a statement that appears in the Declaration of Helsinki, and Alex has referred to this. Here's the whole statement. "In any medical study, every patient, including those of a controlled group, if any, should be assured of the best proven diagnostic and therapeutic method." Now, critics in the AZT controversy charged that in the placebo-controlled trials neither the subjects in the experimental treatment arm nor those in the placebo arm received the best proven therapeutic method that's available in the world today.

Subsequently, in an article that was published in the journal *IRB, a Review of Human Subjects Research*, Robert J. Levine argued that the proper interpretation of the phrase "best proven treatment," (this was the interpretation that Levine claimed was intended by the original drafters of the Declaration of Helsinki), should be interpreted to mean best proven treatment in the country or region where the research is being conducted. So right there you have the conflict.

A second statement that was cited from the Declaration of Helsinki is as follows: "Concern for the interests of the subject must always prevail over the interests of science and society." Critics charged that in the placebo-controlled trials the interests of society prevailed over the interests of the subjects enrolled in the study.

However, supporters of the AZT placebo-controlled trials could cite a different Helsinki principle: "Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject." And, indeed, spokespersons from Thailand and Africa, who were from the very countries in which the placebo-controlled trials were carried out, claimed that because the pandemic is so severe in their countries, the importance of the objective was indeed in proportion to the risks that were posed to

those subjects.

Now similar difficulties arise in the CIOMS guidelines. I'll just give one example here. One paragraph states: "In a randomized clinical trial, the therapies or other interventions to be compared must be regarded as equally advantageous to the perspective subjects. There should be no scientific evidence to establish the superiority one over another. Moreover, no other intervention must be known to be superior to those being compared in the clinical trial." And it goes on. Well, it's clear here, as critics charged, that the placebo-controlled trials failed to comply with these conditions.

So these few examples, and we could cite more, serve to illustrate the problem. Which ethical guidelines should be followed? What should be done when ethical guidelines themselves or elements in the guidelines come into conflict? One cannot expect guidelines, being general as they are, to give all the very specific answers. On the other hand, they're supposed to be useful. And if critics and supporters of one and the same trial can cite different elements from the guidelines both in criticism and in support of the trials, it indicates that some next steps ought to be taken.

At present, the Declaration of Helsinki is undergoing revision. I don't know how much to say about that. Maybe I'll just leave it to questions or in the discussion period. There is a process of revision which is probably not going to resolve these problems, but it is a process that is involving a lot of consultation with national and international medical associations since, to remind you, the Declaration of Helsinki is a document that is promulgated by the World Medical Association. So unlike the World Health Association, which is an international United Nations body, the World Medical Association is a consortium of national but not governmental, medical associations.

A second question that arose out of the AZT controversy is whether such disputes might be identified and addressed in advance of initiating the research. And that's precisely the path that the UNAIDS group has begun to embark on. Alex described the process and I will not repeat that except to say that in addition to a planning meeting that was held in Geneva last September, there were some papers, and I believe, am I right, Eric Meslin, that at least one, maybe exactly one, was distributed to the Commissioners. This was a very thoughtful and useful paper by Dr. Lie.

There were four papers altogether. Let me just tell you what the other topics were. These were focused on vaccines but the UNAIDS group, and, indeed, I think World Health Organization more generally, would like to see this process carried out not only for AIDS research and not only for vaccine research. The other papers were one on protection of study participants, there was one on justice issues by John Harris, a philosopher and bioethicist from the U.K., and a fourth topic on community consultation which was written by a woman from Nigeria, a physician and community activist.

The process of community consultation was actually the model for these regional consultations. In AIDS research, and almost exclusively, although this has begun to spill over into other areas, the idea that one should or perhaps a mechanism should be established for consulting with the community, left vaguely because it is hard to define, in advance of and during

the conduct of the research was an idea that came early on in AIDS research and has been suggested in some other contexts as well.

It was that model of community consultation that the UNAIDS group thought would be useful to conduct in a regional sense, and that's why in the three places that were chosen—Thailand, Uganda, and Brazil—are the countries in which the first vaccine efficacy trials will take place. So that was, in a sense, a regional consultation and it included, as Alex mentioned, people from countries in the region other than those particular countries where the trial will take place.

Let me move on and tell you rather quickly a few of the issues that were identified in this process of regional consultation. Again, I'll try to skip over ones that Alex has already mentioned.

There was a series of procedural issues that pertained mainly to the process by which the sponsors of the trials and the researchers and communities in the host country should make decisions before, during, and after the trial. People in the world of bioethics will recognize this as the classic "who should decide" question, which involves not only the who, but also how the decisionmaking should take place and when. The subject matter of these decisions includes aspects of the trial design, treatment and care of participants who become infected during the course of the trial, who should receive vaccines of some proven efficacy, and similar questions.

Alex mentioned this but I think it needs to be underlined. Participants in all three regional workshops strongly agreed that communities in the host countries should be involved in developing and conducting vaccine trials in a fully collaborative partnership. This, I think, is clear is a distinct departure from the way things have worked in the past. Two out of the three regional groups agreed that the point in research development at which the community should become involved is the earliest possible time. And the shift in concern from what used to be a worry about exploitation, that is, of developed countries and wealthy countries and international organizations barreling in and conducting research on vulnerable populations, this notion was turned on its head in a sense and there was an anti-protectionist, anti-paternalist stance by all of these groups that have now developed in these countries that have themselves capable researchers and mechanisms for review.

That brought us to the discussion of the adequacy for procedures for conducting scientific and ethical review. This is another significant procedural issue. It was agreed at these regional consultations that a necessary condition for carrying out research, collaborative partner research in developing countries, a necessary condition is that there be in place adequate mechanisms both for scientific and ethical review. At least one of the workshops—I attended two of those three workshops, one was the one in Entebbe, Uganda, and the one in Brazil—it was suggested that another layer of review, perhaps at the international level such as the UNAIDS committee, might be desirable.

Let me turn and very briefly mention a few of the substantive ethical questions that go to the heart of the design of both vaccine trials and, as Alex mentioned, the ancillary care and treatment of participants. It's assumed, I think, by everyone, not only scientists for the best trial design but others, that a placebo control arm is methodologically necessary and ethically

acceptable at the outset of vaccine trials. At the outset is a different situation from what happened with the AZT trials.

However, there will come a point at which a vaccine is possibly effective, marginally effective, or not very effective, and the question then is what should the design of subsequent trials look like. Would it be unethical in subsequent vaccine trials to withhold a partially effective vaccine from people in a control arm when the new vaccine is being tested, and will that compromise the ability to measure what has to be measured?

Alex already mentioned the question that participants in the regional workshops thought was the thorniest question, and that is the type and level of medical treatment to be made available to trial participants who become infected in the course of a vaccine trial in spite of the counseling on risk reduction. Now, this is probably the closest analogy with the placebo-controlled AZT trials, because people who argue that participants in vaccine trials should be given the “best proven treatment,” or the treatment that is available in developed countries, argue to withhold what would be analogous to conducting the placebo-controlled trials and withholding a proven known effective treatment to people in the trial. So the problem will not go away - even if we have a different substance and a different type of study.

One of the regional groups came to the fairly strong conclusion that the appropriate type and level of treatment should be decided upon by the host country, the host country being, of course, the country in which the trial is to be conducted, not by the sponsor, not by the manufacturer, but by the host country. And there were discussions, as Alex pointed out, about what kinds of criteria should be used for determining that standard.

One series of questions that Alex did not mention, and I’ll close with this, because this was also important for the international collaborative work, this was a series of questions that were not resolved neither in those three regional workshops nor at the Washington meeting. What should be available to whom after the trial is completed? Or, to put it a different way, what are the obligations of the sponsoring country, the manufacturer of a vaccine, or we could argue other drug, to make available in a region with a high degree of need a product that is proven to be effective, particularly if we’re talking here about something like a vaccine for AIDS? Should trial participants who receive the placebo be entitled to a vaccine? Should individual or groups in the country who are thought to be at high risk for infection receive the vaccine? Should all with a perceived need in the country receive the vaccine? These are questions of justice or distributive justice and they are among the most difficult to answer from a theoretical point as well as from an economic and practical standpoint.

The strong consensus that emerged at all of these regional conferences was that the answers to these and other questions should be derived by a process of advanced negotiations among all the relevant parties—representatives from the sponsoring countries, the host countries, including potential trial participants themselves, opinion leaders in those countries, the vaccine manufacturer, and others—even though some people pointed out that this departs from what has been standard practice. No one has generally negotiated in advance of research and development of a product who’s going to get it afterwards.

This is a new model, and it’s one that’s being urged. The hope, as expressed at the

regional meetings, was that adopting some such procedural mechanism can succeed in preventing the sorts of controversy that arose well into the conduct of the perinatal transmission clinical trials and one that the UNAIDS organization is trying to head off by holding these consultations in advance of initiating the vaccine efficacy trials. Thank you.

DR. SHAPIRO: Thank you very much. Let me see if there are questions from Commissioners before we go on to our next guest.

Yes, Alta?

PROF. CHARO: In some ways this may anticipate what Dr. Nightingale is going to talk about. But I'm struck in this discussion by the degree to which the debate about the ethical standards is being driven by what we perceive to be immovable structural and systemic issues like extremes of wealth, extremes of development, and assumptions about incentives toward exploitation which drive the skepticism about the motivations of the pharmaceutical companies and researchers. It makes me wonder if one could work at that level instead of trying to figure out how one could create a set of ethical rules that govern your behavior against a backdrop of such extreme circumstances.

I don't think that any commission can handle the problems of extreme wealth and development. But it does make me wonder about the pressure point of the incentives to exploitation. If companies are going in to do testing on interventions that will never have an application in the developed world, for example, with the AZT trials, I think that raises very different issues than if they're going into countries where they think they're going to be testing something that they might be able to bring home to a developed world, to a large market, and they want to test it in a place that they perceive to be easier or cheaper for their testing.

That raises the question about the usefulness of foreign data for local approval of drugs for this particular market. If that's the scenario that raises the concern about exploitation, the question is whether or not the data from those countries in fact is all that usable, since I presume that the background health status of most of the subjects is likely to be different enough that it raises questions about the generalizability of that data to the American population, as one example. But where it is usable, the question would be, should we discourage its use? And I gather that there has been an active debate within FDA about the acceptability of foreign data generally, not with special reference to data developed in developing countries, with conflicting tendencies; some wanting to use more of it in order to speed the approval process, and others wanting to keep it out in order to have more control.

I wonder if this kind of use of domestic law and domestic policy to change the incentives to exploitation, if you think that this is a productive avenue, or if you think that it's too politically complex domestically, to take away some of the seeming pressure toward exploitation that's driving some of these finer, more "nuanced," decisions about the ethical standards to be used?

DR. MACKLIN: I'm going to let Dr. Nightingale answer that part, that is the part that particularly has to do with the standards and the FDA standards.

But there are additional complications and let me say quickly what they are. First of all, on the notion of exploitation, the countries in which the vaccine trials will begin are extremely

eager for these trials. The community leaders, the people living with AIDS, the ministries of health, and the researchers are all extremely eager for it because it's really the only hope for a vaccine. What they're worried about is that the testing will test the prevalent strain of HIV/AIDS that are prevalent in the developed countries, in the Western world and not the particular strains that exist in—there's a scientific question here, whether they can get cross-immunity across these strains. I won't even go into that. But that's one of the worries.

The thing that makes this a problem analogous to the AZT trials, and Alex referred to it and let me just say it again in a clear way, is that the trial of an AIDS efficacy vaccine could not be done in the United States to get the answers that you want to get from a vaccine test because it would mean withholding triple therapy, the AIDS cocktail, which would destroy the scientific results because it would immediately reduce the viral load.

So the worry about exploitation is as follows: Here is a trial that could not be done in the United States because participants in the trial would be made worse off than they would be if they weren't in the trial because the routine treatment is widely available. So you would have to withhold it from participants in the trial and, therefore, arguably, it's the kind of trial that could not be done for ethical reasons because you would make people worse off. However, in the countries where it is absolutely not available because of the health infrastructure and, of course, the economics, there are places where nobody would get triple therapy. So this is a perfect example of conducting a trial in a region where one can do it and could not conduct the same trial in the United States.

The groups in those countries, however, do not view this as exploitation. And it was only in Brazil, which was the country where they are providing triple therapy to people who are HIV infected, that they argued that they should get the antiretroviral treatment just like in the United States.

DR. SHAPIRO: Alex, and then Arturo.

PROF. CAPRON: To add a further layer to that, Alta, you made two contrasting categories between something that would be tested there basically to be exported back to the United States versus something that would be relevant. The difference between Brazil and the other countries I think underlines that Brazil has made a choice about the allocation of its dollars to say that it will make antiretroviral and, one assumes, if the vaccine became available, the vaccine widely available. Another country might say we're putting our scarce dollars into other forms of medical treatment, or education, or other things that we regard as important. And the question then would be, ought anyone viewing the situation or negotiating in the situation, or criticizing the situation—as the kinds of criticism that came up from various people in the United States about what was going on in Africa—be viewed as making immoral choices if he or she is going to conduct studies there?

Because it becomes a question not just, “Would you say that the country is making bad choices,” but then an American researcher from an American research institution, who has to go before her or his IRB to get approval to participate with a study, in effect, has to then say, “This is the circumstance in the country.” It certainly isn't the only way the country could choose to spend its dollars. And the question then is, are they implicated in the results if realistically the

country isn't going to be able to afford to buy the drug or vaccine after it has been developed because they've made choices about how they are spending their dollars?

And so it becomes a very nuanced situation-dependent question. And it's clear that for American research workers, both at the CDC and private universities, this will be an issue that their IRBs will have to struggle.

DR. SHAPIRO: Arturo?

DR. BRITO: I think Alex mentioned the concerns of American imperialism, and I think you, Professor Macklin, implied this also when you mentioned paternalistic type of concerns at the deliberations over the AIDS vaccine trials. I can appreciate that there would be concerns in this area. But I question, and I'm a bit skeptical about, when these deliberations are ongoing and the community leaders and the scientific leaders from those countries, are they not actually more similar to the scientific leaders of this country and, therefore, not truly representative of the individuals of their host countries? That's where I become a little bit skeptical.

Now, the way the CIOMS guidelines are written, they're written more to protect the subject, and you quoted one of the guidelines there protecting the subject over the community, and this is more individualistic, which is not just an American ideal, it seems to be in international guidelines. Some of the justifications for the perinatal transmission of HIV and the use of AZT, some of the justifications have been more utilitarian in nature, not individualistic. And these were endorsed by the World Health Organization which, in itself, was partly responsible for the formation of CIOMS guidelines.

I guess I'm a bit skeptical about the leaders of other countries making decisions for their "communities" when they, in fact, are more similar in nature or have more in common with the American leaders. So I'm not real clear why we continue to go back to concerns of paternalistic attitudes when those community leaders are also paternalistic in themselves.

DR. MACKLIN: Yes. I think you've hit on a major problem, which is the difficulty of identifying the relevant community and the greater difficulty of saying who represents the community. What I should point out about these regional consultations is, first of all, they did not include governmental officials who will of necessity be involved in this in those countries. This was nongovernmental; it did include the researchers who, I think you're quite right, if they're not trained in the U.K. or U.S., may be similar in outlook.

But most of these countries, most developing countries, not all, but most have a very well developed structure of NGOs, nongovernmental organizations, that are much more like grassroots organizations. Those were all represented. There were very many of them in the world of AIDS. And so they don't represent the community in the sense of the rural group from whom some research subjects might be taken, but they do represent people living with AIDS, families of people living with AIDS, and those who are health advocates from the grassroots movement.

Now this doesn't fully answer it, but at least it says that these consultations are not limited to, and the aim is not to limit them to the researchers, the Western trained people, and certainly the governmental leaders.

PROF. CAPRON: If I could just add just one quick point. I mentioned the problem of

so-called undue inducement vis-a-vis individual subjects. The same issue arises at the governmental level in exactly the way Arturo is describing. If a condition is placed on the sponsoring company or country coming in to do the research, we want the following things to help in our infrastructure, all of this seems very legitimate. But at some point, it begins to seem as though the interests that are being served are those of the research establishment, when you hear that a major concern is authorship on any resulting papers.

On the one hand, it seems perfectly appropriate to say that people who are going to be participants in the research should be involved in its design and recognized for their contributions; on the other, it's as though there is a group of subjects which we can offer you if the proper inducements are there.

And that comes down to the other question, which Ruth and I have both mentioned, and that is the after-experiment, after-research obligations. Because if a drug or vaccine is developed and if the relevant moral unit is regarded not just as the immediate subjects who were in the first trial and you have some ongoing obligation to them, and not just the immediate community but maybe the nation, then you can even imagine a situation in which neighboring states, each with populations that would be "good research" populations are, in effect, making competing offers to the sponsors of saying "come and do the research with us and this is what we will expect in return," and it would even be, ironically, we're talking about this, an advantage to be a smaller country because you'd say your after treatment burden will only be providing free treatment for a million people in our country, whereas our neighbor has 5 million people, it's going to be much more expensive for you. And then you get to the question why is the country a relevant moral unit in any case for dealing with international epidemics?

So the questions simply become more and more complex and it's harder to get a firm footing that doesn't sound, as you say, paternalistic from one side or the other or exploitative from one side or the other.

DR. SHAPIRO: Steve?

MR. HOLTZMAN: Just a question to Alex on that last point, and maybe Ruth. To what extent in these discussions were there participants from the pharmaceutical industry, and these hypotheses about the costs and attitudes and their inclinations to do trials that are in this or that place, was that discussed with them, or is this all hypothesis?

PROF. CAPRON: Ruth, do you want to comment about the regional?

DR. MACKLIN: Yes. At the regional workshops and also at the Washington meeting the decision was made not to involve representatives from the pharmaceutical industry at this level because we didn't want the economic issues as seen by the pharmaceutical companies to swamp the ethics. The pharmaceutical companies will be invited, however, to the June meeting, which is the result of all these consultations. There was debate about this, by the way, at what stage representatives of pharmaceutical industries should be brought in.

However, there is a process of negotiation that is going on at the highest WHO/UNAIDS/pharmaceutical company levels with regard to providing AZT. This is a negotiation that is now going on that people from the NIH say should have taken place before the

AZT trials and not afterward. But there is actually an agreement being forged, possibly even as we speak, to try to make those drugs available now. And that's why the urging here was to have this conversation in advance of conducting the trials. So there's every intention to bring in the pharmaceutical companies.

Just to put this in perspective, and going back to Alta's comment: Uganda has a per capita expenditure—the government and the people can't afford anything—so the government has a per capita expenditure on health care annually of \$5 to \$7. Now when they asked even is the cheaper AZT regime available to all of the pregnant women in Uganda, the answer is going to be no, it's not. So, clearly, if there's going to be any justice in the aftermath of these trials, it's going to need some assistance beyond the countries themselves, because Uganda will never be able to afford more, unless there are some radical changes within the country.

DR. SHAPIRO: I recognize David, and then I have a question, and then we should go on. David?

DR. COX: I'd just like to sort of make a comment about research in general. It's like playing chess; most of the time you're not just looking at the first move in playing chess or the move ahead of you - or you lose. In terms of research, it's almost always in the context of a specific hypothesis but toward a specific purpose, at least when it deals with health.

Listening to these conversations, I think that without really looking at the situation and looking at the context, that you can do as you described, Ruth, take one part of the Helsinki Accord or another part of the Helsinki Accord. I would just like to make a plea for a very straightforward reasoned and long-range research goal out of all of this and not each trial by itself. But in each particular case, what are people trying to do? I think that without that situational perspective, this is not going to be something that can be solved. I don't see that it's something that can be solved in a general way.

It's a little distressing to me that, it's not that people haven't thought of this, but that perspective doesn't seem to be much on the agenda. Could you comment on that?

DR. MACKLIN: Yes. I can make a brief comment. The regional conferences were three-full-day meetings; the Washington meeting was a two-full-day meeting. There wasn't time in our 15 to 20 minutes to go into all of the issues. What I should say is that at both the initial meetings and at the regional conferences there were vaccinologists as well as ethicists. These were people who know what the hypotheses are, how one tests a vaccine, and what the steps in the research process will have to be. So there was a very long prospective look at subsequent steps. I referred very briefly to one of them; namely, once you get a partially effective vaccine, what should the design of the trial look like after that?

So these things were looked at sequentially, I mean not laying out the entire research agenda, but with adequate, I hope, input from vaccine experts who are the ones who would be best able to tell us what the research agenda and hypotheses should be.

DR. COX: Well, I wasn't implying that the researchers should set the agenda because, certainly, it's a social and cultural context, but at least by being involved with the rest of the people they can say what the goals of the long-term consequences are. Without that, I don't

know what the research is all about.

DR. SHAPIRO: Ruth, I have a question which may, in a small way, be similar to David's. You made a comment regarding the acceptability of placebo trials at some initial stage, but then as the vaccine might be partially—you get some information. The question is at what stage do they become unacceptable? And you just left that as a question or as a proposition that has to be resolved.

I want to ask a question about that, because my own reading of the paper that you mentioned, if I pronounce the name right, Professor Lie — Professor Lie's paper comes to the conclusion that, indeed, in these matters it's a rather almost sophisticated statistical matter as to whether some things are ethical or not, which people can disagree about. The same thing would be true in the example you gave; that is, when do you have enough information to begin rejecting the placebo trials is a very complex matter of which, at least some of it, is statistical in nature. My question is whether that kind of expertise was available to you and others who were participating in these regional and/or Washington discussions. And if not, do you think that's important or is this kind of a secondary or tertiary issue?

DR. MACKLIN: The short answer is, yes, that expertise was available and there were extremely high level debates, because, of course, as everyone knows, even experts in a field disagree. And so the experts were available and did give their input. There was disagreement.

And, ultimately, there are value choices, too, even with the expertise. So even when they agree on what are the statistical methods that are required, there is still the overlay of the value questions. Is the highest priority getting an answer quicker and, therefore, making the vaccine available even if it means that some people will be less protected, or is the higher priority to be on protecting or providing some benefit to the individuals in the trial? You're going to get a faster answer with the placebo, but you're going to get more protection for the subjects if some of them receive the vaccine.

And I guess the other wrinkle about this is once you get a vaccine, you can't get a better vaccine for those individuals. So people who get a placebo might themselves be better off getting the placebo because if a more effective vaccine is developed and they're still zero-negative, they'll get the more effective vaccine.

DR. SHAPIRO: Well, I appreciate your response. I didn't mean to imply that there were no value questions that always overlay this. Of course, that's true. But do I understand, you didn't say this directly, may not have implied it, so you'll excuse me if I pose the wrong question here, that it's true experts will disagree on some of these issues, as will those who are trying to bring different value perspectives to it, and that at some level irreconcilable differences appear? How does one think about dealing with that issue? Is this just a process issue, that is, there has to be a process for discussion and decisions made, or after you've eliminated all those areas where you can achieve agreement, what do you do next?

DR. MACKLIN: You mean if you're left with residual disagreement?

DR. SHAPIRO: That's right.

DR. MACKLIN: Then it is a procedural or a process issue. But I guess I would say not

just a process issue. If there is residual disagreement, whether about the ethics, the statistics, the science, or the trial design, then it's extremely important to have an acceptable procedure for reconciling those differences.

PROF. CAPRON: May I try to underline what I think is the implication for NBAC out of this. If we're looking at what the role of the U.S. ethics standards are in all of this, we're not going to be designing the trials and so forth - suppose you have a situation in which the host country within the international process looks at a situation and, in light of the statistics and so forth, says we are going to interpret the ethical obligation as providing for, for example, the control group and for people post-study at the presently prevailing medical standard in the country in question, and we think that is adequate, the researchers say that will allow us to do a good trial, and we think ethically that's fine, and now a collaborating institution in the United States is reviewing this and trying to apply U.S. ethical standards. If they think, wait a second, we could come in as researchers and bring with us better treatment for the people in the control group, the host country isn't requiring it and the representative, the Health Minister from Trinidad and Tobago say, "We don't want you to do that, we don't want to set up a small group that gets this, this is not in our interest, we cannot do this for everyone, we don't want you to do it," should the U.S. IRB receive guidance from the U.S. guidelines or requirements that would say in this circumstance that's adequate? Or, in this circumstance, if you have a different sense of what is ethically obligatory, you should say that your researcher should not be participating in this and your institution, whether it's the CDC or Case Western Reserve University, ought not to be a sponsor of this work. That's the question as it comes home for people here.

DR. SHAPIRO: Okay. Thank you very much.

Eric, it better be very short.

DR. CASSELL: Well, it is short. I think that is really our issue. Our issue is not whether you should do placebo control or not placebo control. That's not our issue. Our issue is simply that point: does the host country's ethical approach to it prevail or must we prevail with our "superior" approach, and so forth. That's the real issue that we're about. We don't have to resolve a lot of that other [stuff].

DR. SHAPIRO: Okay. Thank you.

I want to introduce our next guest here. I just in advance of that want to welcome our colleague Tom Murray, whom I think of as an unofficial host or perhaps even official host, I don't know. Tom, as a few of the rest of us, was a little late this morning. He had a much better reason than at least I had; namely, he received the Distinguished Alumnus Award from Temple University yesterday. So congratulations, Tom.

DR. MURRAY: On behalf of Dr. Shapiro, I want to argue that his reason for not being here was equally valid.

**Basic Protections for Human Subjects in International research, The FDA Perspective:  
Stuart L. Nightingale, M.D., Food and Drug Administration**

DR. SHAPIRO: Okay. First of all, let me welcome Stuart Nightingale. Thank you very much for coming today. We very much appreciate it. Dr. Nightingale is Associate Commissioner for Health Affairs in the Food and Drug Administration. He'll speak to us on the FDA perspective on the issues that we're trying to address. Thank you very much for being here.

DR. NIGHTINGALE: Thank you. I'm very pleased to be invited here. I think the FDA has an important contribution to make to the work of the group. We do have a number of differences from others that you've heard from. I'm going to try to describe what we do and how we do it. You have some background about FDA in general and what we do as an agency. I am going to try to provide basic information today, not to get too deep into some of the issues, but to tell you more of what the process is. But I will make a few additional comments about some of our involvement in related areas.

Basically, we do regulate the clinical trials when they involve products that FDA regulates—drugs, biologics, medical devices, and other products. While our requirements are similar to OPRR/HHS regulations, they are not identical, and I will get into some of that a little later. But basically, a very major difference is that we have an inspection program that we use to enforce the regulations. And a major hook that we have in these, as far as studies go, is that unless the studies are conducted in an ethical manner, we don't accept them if they are studies submitted for approval of applications for licensing.

At the last meeting, there were some questions about FDA. One was, do we have information about the funding of foreign clinical trials? The answer is no. I think the secretary was going to get that information from PHARMA. What I can say is that there is an increasing number of foreign clinical trials that are occurring and this is reflected in the increased number of inspections that are occurring overseas.

In order to approve the applications, we have to have information that meets the criteria of the agency. And, therefore, when they are submitted to us, they are looked at for meeting our requirements. And as far as foreign data are concerned, it has to be whether the clinical trials are considered to be pivotal in showing safety and efficacy. And it is those trials that we inspect specifically to see if they meet our requirements.

We are not prohibited from approving a product solely on the basis of foreign data. This has occurred. We have approved products based on foreign data only a number of times with drugs. There is some variation across FDA in terms of whether or not the centers like to have clinical trials done in the U.S. as well as foreign trials. The Center for Biologics usually does require domestic clinical trials.

Of the foreign clinical trials that are inspected, only about half are performed under INDs. However, if they're not performed under an IND, they still must adhere to the same kinds of requirements that we have domestically. The non-IND studies are accepted as a basis for showing stage and efficacy for approval with requirements are, we think, similar to ours but not exactly the same. You have some background on that in the handouts.

As you have seen, the Declaration of Helsinki itself has a special status for FDA. It is not just an international code, it is actually mentioned in our regulations and it appears there. And it

is the international standard that we refer to if there is not an IND in place. So it is the Declaration of Helsinki or the domestic legislation/regulations, whichever are the higher standard.

Before going into further detail about the specifics about how we do our work, I'd like to return to FDA's approach as compared to OPRR/HHS. We have process regulations and as a regulatory agency we perform compliance inspection to enforce them. We do not have an assurance mechanism. Instead, we have trained inspectors and headquarters experts who make site visits to assess compliance with the regulations. The same compliance program is used internationally that's used domestically. This is actually true whether you're dealing with an IND or non-IND approach.

We have what we call a Bio-research Monitoring Program, which has two purposes. One is to ensure the validity and reliability of the data that are collected, and also to assure the protection of human subjects of research. This program covers many different areas. Some of them are pre-clinical, like *good laboratory practices*. But there is a constellation of regulations that I'm going to talk about today which we informally refer to as *good clinical practices*. This is the complex that includes IRB regulations, informed consent regulations, clinical investigator regulations, the IND or the IDE, and sponsor monitor and contract research organization regulations. Some of these occur with guidelines, and it is this constellation that we'll be mostly discussing.

I also will touch upon some international harmonization issues, particularly a program called the International Conference on Harmonization, which is different from some of the things you've heard about so far and I think is a major issue for the group to hear something about.

Now, I talked about the foreign clinical studies, the earlier slide, and showed that if there are two adequate and well-controlled U.S. studies there may not be a foreign inspection occurring at all. However, when the international study provides a basis for a drug approval, for example, and it's needed, then a study is done. Again, this is for pivotal studies.

With the IND studies, if there is an IND in place, the IND regulations, the IRB regulations, and the informed consent regulations are all in place. These, again, are the same domestically as they are internationally.

If there is no IND in place, then the foreign non-IND studies are governed by a variety of approaches. Basically, about half of the foreign studies that are inspected are non-INDs, about half and half. Clearly, they have to follow the same kinds of criteria in terms of well-designed and conducted, adequate and well-controlled studies, qualified clinical investigators carrying out the studies, and, to go back to Dr. Shapiro's earlier comment, they must be applicable to the U.S. population and practice. So this kind of determination is made by the reviewers looking at the applications for approval.

Then, of course, we have the Declaration of Helsinki with the special role that I mentioned at the outset. And then you'll notice below that we have the ICH Good Clinical Practices Guidelines which I'll talk about later.

A very important part of what happens occurs before the inspector goes on a foreign inspection, and that is that the sponsors provide by regulation a variety of documents that assist

the inspector when he or she actually goes on-site to the foreign country. The cooperation of the sponsor in providing information is extremely important because without this the FDA inspector will not have the information needed to compare on-site when looking at the raw data that exists. And the inspector will go with the case report forms and other data submitted by the sponsor and look at what's happening on-site. This is an ideal list. It doesn't always occur with international studies. But this is taken care of on-site.

Particularly important is the fact that there is a written assurance given by the sponsor that the records exist, that there is access to the records granted to the inspectors, permission to copy records, acceptable dates and times for inspection are arranged, and a copy of the local GCP requirements is put forth. Again, this means that the inspector has to have national laws and regulations, local IRB or ethical review committee protocols, procedures, and requirements present to compare when the inspector goes on-site. There are, of course, other requirements as well. So all this is done before going there.

At the opening interview, the inspector will look for a number of things inquiring as to who, what, where, when, and how the study was conducted. Unlike a domestic inspection, the inspector will not present credentials, a badge, if you will, or a notice of inspection because this is a foreign country, they really are not conducting this under our jurisdiction in terms of a right to go in and do what we're doing. However, as I mentioned earlier, the fact that the data is needed to be able to consider approval of the applications is a very potent force and gains entry pretty much universally so that we're able to go in and perform our review.

The inspection itself, again like a domestic inspection, will look at the clinical investigator issues, how the study was conducted and supervised, it will look for protocol adherence, look at the data and the records that are there, and drug accountability. All the usual things that we do.

The inspection will verify a number of issues. One is the consent and the ethical review committee issues, making sure that the subject's rights, safety, and welfare are protected. Now, we do not do foreign IRB inspections. So we get at the human subject protection issues like informed consent and how the ethical review was performed by actually looking at the records of the clinical investigator. But the records that we want to see include the actual information on the informed consent. The informed consent will actually have been sent as part of the package by the sponsor prior to the inspector going on the study. What's the ethical review committee's make-up, who is on it, records of what they did and how they did it are all available that way.

So although there's not an IRB inspection, there is a review of the IRB informed consent issues through the clinical investigator inspection. And by the way, this happens domestically as well but there is the addition of an IRB inspection also. However, the IRB inspections that are done in the United States are not tied ordinarily to pivotal data. So that the IRBs are inspected on some routine basis unless there are problems found with a particular IRB. So it's not really part of the constellation of the New Drug Application approval package. So the overseas in a sense is like the domestic in that respect, going for the clinical investigator that has the data that would be pivotal for approval.

This is just a summary of, I guess over the years, up to September of 1997, of the countries that we have done foreign clinical investigator inspections in. I believe this is for drugs

only. You will see there are about 26 countries and the list includes developing and developed countries. There is, obviously, more involvement of the developed countries, but there is a broad spectrum. The mix is there. And there are, as I said at the outset, more and more foreign clinical trials occurring. So back in the early 1990's there were between 10 and 20 foreign inspections of drug trials occurring. The figure for 1997 that I have is 76. So this is part of a trend that is increasing in drugs and biologics, but I don't believe in medical devices.

This in a way is a slightly misleading slide. It talks about most common deficiencies of foreign studies—non-adherence to protocol, inadequate records, inadequate drug accountability, consent problems. This is quite similar to the kinds of problems we will see with domestic reviews of clinical investigators. So, in a way they are similar. Some of the informal comments that I've heard from inspectors that have gone is that clearly a little more training of the clinical investigator might have helped in some of the non-adherence to the protocols, but, quite frankly, as you're all aware, that same complaint has been leveled against the system here, that there's not enough training and education for the clinical investigators.

This is what I promised you earlier as a slightly different issue, and that is that there is something called the International Conference on Harmonization dealing with drugs and biologics issues. It is an activity which is really not a conference, it is a series of working groups, with a steering committee and expert working groups, that has been in existence since about 1990 that is developing guidelines for safety, efficacy, and quality areas of the kinds of regulatory requirements that are needed for submissions for approval of products in drugs and biologics.

So far, there are about 45 guidelines that are under development and about three-quarters of those have been adopted by the tripartite groups involved—United States, Japan, and the European Union. This is where about 90 to 95 percent of drug development occurs, so although it's three countries or regions, it represents a very major portion of the drug development areas. The secretariat for this is the International Federation of Pharmaceutical Manufacturers Association, that is the international trade group that PHARMA is the U.S. representative of. What is very unique about this is that it is a joint industry and government regulatory authority effort which involves, for example, in the United States, the FDA and PHARMA, and in Japan and the European Union, similarly, it's the regulatory authorities and their research-based drug industry associations. There are observers to this process that include WHO, the European Free Trade area, and Canada.

The benefits of the development of these guidelines are quite substantial. The idea is to reduce the need for duplicate pre-clinical and clinical testing. And this covers, as I said, safety, efficacy, and quality as major areas. It maximizes the efficient use of human, animal, and material resources, maintains high scientific standards to safeguard public health, that is not negotiating down in terms of the standards, and fosters a worldwide collaboration and communication on important scientific issues. I would say, in particular, the fact that you don't need to repeat tests is an important ethical precept in this, so by being able to accept data from foreign studies that are done according to the U.S. ethical guidelines. And by the way, these do include the Good Clinical Practices guideline, which is very similar and consistent with FDA's constellation of IRB informed consent, clinical investigator, and sponsor monitor regulations.

There is a global impact of the ICH on clinical trials. Consistency in trial design, a single standard for both conducting trials and reporting trial data, there is a shared understanding of how to analyze trial data and of clinical development principles. Getting at many of the issues actually that were discussed earlier with the group.

The Good Clinical Practice guideline that I mentioned is an extremely important one. It was agreed to by the three regions in 1996, it was adopted in 1997, and it's adopted through the *Federal Register* in the U.S. and the similar kinds of adoption mechanisms in the two other regions. It does provide for unified standards for preparation, for designing, conducting, recording and reporting, and archiving clinical trial data and information. And it provides a basis for auditing and monitoring of studies.

And what it does do is sort of set up a process-type requirement or guidelines that are very similar to all the FDA Good Clinical Practice requirements as well. So that, therefore, IRB and informed consent issues are quite consistent in this with ours. And frankly, the European and Japanese regulatory requirements increased really to reflect more of what we do.

And then, finally, you might think that this is elitist and only involves the drug development regions and countries. In point of fact, the ICDRA is the International Conference of Drug Regulatory Authorities; it is WHO's grouping of regulatory authorities worldwide. Well over a hundred different authorities are participating in this.

At their last meeting in 1996, the joint WHO member countries got together and came up with recommendations concerning the ICH. The first: Assist globalization of the ICH documents. Utilize the ICH guidelines when drafting WHO's normative global guidelines. That would be the guidelines that come out of WHO for things like Good Clinical Practices themselves, or Good Laboratory Practices, et cetera.

Integrate the ICH guidelines into WHO training and education. In other words, let all countries learn what is happening and incorporate those items in ICH that are the most relevant to their needs. It may only be the quality aspects, for example, of the ICH guidelines.

And then, finally, they said make ICH guidelines available on the Internet. This, of course, has occurred and they are widely available, both through the FDA, IFPMA, and others.

And I just mention this, to finish up, because I think it's a very important issue, especially with globalization. And while these are process issues primarily, and this is not competing with the Declaration of Helsinki, if you will, or the *Belmont Report*, it is extremely important as a process approach that's becoming more and more accepted worldwide.

We think it is extremely important; and, certainly, the preamble says they are supposed to be updated to reflect current concerns. I would just echo what you mentioned about the Declaration or areas that clearly need to be worked on and improved. So, we are hoping that will lead to an improved process. All I will say about that, which is a little more than you did, is that what is happening right now is much more open than any other time the Declaration of Helsinki has been realized over the past many years; and that the medical associations worldwide are really jumping into this and offering their views as to what they think needs to be changed and why. What is really interesting about it is that I noticed that the UNAIDS group had commented on those, and I

thought that was a rather interesting, somewhat surprising issue. Now, I understand perfectly why that occurred, and is, of course, very welcome. But it is an open process, and I think it is an important process. I think that when you are looking at the codes, the Helsinki really stands up as being an extremely important one, more so than some of the regional or national efforts I think in terms of its importance worldwide. Thank you.

DR. SHAPIRO: Well, thank you very much. Let me just ask a small question with respect to your presentation. You refer to inspected foreign trials. You mentioned a couple of times “inspected,” and that let me think, well, inspected versus noninspected. Now, is any trial, which is going to submit data to the FDA for some purpose, required to be inspected or not?

DR. NIGHTINGALE: Well, the approach is --the policy is to inspect only those foreign trials that are submitted that would be pivotal to approval. So, there are lots of data on foreign trials in New Drug Applications, for example, at FDA—a great deal of it. But the ones that are inspected by FDA are those that are pivotal studies.

DR. SHAPIRO: Also, I think it’s true from what you’ve said that any new approval by FDA from trials abroad would have had at least an inspection.

DR. NIGHTINGALE: Yes, that’s right. And it would have been looked at with all of the various criteria that were mentioned in the regulation.

DR. SHAPIRO: Yes, that’s very helpful. Yes, Ruth?

DR. MACKLIN: I have a very specific question, but it’s --I’m going to end with a broad point for the NBAC’s work. At various points, Dr. Nightingale, you referred to the informed consent problems, the informed consent process, inspection of the informed consent, the informed consent standards, etc. Now, there is something that comes up all of the time in the international arena, particularly when studies are conducted in developing countries--and this is both for WHO and UNAIDS. And it is the question of signing consent forms. I am not now talking about having a written form, because there is no country or region that says we should not write out the informed consent and present it. But in very many countries, unlike people in this democracy, and, perhaps, in Western Europe, people are very fearful of signing things. They are fearful of signing things because there has been a history of oppression; because they are afraid they are committing themselves to something; they don’t know who’s going to sweep in, etc. So, the resistance to signing consent forms has led to a bone of contention, and people have referred to what they call the United States Standards/United States Principles and other high-sounding words, when what we’re talking about is putting a signature on a piece of paper. Now, my question for Dr. Nightingale is when you do these inspections and look at the informed consent things, does the FDA care about the signing of the consent form? That’s the question. My suggestion to NBAC is: It would be very useful in the study of the international work to

distinguish between ethical principles and standards, on the one hand, and procedures. I consider signing a consent form a procedure that documents that a process took place. And I would not like to place the notion of signing a piece of paper on the same level as an ethical principle. And, yet, when people look in the international arena and worry about adherence to the United States standards, they say, “Well, the United States has this standard of signing a consent form. And if we don’t adhere to that, then we can’t get our research approved, and then we’ve got a problem.” So, my question or suggestion to NBAC is, perhaps, there should be a way of clarifying this and distinguishing clearly between what are the procedural requirements in the U.S. regulations, and what are really ethical standards.

DR. SHAPIRO: Thank you. That’s very helpful. Let me see. I’ll get back to you in a moment, Dr. Nightingale. But let me see if there are questions from the Commission, and then we’re going to take a break. Alex, do you have a question? Stuart, do you have a response for this?

DR. NIGHTINGALE: Yes, basically, it’s interesting. We do have that requirement for signing informed consent. It is a process issue. It’s not an ethical issue, in the sense its principles, that I would agree with you on that, are ethical issues. However, the ICH guideline, now with Europe, and Japan, and the observers and all, also go along with this as an important issue that you need to have a signed consent. Now, I know what you are saying that there are certain cultures where you don’t sign, or it’s very difficult to do. What has FDA done about that? I have seen correspondence between FDA inspectors and headquarters staff addressing this to sponsors saying these are deficiencies. Have we ever allowed that to occur? I really can’t give you the answer to how it’s being dealt with. But I think it’s a very good issue for the Commission to look at, because, clearly, there are cultures wherein even the individual is not empowered to do something like that. How you deal with that and ethical issues deserves some further review.

DR. SHAPIRO: Thank you. Eric.

DR. CASSELL: Well, I wonder how many times it happens that the FDA says, “We won’t accept this study. It doesn’t meet the standards,” or what negotiations take place. In other words, when inspectors go and do something, what happens when it doesn’t go right?

DR. NIGHTINGALE: A variety of things.

DR. CASSELL: First of all, is that a common thing to happen?

DR. NIGHTINGALE: Well, there is a series of things. First of all, in domestic studies, the compliance program used by inspectors is geared and tied directly to what the regulations say. So, they go in and they look at what’s happening, and compare that to what

should be happening. They also will look at protocols and procedures that are submitted as part of the application, and then they will compare what's happening, just like an IRB procedures document, and see how it stacks up to what it was supposed to do. Then the actual field investigators usually fill out a form reporting on what the findings are. That is submitted to headquarters and final action is taken on the situation. And the kinds of things that can occur range from anything from a warning letter to prosecution, depending on what the situation is. You can stop a person from -- you can disqualify a clinical investigator, for example, through a procedure from participating in clinical trials again, or you can place restrictions on a clinical investigator. But when you --the actual site visits are classified as to whether or not there is no action indicated; whether there is voluntary action indicated; or whether there is official action indicated. But as I said, with the foreign studies, since it's a different situation, for example, the key issue for, say, a foreign clinical investigator, really relates to the sponsor's ability to have the data used as part of the application. So, it's a little bit of a different situation. But, of course, as an enforcement agency, we have a wide range of things that we do, and they are done, including prosecution.

DR. SHAPIRO: Let me ask a follow up question. How common is it that you disallow data, foreign trials, because you think they have failed to meet the requirements that you laid down, not only the scientific requirements, but requirements, for example, to protect human subjects that you have adopted?

DR. NIGHTINGALE: I really couldn't answer that here. And it's a very difficult one to --I think we would have to do a survey within the agency on that. And I --although I tried to be as brief as possible on some of these issues, that's one that you really have to talk to different division directors, and see what the experience is.

PROF. CAPRON: Can we request that information then? You have 215 international inspections?

DR. NIGHTINGALE: Yes.

PROF. CAPRON: Is that right? Out of the 215, how many resulted in a refusal to use data because there had been a lapse in the human subjects protection standards?

DR. NIGHTINGALE: I would have to go back and --I could use that as an example.

DR. SHAPIRO: Well, we would appreciate information like that, if it's available to put together.

DR. NIGHTINGALE: All right.

DR. SHAPIRO: Steve, then Alta.

MR. HOLTZMAN: Dr. Nightingale in his presentation said that the reasons for rejection of foreign trials were similar to those for rejection of domestic trials. And so, if we are going to seek this information, and we need to get it for the domestic as well. Alta.

PROF. CHARO: First, forgive me if this has already been said. I am suffering from multiple time zones.

DR. SHAPIRO: Caffeine is not strong enough to overcome this.

PROF. CHARO: It never is at these meetings. You need to have somebody come with the stuff that comes in an espresso machine.

DR. SHAPIRO: Yes, I have to remember that.

PROF. CHARO: I appreciate the procedural rules that apply. It's the substantive rules about this study design that would or would not be applied by FDA that I am still confused about. Let's take both the AZT trials that were the subject of such discussion three or four months ago, and the vaccine trials that Dr. Macklin was talking about. Both are sets of trials that could not be pursued in the United States, because of prevailing norms of treatment. How would the FDA view the data from those trials were they to be submitted in the U.S., because a new application of that information had made itself appear in the U.S. context? Would the FDA be willing to accept data for trials that were designed that way, assuming that you had all of your various forms that had been signed, and you'd had various groups that had been consulted in the review process?

DR. NIGHTINGALE: Well, that's a very complicated question, in a sense.

PROF. CHARO: It's kind of a --I mean I thought maybe I had missed it, but it's kind of a bottom line --

DR. NIGHTINGALE: Yes.

PROF. CHARO: --in trying to understand substantively how FDA reacts to the foreign trials, as opposed to the procedural norms.

DR. NIGHTINGALE: Well, I hadn't said that. I think it's very -- it's the sort of individual -- it takes looking at the application, the trial, and everything that goes along with it, at the level of the division. So, it's not even so much as FDA perspective, it's --

PROF. CHARO: Right.

DR. NIGHTINGALE: --what's happening.

PROF. CHARO: But if we could --and I understand that you may not be able to commit anybody at the agency without having have them make this finding. But going back to those particular trials, in both cases, the fundamental dilemma is one that is analogous to the dilemma we face over and over on whether or not we ought to have minimum wage laws, where if people who are miserable ought to be allowed to work for 92 cents an hour, because it's the best thing they can find. I mean it's a classic dilemma of what to do against the backdrop of abject poverty. Have you observed FDA, either the Division of Biologics or the drug approval people (these are two different examples, one biologic, one drug)—reacting to this dilemma, in which they have the procedural reviews by the appropriate parties, they have got the technicalities of consent adhered to; and, yet, there is at the center of it a question about whether or not we are willing to allow people to be exposed to certain kinds of choices. Have you seen FDA react to this dilemma in the past? And, if so, how has it done so?

DR. NIGHTINGALE: I mean I have been present at debates about some of these issues, in a sense. And I think the people at FDA are enthusiastic that the Commission would be looking into some of these issues. But I don't think I could give you a definite answer about that.

DR. SHAPIRO: Thank you. Well, let me suggest that we take a break. Let's try to keep it to ten minutes. [BREAK]

**Basic Protections for Human Subjects in International Research: Marjorie A. Speers, Ph.D., Centers for Disease Control and Prevention (CDC)**

DR. SHAPIRO: [Dr. Speers Introduction - inaudible]

Dr. SPEERS: [Inaudible]...and access to health care is limited. Public health infrastructure is weak in many of these countries; that is to say, that in many countries these -- they do not have systems for collecting national data on diseases, as we have in this country. They do not have clinics necessarily available. They do not have the medical supplies, and so on, that are often needed for treating even the most basic conditions. I'd also like to distinguish that the difference often lies in economics, and not in scientific, or in the ethics arena. And what I mean by that is of these 50 countries that we work with, only between three and five of them do not have an ethics committee in place. In the other countries, they all have an ethics committee that we have worked with. And those ethics committees in those countries aren't lacking necessarily in their understanding of ethics and their practice of ethics, nor are they lacking necessarily in their ability to provide scientific and peer review to protocols. Another distinguishing feature of many of these countries that we work in, is that we are working with people of color, which makes it somewhat different from the situation often in the United States, and often opens up discussions about exploitation for the research that's conducted in these countries. May I have the next overhead please? In this next overhead, what I have listed for you

are the various diseases, and conditions, exposures that we are studying in these countries. And I have put this up there for a couple of reasons. One is to give you just a very quick sense of the breadth of research that CDC is involved in internationally; also to point out to you that we are dealing with, in many cases, global problems that when we look at issues around HIV, tuberculosis, other sexually transmitted diseases—these are global problems. They are not problems that we just have in the United States. In addition, you can see that many of the conditions that we work on are infectious diseases, infectious in nature. They are diseases or conditions that do not exist in this country. In fact, many of you may have never heard of some of the conditions that are listed here, which allows me to make the point to you that the research that we conduct is research that is relevant to the host country. And I will come back to this point and make this point again later; but that when CDC collaborates on international research, it is because it ultimately benefit the host country for that research to have taken place. Next one. I want to talk a little bit about the characteristics of our collaborations. Generally, when CDC conducts research in a foreign country, it is as the result of a relationship that CDC has developed with the Ministry of Health in the foreign country; that is to say, that it is a government-to-government collaboration, one in which CDC has been invited in. And, generally, what this means is that decisions that are made about research are not unilateral decisions; that it is both the government of the host country, as well the CDC that is making decision about research design, methods, data analysis interpretation, and so forth. In cases where we do not work with the Ministry of Health, we then generally are working with an NGO, a nongovernmental organization. Very rarely does CDC work with a university in a foreign country. It is generally, as I say, with an NGO. That will usually be in a country where we may not have diplomatic relations; for example, in Cuba, or in Nigeria, where the U.S. Government is not able to work directly with the government of that country, we will be working with an NGO in that type of country otherwise, we are working with the Ministry of Health. Secondly, another characteristic of our collaboration is that we have usually not given a grant, a cooperative agreement, or contract to the foreign country. The funds that are used to support the research either come from another U.S. organization such as USAID, who funds a lot of the research that we conduct in foreign countries, or may come from the World Health Organization, or from the foreign country. Some funds may come from CDC to support salary of our staff, which I will talk about in a minute. But it is generally not the model where we have provided a grant to a foreign country to conduct the research, which leads me into the last point, which is that in virtually every study that we have ongoing, we have on-site investigators involved in the study. They generally fall into one of three categories. One may be that we actually have a field operation going on longstanding in the country, such as in Thailand or in Cote d'Ivoire. We have had a field station there for over a decade, where our researchers work side-by-side with the in-country researchers. If it is not that situation, then it is a situation where we will have a field assignee assigned to the Ministry of

Health in the country, who essentially works as an employee of that Ministry of Health involved in research, the third situation is where we will send investigators in for a short period of time, for six weeks, for two to three months to conduct a study, and then they will leave and come back. It is very rare for CDC not to be directly involved in conducting the research by having investigators in the country at the time. This means that for many of the countries where we were, we have had a long-term relationship with the country, and we expect to continue to have a long-term relationship, and to help that country develop its public health programs, its program health research agenda, and its capability to conduct public health research, and to implement public health programs. Move to the next overhead. I'd like to talk a little bit about characteristics of the research in which we engage. The first, as I said earlier, is that the research that we undertake is relevant to the host country. It has relevance to that country, and it is undertaken to meet some type of local need. The agenda for research is set by both the host country and by CDC. The research is generally part of a larger public health program collaboration; and that is to say that often when we negotiate a working relationship with a Ministry of Health. What we are negotiating is a working relationship to help them develop their public health infrastructure, and to implement public health programs nationally within that country. Research will be a piece of that, and is undertaken generally for one of two reasons, which I have highlighted here as well, which is, it may be undertaken to help us better understand a particular condition; that is, maybe the problems of the condition, or risk factors associated with it, so that the results may be directly fed back into the program; or the research maybe undertaken in order to set policy in the country; and that is to say, that before the Ministry of Health is willing to implement the public health program, it wants to have information that will help it then set the policy to move forward. The next overhead. When we engage in research with foreign countries we follow, as I mentioned earlier, the Federal regulations for the United States, which is 45 C.F.R. 46, that means for all of these host countries, we have negotiated for these countries with the Office for Protection from Research Risks approved assurances for these host countries, that is, for the Ministry of Health, and those Ministries of Health have ethics committees. Those ethics committees meet the requirements of the U.S. regulation, and they review protocols according to our regulations, as well as according to the ethical guidelines that are followed within the host country. The CDC IRB approves the protocol as well as the host country ethics committee approves the protocol. CDC has four Institutional Review Boards in Atlanta that reviewed these international protocols. On each of those IRBs, we have members who have had international experience. That means that they either themselves have conducted international research, or they have served for some period of time living in at least one foreign country. The other thing that we often do before we conduct international research, is we do what I have listed here as some preparatory studies. Studies may be a bit more formal than what I mean here. But in many cases before we have gone --we go in and we conduct a study, there will be meetings that will occur with the community.

We consult the community, and the community is actually the population from which we --with which we expect to conduct the study. Sometimes, we will be involved, for example, in conducting focus groups that will help us design the consent form, raise the issues that are going to be raised for recruiting individuals to participate in the study, try to address the issues that we know are going to come up and be issues that will be involved in recruitment and enrollment of individuals into studies. So, a lot of preparatory work often goes into developing the protocol before that protocol comes to the IRB at CDC, or the ethics committee in the host country. Okay, the next overhead. What I'd like to do very quickly is bring to the Commissioners several issues that we have encountered in the process. And I've actually divided the issues into three categories: The first is assurances; the second is consent; and the third is what I'm going to call standard of care. We have touched on many of the issues today, first, in Alex's presentation, and then in Ruth's, and then in Stuart's. And I am not going to go back over those same points and details, but just touch on some of them very quickly. As I say, one of the first issues that I want to talk about is the issue of assurances. Because CDC is a Federal agency and is governed by the Federal regulations, we are required to negotiate in the countries where we work assurances, assurances that are in compliance with our Federal regulations. You have to remember that we are working with sovereign nations -- at least, they perceive themselves as sovereign, and we need to be respectful of that. In requiring that they sign the assurance document, I believe those documents have been shared with the Commissioners from OPRR, we have often been accused of imperialism; and, in some countries, asking them to follow standards that they consider even lower than their own standards. Secondly, in these countries all of them follow and list as their ethical principles, either the Declaration of Helsinki, or the CIOMS guidelines for conducting international research, which is acceptable to OPRR and to CDC; that is to say, they do not have to list the *Belmont Report* or Federal regulations as their guidelines for ethical principles. However, what we do require is that they then follow the particulars of our regulations, which specify very clearly what an IRB, or an ethics committee needs to look like, and how protocols are to be reviewed, which can be different from what is required in the Declaration of Helsinki or in CIOMS. The second point that I would like to make, with regard to the Declaration of Helsinki and CIOMS, is that --and Ruth mentioned this --and that is, there is inconsistency between those two documents and within those documents. If you then put our documents, that is, the *Belmont Report* and the Federal regulations up as well, there are inconsistencies across then those three or four documents. Some of our regulations are silent on some of these issues, whereas, the other documents are not, and some harmonization across documents would be very useful for us who need to implement these documents if the Commission were to consider them. I just wanted to talk about ethics committees. As I mentioned, these countries do have ethics committees, and they do comply with our Federal regulation, in part, because we have required that they do that. We have had some countries that have refused to work with us, and some of

these countries have been the Arab countries, where they refuse to put a woman on the ethics committee. So, sometimes issues around the make-up of the committee, particularly, around having a woman represented on the ethics committee has been an issue for us, which has actually led to a breakdown in the negotiations with the country. The other is in defining a nonscientist, and how that -- how a nonscientist is defined. It is not as clear as one would, perhaps, think that it should be. The other issue around assurances, the two situations that we encounter, where this has been an issue, is in countries where there are -- where there is a civil war, where we have not necessarily been able to negotiate an assurance in a country where there is a civil war. And there has not been any other organization necessarily that we are working with, or that could take over where the government was working with. So, we have had in the last year five instances where we have had to stop research because of civil war, where an assurance could not be put in place. The other issue is in working with refugees. Who represents refugees? What organizations? And, again, how do we deal with this issue of assurances, where there does not seem to be an entity for which there --for whom that person is in the role as a collaborator, and, therefore, where we would obtain an assurance if we needed to do so? Next overhead. Issues around consent. We have touched on some of those today. I was actually going to mention the one that Ruth mentioned earlier; and that is, that a signature on a consent form has a very different meaning in some of these countries from what it has in this country. It is a big deal for some individuals to put their signature on a consent form. And it is important I think for some deliberation about that requirement, and that that requirement is not the same as an ethical principle --the ethical principle of informing, and then having a procedure in place for documenting that that has taken place. In many of these countries, we are dealing with illiteracy, illiterate populations. And so, again, around this issue of consent, there is the notion of a written consent, having the consent signed, many issues around having a consent process that is understandable to the people that is not different in many cases from issues that we have in this country. It is only highlighted more in some of these countries, where an illiteracy rate can be quite high. In some of these countries, the notion of getting individual consent is a notion that the U.S. is imposing upon the citizens of that country. In some countries, it is perfectly acceptable to get community consent, or consent from tribal leaders, or it can be consent from husbands, instead of wives. And we have had to deal with that issue. The issue of minors— that is, when is an individual of legal age to give consent comes up repeatedly in foreign country, where age limits are quite different from what they are in this country. Generally, we think of the age of the majority in the United States as being 18, but in some of these foreign countries it is much younger. What we have come across in the countries that were part of the former Soviet Union is that there is no concept of consent --of them giving consent. And so, when we have gone in to work in these countries and made a requirement straightaway that they must get informed consent, it literally freaks out the people who participate in this study, because it raises concerns

that there must be something wrong with this, if you are asking for my permission to do it; and that is to say, that we --that is, I don't want to imply that we don't want to move to that ethical standard, but what we need to build into this process is time for countries to change, particularly, those countries where for 50 years they lived under a particular type of regime that has changed now, and now we are working with them. They are now developing research agendas and studies and trying very hard to live by a set of ethical principles --of the ethical principles of either the Declaration of Helsinki or CIOMS and they want to rise to that standard, but it takes time to do that. The last one that I want to mention is the --in 45 C.F.R. 46, there are the eight required elements of informed consent. For the most part those can be implemented in foreign countries, but not all of the time. For example, we require that to be very up-front that we're conducting a research study and state that. In some African languages, there are no words for research study. And so, when we write consent forms, we translate them; we ask for that translations. We often get something back that looks different from what we had, not because it's a bad translation, but because we had differences. There are differences in language; there are differences in culture that are transformed into language. And so, a foreign consent form does not necessarily -- is not necessarily deficient just because it is different. We need to be very sensitive to that issue. Some of the requirements that we do now. For example, we require in consent forms that we list the name of a research contact, and a human rights contact with a telephone number --can't do telephone numbers in a lot of these countries. And so, we have to look at ways that we can clearly implement the spirit of the regulations, if not the actual letter of the law. The last one --the last overhead I'd like to go to is to talk just very briefly about this issue of standard of care. This has certainly come to your attention as a result of the perinatal AZT trials. Do remember that CDC did conduct two of those trials, but that is two trials, or two studies out of the 120 that we have ongoing, and this issue of standard of care is an issue in most of those studies. Because in many of the studies that we conduct, what we are looking at is trying to implement interventions, whether it's drugs, educational programs, HIV testing and counseling, whatever the intervention is, it is often an intervention that is below what is the standard in this country, but we are trying to implement something that is feasible in the developing country, feasible in terms of costs, and feasible in terms of their public health structure, infrastructure to implement it. The issue of standard of care has clearly come up regarding placebos, and I am not going to discuss that. I want to mention two other situations that we deal with. One is with screening and treatment; and that is to say often in studies we are not even able to offer the best screening techniques for diagnosing conditions, and we often cannot offer the best treatment. Many of the studies that we have going on now, that are looking at ways to prevent and control malaria, tuberculosis, we are not using the best treatment available in the U.S. to test in these countries. We are using treatments that will work, we believe are feasible in those countries. Secondly, often in studies that we undertake what is considered an acceptable outcome, in terms of health, often will differ

from in this country. An example of what I'm thinking of is, we have a number of studies involving looking at anti-malarial treatments, and this is looking at this treatment in children. In these countries it is acceptable for children to have very low levels of parasitemia; that is, to actually have the parasite living in them. And it is only when it reaches a certain level that it would then invoke treatment. That is not --would not be acceptable in the United States. We would not allow any child or adult to live with parasitemia; and, yet, that is acceptable. So, how we define healthy, if you will, differs as well. Which brings me to the last issue of how one defines normal healthy subjects, which is what we often use for controls in this country. Again, we adjust that definition because in these foreign countries people will live with conditions that are considered in that country to be normal and healthy. So, this issue of what is the normal healthy subject or control also differs. I'd like to end by asking the Commission to consider four issues, if you would --or at least raise them for you to consider. One of the issues that we would like the Commission to consider is in international collaboration, where the United States organization, in this case, CDC, but it could be certainly more broadly any -- the U.S. organization follows 45 C.F.R. 46, and the host country is following one of the other accepted guidelines, Declaration of Helsinki, or the CIOMS guidelines. Whether it is appropriate for the U.S. organization to defer to the code of ethics used in the host country; that is to say, particularly, when there is a difference between the guidelines, which ones do we use, which one should we use? And we would like to have some thought or discussion about that issue. Another is that when a foreign country follows a set of ethical principles and has an ethics committee, and has a comparable review process, should we require the assurance as is required in our Federal regulations? As I said, we have negotiated now almost 50 of these assurances. The concern that we have is that that has cost us, in terms of credibility and in trust, often with this countries. Because it is --as I had mentioned, it is often viewed as imperialistic of the U.S. to require this assurance. The third issue is, how do we incorporate the host country's cultural norms into our IRB process? Our Federal regulations clearly state that a country's cultural standards and norms should be taken into account, but doesn't go much beyond that, in actually telling us, or giving us guidance how we do that. And the fourth issue is actually a broader issue, that doesn't relate just to international research, but applies domestically as well; and, that is, the broader issue of how public health research is covered or is not covered by U.S. Federal regulations. Thank you.

DR. SHAPIRO: Thank you very much. We have only five or, at most, ten minutes this morning. We can come back to this after our session, but we do have public comments shortly. I don't want to keep those people waiting too long, but we have time for a few questions. Bette?

MS. KRAMER: It really was excellent. It really flushed out the problems quite well. But, apparently, though, your protocols --if I understood you correct -- if I understood the

--what was inclusive; for instance, when you come up against problems like consent issues, where you have got the husband's consent, or the wife, or the tribal consents for the entire tribe, which are contrary to our regulations, do you go forward under these instances? In other words, where there is a discrepancy between the local guidelines and U.S. guidelines; and if, in fact, your protocols do go forward despite these discrepancies, and a product emerges, such as a drug or a vaccine, what happens then when you come back and seek FDA approval, which I presume you have to get?

DR. SPEERS: That is actually two issues there. The first one is: What we tried to do is, we tried to strike a balance between what is the norm in the country, and what is required by our Federal regulations. So, that is to say, we try very hard, for example, when it would be okay, for example, to --in a country to obtain community consent, but we require individual consent to try to move the country to get individual consent, so that we will often do a combination or get community consent and individual consent, as well. In some countries, if they have refused to do that, then we have not done the research. I can't tell you how many instances as that occurs. I only know about it at the point where a protocol is going through our IRB, and then negotiations break down, and I know about that failure. What I can tell you are the number of cases that don't ever make it to the protocol stage, where there is a breakdown in those negotiations. Another example --and I don't want to focus too much on the AZT trials. But because I know you are aware of them, I will use them as an example. In those trials, because we were intervening with pregnant women, there is a requirement in our regulation that father's consent is obtained. And if you don't --and there are criteria in the regulations, where if it's not feasible to get the father's consent, then that's not necessary. That was a particularly problematic issue in Cote d'Ivoire, where about 60 percent of the women in that study are not married. So, it is often difficult to know who the father is, or to locate the father. The fathers do not come to clinics. Because this is a study about HIV—to go out into that population and try to find the father would then expose to that community the woman's HIV status, just the fact that she had been in that clinic. So, the way that we compromise, if you will, in that situation, is we have a consent form and process that allows for father's consent if the father is there and it is easy to obtain it. But if it can't be obtained, we do not go out and try to find those fathers to do it.

MS. KRAMER: And you go forward with the woman's consent alone?

DR. SPEERS: We go forward with the woman's consent in that case. Then your question regarding FDA, what do we do in those cases? In many cases, when we are conducting studies that involve a drug or a vaccine, we are not doing --we are not working with experimental drugs for the most part. These are drugs that are generally licensed for commercial use. And we may be using them off-label, perhaps; or we may be using them slightly differently. But our intention in doing that is not to change the FDA's regulation of those drugs, or the labeling of

those drugs. We are using them because we are trying to change policy in that country. So, often we are not reporting information back to the FDA, particularly, in the international setting, where that issue would come up.

MS. KRAMER: Thank you.

DR. SHAPIRO: Okay. Alta and Eric, then we're going to take a break. Alta.

PROF. CHARO: I'd like to take you up on your invitation to discuss the assurance process for a moment. And, first, I want to make sure I've got my facts right. I'm under the impression that the CDC seeks assurances in large numbers. It is my impression that the CDC process of actively seeking assurances is relatively new. I mean the two AZT trials that have been the subject of such discussion took place without any assurances in place. And you mentioned 50 assurances that you have gotten, but there were more than 50 countries out there. So, I'm curious about your experience in what happened last year seeking assurances, and your description that it occasionally has engendered criticism as being somewhat imperialistic. My understanding was that the assurance can be that the host country's institution is going to be following either U.S. rules or rules that are based on the Helsinki or CIOMs guidelines. In other words, there is a lot of flexibility in the set of particular rules that are used in this country, so long as they adhere to the basic principles that are shared by all of these various organizations and regulation statements. So, where exactly is it that you have run into this complaint about imperialism? Is it so serious that you find that you would actually like to get out from under the requirement that you comply with the regulations that have asked for years for you to have assurance?

DR. SPEERS: CDC has obtained assurances for --I just want to be clear on this. CDC has obtained assurances, and always has for the past several decades, for the domestic research. We did not obtain assurances for our international research until last year. It has actually been about one year that we have been obtaining assurances. Part of the reason that we did not obtain assurances is because there were basically two mechanisms that were available. And I think you've heard about multiple project assurances, and single project assurances. When you look at the language of those assurances, there are several things that you will notice: One is that they are very difficult to understand. The legalese of the language is difficult to understand. Secondly, in these countries where we work, those countries see themselves as equals -- equals to us, or we see ourselves as equal to them. And so, we have them sign a form that says you will do this, you will set up an Ethics Committee that's got five people; and you will have annual reviews -- because not all of them would do annual reviews on their research; that you will keep minutes, and you will keep records. It is the nitty gritty detail that goes into the assurance that these countries have found offensive in the past. We had been working with OPRR for two years prior to last year, to develop an assurance document that was more readable, and that was more

respectful of the sovereignty of these countries. And we actually did develop that document, and that's what we are now using. It comes under what's called a cooperative project assurance, which is kind of in-between a single and a multiple project assurance. And it's been specifically adopted so that it meets the kind of research that we do, and it binds CDC to do the same things that we are asking these countries to do, which has been a very strong negotiating point with these countries. Part of the difficulty for us was that when we began to implement assurances last year, we had almost 100 studies at that time in place that were not covered by assurance, and we went into these countries where we had been conducting research for ten years or more, and said, "We have to do this, and we have to do it now." They could not understand the C change, because this had not been part of negotiations. In many of our cases, our negotiations start initially with the State Department negotiating a memorandum of understanding between the country and the U.S. Government, and then coming down to us.

PROF. CHARO: I'm sorry. But why is this subject to the regulatory requirement of assurances prior to one year ago? But why are you subject to the requirements to seek assurances from one year ago, when --

DR. SPEERS: We were subject to that requirement. There had been discussions over the year with OPRR about how we should handle this and what the issues were. The advice that we had gotten previously from OPRR was conduct the research according to what's required in the regulations. They'll have Ethics Committees have reviews, and so on. Follow the spirit of the regulation, even though you don't have these assurances in place.

Dr. SHAPIRO: Thank you. Eric.

DR. CASSELL: It's really follow up and reflects the same thing. So what happens when you are in a host country, which is the only place that you can study the disease, and, yet, you are not satisfied with their protection of human subjects?

DR. SPEERS: I'm hesitating on that question, because I am trying to think of a country that has not had an Ethics Committee, or a --or a review process that either hasn't been up to our standard, if you will, if you consider our standard the high standard. I am very sensitive to that, because some countries think the U.S. standards are low --or has not been willing to change over some time, that are willing to change. And I have trouble thinking of a country that falls into that category, other than the former Soviet --countries that were part of the former Soviet Union. In that situation where it occurs, we don't do the study. I mean we either --we have either --we either have not done the study at all, or we delay implementing the study until we can get everything in place. We have several studies that have not started, and they may have been a year. They may have been postponed as long as a year, because everything is not in place yet for them to start. Let me give you maybe an example of what you're talking about as Cuba,

for example. We are involved in conducting research through Paho in Cuba. We do not have diplomatic relationships with Cuba; and, yet, studies that we're doing there is the only place in the world where these studies can occur because of the unique situation that exists; and, yet, the information we get from this information can be used worldwide. What we have negotiated is through the State Department, and with the Cuban government. We have negotiated a way that we will eventually be able to sign an assurance with Cuba. And so, we have, through now eight months of negotiation, gotten to where we can actually sign the assurance. So, we often take the steps within government that we need to make things happen. The problem is it takes time. And for many of this conditions -- for example, malaria, you have to go in and study malaria during the rainy season. So, there may only be a window of opportunity in certain countries over a three or four month period. If you missed it for that period, then you wait till the next year; or if you have the case of Ebola, for example, if Ebola breaks out again, we will, as we did the last time, we will go in and we will do patient care, and we will do research studies. If we miss the opportunity to do those research studies, then we have to wait until there is another outbreak in order to undertake those studies.

DR. CASSELL: That is precisely the point, which is here is an opportunity that it will disappear, and you won't get another chance unless there is another outbreak. What I'm trying to find out is how much are you willing to give up ethical standards for research in order to take advantage of that outbreak? After all, if you find something that helps the people with Ebola, what's the price --and the price is some deterioration in ethical standards, what difference does it make?

DR. SPEERS: Well, that is a very difficult question for us, and one that we would like the Commission to consider as well. Because in --if you look at the emergency situation, if the emergency situation does involve research, then I think you have to look at the ethical standards in two ways: The ethical principles that must be upheld; and the procedural issues, or the procedural standards. And which ones can --which ones are negotiable, and which ones aren't?

DR. CASSELL: Well, that's what I'm really trying to find out from you, which ones have been negotiable, and which ones have not been negotiable. Because you're in the particular positions -- it's not like a drug study. You're in a position where the disease, or the condition pushes the schedule, rather than your interest pushing the schedule.

DR. SPEERS: Right.

DR. CASSELL: So, I'm truly trying to find out what's actually happened. What I hear you saying is that most of the time, and, point of fact, and our host countries are equal or better, etc., but sometimes they are not. So, I hear you and I hope I am being fair to say, and

sometimes when we are not we have to proceed anyway because the urgency of this situation demands it. Is that a fair statement?

DR. SPEERS: That's a fair statement, although what I --I guess in the past year since we have been implementing assurances, which is one of the major --is potentially one of the major barriers for going forward with this study because of the length of time it takes often to negotiate the assurance. In the time that we have been doing that, the assurance has not been --there has not been a barrier to us proceeding with research. Even in the case where there was the outbreak of Grafalli fever in Kenya in February, we were able to get two protocols through an assurance approved by OPRR in a matter of days. So we have actually been able, in the one situation we've had, been able to move very quickly. Now, Kenya is a country where we have some history of working. In some of these other countries where our history is not as long, or there is a greater difference in where we are on ethical issues, we might either not be able to do the study. I can see where we would absolutely not do the study, rather than proceed.

DR. SHAPIRO: I have a suggestion, because we're going to have to end the questioning, to move to public comments. And we do want to have some time for lunch. It would be helpful, if possible, or plausible under the circumstances to understand rather more directly when you have a moment, or when your colleagues have a moment, illustrations of what kinds of standards are relaxed, in what kinds of situation - a very straightforward question I think. I understand the situations. Things are complex and require judgment. And I'm not trying to imply any moral values here, I understand these points. But it would really help me, in any case, to understand in what kinds of situations you make what kinds of sacrifices, from either our own regulations, or someone else's regulations. We don't have time to discuss it today, but that would be helpful. If I could make one editorial comment before we go to public comment. On this issue, there are two words, which are used over and over again here, both by us and others, which I think obfuscate the issue. One is "imperialism.". That's an insult of the well-known pedigree, and it just obfuscates the issue when we talk about it that way. The other is "equals." Of course, we are all in favor of equality, and we are more equals of each other, and so on. It has, as far as I can see, no implication for how you act. Because you either have some principles, or you don't have. The more you have some mixtures. It has nothing to do with whether one is morally -- declaring oneself morally superior to someone. I can disagree with someone, even though I don't think I am superior. I just disagree, and have a different set of moral values. It strikes me that we, ourselves, on the Commission, as well as others who talk to us, use these terms all of the time, as if that settles an argument, rather than enlightens the arguments. So, maybe in our own discussions, at least as we have discussed, leaving everyone else to their own devices, we will not use those words because I don't think they help us move the discussion forward. But I want to express my great thanks to all three presenters this morning. It was very, very helpful.

Obviously, you had spent some time thinking about this, organizing your presentations in ways which I found extremely helpful. I am very grateful to you for the effort, to say nothing of your ongoing work in these areas. You, of course, are welcome to stay. Any part of this meeting, if you'd like to participate. And we will have a chance later on to come back to other questions as time allows, because I know I'm cutting the discussion period short right now. But I do want to go to public comments. And I wanted to --I want to apologize to Tom. I had thought I was going to give him an opportunity to welcome us all formally. I went right into the session. I am going to give him that opportunity to say something about what options are for lunch in a few moments. But that kind of priceless information will wait following public comments. I think we have two people here this morning who have signed up. First on my list is Ms. Vicki Casagrande. --I hope I have pronounced that correctly -- from West Bloomfield, Michigan, who wants to talk to the Commission regarding the human telebiostimulation and control. Just let me remind you that the rules here are five minutes each person for public comments. And I'd ask you to keep it that, if possible, please. Thank you.

### **Public Testimony**

MS. CASAGRANDE: Thank you for having me today. You should all have a booklet that looks like this. I am here as a representative of victims of telebiostimulation and control resource, but we call it research. If you could turn to page --there is a definition just below for you who aren't familiar with the term. Telebiostimulation and control is the manipulation of biological processes by the use of --

DR. SHAPIRO: Excuse me a moment. I really want you to wait until we can really hear properly to give you an opportunity. It's still not working. It's still not working well.

DR. SHAPIRO: If you would like, perhaps, to sit on the corner here. You just use that and you just sit in the chair there.

MS. CASAGRANDE: Here at this one?

DR. SHAPIRO: Either one would be fine.

MS. CASAGRANDE: Is this better?

DR. SHAPIRO: Thank you very much.

MS. CASAGRANDE: Oh, no problem. I am here as a representative of victims of telebiostimulation and control. If you'll turn your page, I have a definition just for those of you who aren't familiar with the technology, and what it's all about. Telebiostimulation and control is the manipulation of biological processes by the use of telemetry. This technology tapped into the networks of research or targeted living organisms and input signals into the organisms

neuronetworks. Telebiostimulation and control were used in neural networks where the brain goes beyond simply recording thoughts as they are processed within the mind. Instead, technology is capable of placing thoughts, feelings, sounds directly into the mind and relaying signals to muscles, making them contract and/or release. A little bit about myself. I am an engineer. I have a masters degree. I have worked for one of the Big Three in Detroit. This technology is being used on myself, and subsequently I have lost a lot of my life. I am now working again. I'm a senior engineer for a small firm and trying to regain my life. And I'm here today to explain the technology and try to add credibility to what's going on out there. The next page is a listing of nonprofit organizations that are either existing or becoming existing, not something most mental patients usually do. We are forming. We are gathering together, and we will be a viable force if we have anything to do with it. The next couple of pages just give you references to those two other organizations. The next page, victims; very nontechnical, but this is what we have. This is how we document what's going on out there. Many victims receive audio communication, which is placed directly into the brain's neural network. As an example of this technology, the sound of a bird singing outside your living room window can be duplicated exactly when you're sitting down in a cave 200 feet below ground level. Victims are frequently subjected to sleep deprivation and dream control. Sleep only occurs when and for the duration determined by the controlling party. Also, a victim could be shaken with panic one minute, and may be asleep like a baby the next. It's that fast. This isn't something that happens in mental patients. It's like that. They control it totally. Muscles can be twitched or contracted, either lightly, or violently. If not to complicate matters, these effects can be placed into the brain as a sensation, meaning that the muscles felt like a twitch, but it's not really. And as a victim it's just one of the many things we go through. Victims have felt cold on an 80 degree day, and we have felt warm standing out in snow in shorts. It overrides everything you actually feel, and makes you feel what they want you to feel. As mentioned earlier, this is a scary party because you can ignore the victims but this is how it effects everyone. Thoughts can be placed unnoticed into the human mind. Also, current thoughts and past experiences can be read from the brains memory banks, and victims are often subjected to memory blockage, and to the retrieval or at the discretion of a controlling party. I realize this is a lot to say, and it's scary. But I'm here today to try and get through, and it needs to be dealt with. It's been covert. It's been under the rug. It's time. It's getting scary. It's going to take a lot of people. And the next page. This is to show you that this is believable. This isn't fiction. Walter Hess, back in the early 1920's to 1940's, started working with electrodes within the brain, not just on the surface. He was able -- and this is in a book that anyone can get from the library. I went to my library and pulled it out. "A cat's sudden changes in behavior startled him. The tiny surge of electricity in the cat's hypothalamus, a part of the limbic system, turned the gentle animal into a ferocious beast." Hess discovered he could also control the animal's heartbeat and breathing. He was controlling an animal's heartbeat and

breathing in 1940. He won a Nobel prize for this technology in 1940. Unbelievable? It's written, it's documented. José Deleagro -- Delgado -- I said his name right. Another scientist came along. He took up where he left out. He did the exact same thing, but by use of telemetry. Wires were not needed. He implanted, used implants. Started in 1950, he was doing this research. Suddenly, we have a break. We don't hear much anymore. Did somebody drop the ball? We're not looking into the mind? I don't think so. It's when an undercover CIA got into it. If you've heard of NK-ultra. It's not talked about. This telebiostimulation has been talked about. Usually, you hear about different things that the CIA tried to do next. I don't have a lot of answers. I just know what's going on. Next page. This is something that we have researched and found. The review of magnetic neurosurgery research. And over here more than 30 years ago investigators using magnetic fields to navigate clinical implants through neurovascular systems. It really ties in implants 30 years go. And now with the advent --and then you have to flip quite a few pages. With the advent of computers, the talking nanochips. If you're --I'm in the engineering field, so I'm very familiar with nano, microscopic. And you're talking computers, microscopic implants. Who knows? We think about as a victims group, we try to get imaging. We even wonder if that would help. Also, we're trying to work with anechoic chambers, trying to see if we are generating a signal. We must be generating signals. Obviously, we are receiving signals from somewhere else. It's hard to get someone to believe you. In groups we seem to fare better. But, again, it's the researchers, what they do first is get us flat-on-our-back broke, and then we scrounge up from there trying to recover what we had. Families often try to put us in mental facilities. You just spend your lifetime -- you spend quite a few years trying to recover. And to be honest, you only recover if they allow you --you wander. Again, the next page is just more proof of how much we know about the human mind. Here is the mapping. This is a mapping photo, but yet they don't seem to ever talk about thought, think you may have thoughts.

DR. SHAPIRO: I'm sorry to interrupt, but you have to draw your comments to a close. We're over five minutes.

MS. CASAGRANDE: Okay.

DR. SHAPIRO: If you could draw your comments to a close.

MS. CASAGRANDE: Outcome, I just know victims, present victims, we hear a lot from those from 1950's, 1970's. They have actual implants that they found in the '60's and '70's, which is believable. We are not finding many implants in ourselves, also believable. Another one is a letter in there from an actual official in New York, who said that we -- that she believes that she admits that the technology is out there, but yet it's classified and she can't discuss it. This is the most interesting thing I have is from the French National Bioethics Committee. I won't read over that, but maybe you've heard about it. They are starting to look into this, because of imaging technology. They're saying it can read thoughts, and it's possible to

read thoughts and I would like you to do the same. The last page may be a little blunt. As victims, we get very frustrated. I apologize for those of you who don't even know what I'm talking about. For those of you who do, please we need your help. I don't have -- I guess that was it. I have a bunch of just listings of names and some pictures of what's going on out there.

DR. SHAPIRO: Thank you very much, and thank you for the effort of putting the material together.

MS. CASAGRANDE: Thank you for listening to me.

We'll continue now with Dr. Tillman Bauknight from Cleveland, Ohio. He wants to address the Commission on the subject of AIDS as a form of genocide in the Afro-American community. Thank you very much for coming this morning.

DR. BAUKNIGHT: Commissioner and Commission members, yes, it's a pleasure for me to be here and be able to present a few of my concerns relative to biomedical ethics. I'm thinking of first the future. As we approach the Year 2000, the next century makes a millennium, a 21st Century. I'm concerned about the clowning -- cloning, rather, of --that is possible right now; and, certainly, about genetic engineering, organ tissue transplants, other areas like anti-aging studies, etc. Relative to organ and tissue transplants, I was very, very upset to find out that at my university of Howard University, director of Organ Tissue Transplants throughout the country, was the first one to suggest and recommend that we in America will allow the people on death row to be taken up to surgery, given injections, and, therefore, harvesting their organs, rather than taking them to the electric chair. Concern for me, as Afro-American, is that probably 90-some percent of the people on death row are black, and probably a large percentage of those people are innocent. So, this is a form of being able, I can see of getting good organs through the back door. And I would like to be sure that these issues are taken up in your deliberations. And I would like to be assured that there will be a continuous input from the Afro-American community on these kinds of issues. The next thing I would like to say is something I really would appreciate the comments that you just recently made. It's relative to being respectful of other cultures. And in that concern, I'm talking about I've heard many times this morning the use of word "developed and undeveloped nations." And what my mind goes to is countries like Mali, where they did cataract surgery quite a few years before any form of medicine like that was known in the world; but, yet, they would be considered an undeveloped country. So, in my mind I think it's a redeveloping country, if you will—Egypt, China, and others. So what to my mind, what this tells me, it's another form of racism, or a condescending approach to people not of your persuasion. And it's not a real fair description historically. These are passwords that denote something less than our peace. And I picked it very clearly, and I'm sure others did, too, in these countries. And I think that there will be problems relative to that, in all of the research that you're conducting. In reading and doing a lot of research, I've taken courses. I have a certificate in biomedical ethics at

Cleveland State, and I've been interested in this for some time. And I was --in reading literature from Hastings Institute about in Africa, it's considered really a fair game to do any type of testing. There is no need for informed consent, because the language is so varied and the population and education -- how nice. So, in other words, this is just a real nice playing field, where we the developed nations can go in and do all the testings that we want to do, ad infinitum. I'm also concerned because just recently, I think last week, or week before, I was glad to hear on the media that we have now taken three species off the endangered list. They were the eagle, the wolf, and the falcon. So, now there is no need for anymore Federal protection of these endangered species. I'm here today because the number one endangered species on planet earth is the black male, 18 to 30. He's not on the list. Eighteen to thirty Afro-American: they're unemployed, they're in jail, they're on crack. They're out of here. A whole generation of our people have been destroyed. Destroy the male, there is no continuity. So, between the jails, the gangs, crack, these items and forces are in the death, that's another good source of organs, because they are fresh and young and 18, etc. That's probably the best source of organs in America is the kids who are dying daily on the streets. But these people, Afro-American youth, especially the black male, is not on the endangered species list. Save Willie is, the owl is, but why not these people? So, when I look at that, then I'll look at the AIDS situation, the dilemma. What happened in my research, and I have papers on it. I was only able to bring in seven copies. We'll get more copies for you for tomorrow. But there are different forms of AIDS. The same word, there are three different diseases. One is the disease that Rock Hudson contracted. There you have the movie stars walking around with the red ribbon. You have Elizabeth Taylor, and others, who --or the guy with the piano. All of these entertainers of white persuasion, mostly Anglo-Saxon white males, homosexuals at first, they give the banquets. The second form of AIDS I feel is the type that Magic Johnson or Arthur Ashe had. These would be restricted to Afro-Americans with some money. The third type, the vast majority of people in America today with AIDS, are the people on the streets, the homeless people. They don't get parades. They don't get the red ribbons. They have what they deserve --same disease, different approach and consideration and treatment. When AIDS first came out, or, at least, publicly, or attention given to it, the Caucasian males primarily in an ACT-UP group acted up. And as a result, very much funding was directed to them, research was done, and their lifestyle forms were changed, and as a result the incidence of AIDS in that particular group has decreased dramatically. So, now what we have is AIDS of a different color, black and brown, women and children, but there is a different form of AIDS. Just recently our President, who commissioned you, refused to sign a bill with free needle exchange, which is the problem in the Afro-American and Hispanic AIDS community. Because it's not contracted primarily due to intercourse, or sexual behavior, it's contracted through sharing a needle due to economic factors. So, how that is best dealt with is give them some clean needles. They already are on the drug. But the clean needle exchange

program would at least reduce drastically the situation of passing that virus on to their wives at home, and their other partners. So this is why it's going into the heterosexual community, and the black and brown communities, because they are sharing the needles at the beginning, and then they go into heterosexual behavior. So, all I'm saying, I have researched all of this and pulled teeth. This is not what I do for a full-time living. But the point of it is, is that it's very clear to me that there is two different types, and there is something that's going on here, that is not into my interest. So when I look at it, and the other thing that I found, is that everyone who is sitting here at this -- can you hear me?

DR. SHAPIRO: Are you nearly through?

DR. BAUKNIGHT: Yes, I'm finishing.

DR. SHAPIRO: Thank you.

DR. BAUKNIGHT: Is because of informed consent. Basically, two classes, or two cases occurred to have the world deal with informed consent: the Tuskegee study, and then the other one was the German --the Nazi Germany situation during the war. But what happened is that the German or the Nazi perpetrators were tried, and convicted, and hanged, and etc. When asked what was the difference, why were not any punitive measures done to the people who instituted the Tuskegee study, who were governmental, public health officials? The answer was, "Oh, those were Nazis." So, I guess it doesn't matter. Thank you.

DR. SHAPIRO: Thank you. If you give us the material, we'll be glad to duplicate it ourselves. Will be very happy to make sure all of the commissioners all get copies.

DR. BAUKNIGHT: Thank you.

DR. SHAPIRO: Thank you very much. Thank you for coming here today. Let me now turn to Tom, who could both welcome us and give us some advice regarding lunch.

DR. MURRAY: Sorry, I wasn't here when you arrived. I actually could have been here in time, had they not closed down most of the lanes on I-71, between the airport and the university, but welcome to Cleveland. A dear friend of mine, also known to many of you, and, who, therefore, shall be nameless, once described a party he and his wife held. They thought it would be really fun to invite people from different parts of their life together to a single event. They thought this would be great fun. It was the worse thing they ever did. They hated each other, their people. Their different, as it were, families couldn't have less in common. Well, this feels to me a little bit like that, a party, but on the good side. It's not a party. It's a serious event, but this is bringing you together to a piece of my life. Esteemed colleagues, and friends of the Commission and staff, and my friends, colleagues, and fellow citizens of this part of the United States, and I hope that you will leave feeling enhanced perception, in fact, and respect for each

other. So, with that, lunch I gather is --we're on our own. There are a variety of restaurants within a couple of blocks from here, but there is also a cafeteria right downstairs. If we need to hurry, that's probably the best bet.

DR. SHAPIRO: Let me encourage the cafeteria option. You'll satisfy other requirements that you may have at some other moment. Because I do want to start at one. We're already well behind. We have a little leeway later in the afternoon. I'd really appreciate if you got back here at one. Thank you very much.

[BREAK FOR LUNCH]

### **Panel Report Update: David Shore, Ph.D., National Institute of Mental Health**

DR. SHAPIRO: ... take up the item that we skipped this morning in Alex's draft proposal and then move on to next steps in the agenda. So let me first turn to Dr. Shore. Dr. Shore, welcome, it's a great pleasure to have you here. Thank you very much for coming. He will of course be addressing the issue regarding reporting to us in the health update, and I think we all have some information to share on that. Dr. Shore.

DR. SHORE: Thank you very much. I appreciate the opportunity to present to the White House Advisory Commission. I attempted in Los Angeles to give you the very quick version; I don't think I did a very good job of it and I appreciate your giving me another opportunity and some time to walk you through some of the points that we considered and some of the recommendations that came out of that meeting. So that people...

Five and twenty years' service on their local IRB. Therefore, they have been wrestling with these risk-benefit, informed consent issues on a fairly regular basis. And we thought that they had some valuable experience to share and perhaps to help guide other IRBs as they seek to address some of these controversial issues.

The group in particular I think was helped by Gary Ellis early in the meeting, reminding us that the current Federal regulations already provide for the provision of additional safeguards by IRBs when potentially vulnerable subject groups are involved in the study. I was asked what was the difference between our approach and your approach and the way I would express it would be the difference between strategy, long-term changing laws, and tactics which was more our approach. Given the system as it exists today, how can we make it function better? How can we not depend on the Congress to change a law or the Department, etc.? Where do we have leverage right now?

These are the members of the expert panel. Ned Cassem is a Jesuit priest as well as a psychiatrist. We have experts on substance abuse, disorders of aging, psychopharmacology, representatives of the Alliance for the Mentally Ill and the Alzheimer's Association, and our

representatives of Arena and Primmer. Laura Roberts, to my knowledge, is the only individual who's formerly trained as a bioethicist and a psychiatrist. So, I think we had a very good group again, virtually all with extensive IRB experience. The presenters are I think well known to this group since you have had on your agenda in recent months several of these individuals. You've heard from Gary. Laurie is, of course, on the panel. Abel Shamo presented as did Alice Wichman of the NIH Clinical Center.

Let me start out with what I would consider some of our shared values--call them biases if you will. We've believed research on the etiology of these disorders is greatly needed. We do not know the etiology of autism, Alzheimer's disease, schizophrenia. And, there are no satisfactory animal models, so such research must involve human participants. Were we to confine such research to the least ill individuals, we would I think be doing a disservice to those who are most severely impaired because they are precisely the individuals who have the most to gain and have the greatest need for the benefits of research that will uncover etiology and new treatment targets.

We also felt that we needed to engage experts on the plentiful disorders and the symptomologies. Again, this was a matter of tactics. We thought that changing some of the laws involved might take a decade, and as you've seen with the sheep cloning, events have a way of overtaking our well-planned schedule, and our concern was that rather than try and focus on what the law should say in ten years, we needed to think about how we can better inform the IRBs that are considering these issues this year and next year.

And, finally, we needed to be very clear that serious abuses of human subjects have occurred, whether Tuskegee or Willowbrook, and we need, as the National Institutes of Health, to recommend steps that will decrease the likelihood that we will see a recurrence of such problems. In the past, as in Willowbrook, people have been subjected to abuses simply because they were compliant. In other cases, the informed consent process was not adequate; people were not properly informed of the risks or alternatives to research. So, the panel asked, essentially, how the local IRBs might best fulfill their responsibilities to protect research participants. Again, we looked at IRB discretion. We considered that, as the biochemist would say, the rate-limiting step because at NIH we do not fund studies that have not been previously approved by an IRB that either has a multiple-project assurance or a single-project assurance. Our process is somewhat different, and that you heard about this morning.

There were attempts to describe what we call points to consider when involving individuals with questionable capacity to provide informed consent. And the four topics on which we focused were the roles and responsibilities of IRBs, surrogacy, and advance directives. The assessment of capacity to consent, which you heard about through Dr. Appelbaum here previously, and the issue of conflicts of interest, and I'm going to touch on each of these in turn.

In terms of the recommendations that came out of this group--this is actually fairly similar to a recommendation that the National Alliance for the Mentally Ill has been talking about for the last several years. It was fairly clear that while the Federal regulations mandate five individuals on an IRB, one of whom should be from outside the institution, if we have an IRB with 20 members and we still only have one individual from outside the institution who represents the views of the community, the views of the consumers, the views of the families, that that outlook is at risk of being diluted and we felt that additional membership of individuals who can represent the views of the community, the views of the subject population, the views of the families would be very beneficial and could head off some of the potential problems that have already occurred. IRBs should be hearing from consumers, advocates, and others who are independent of the institution.

The second, in effect, follows I think from the first, which that, as was pointed out, IRBs already, as you'll see in the handout that's outside with 45 CFR 46 can already require additional safeguards. We recommended--the experts to NIH recommended a sliding scale such that the higher the risks, the lower the benefits, and the greater the impairment of capacity to consent the more safeguards should be considered. Waiting periods, monitoring, frequency of reporting--in particular, the IRBs should consider the potential value of an independent outside monitor either representing the family, the clinician, or the IRB in cases where there seems to be relatively high risk and individuals may be relatively impaired.

It was also pointed out that IRBs may or may not realize they already have the right to observe virtually all of these processes from recruitment through the informed consent process through the debriefing of subjects after a protocol, including the debriefing of family members. So, again, we recommended that greater scrutiny be given to studies that have relatively higher risk. We opted against the rows and columns and figuring in which category a particular project would be and then automatically applying a certain set of procedures. We decided that if the local IRB is really representative of the broader community, it should be able to judge those factors.

The issue, then, of surrogates--we believe that in many cases if an individual cannot understand all aspects of the protocol, a family member may be quite helpful in translating, if you will, the document; and whenever possible a surrogate should make research decisions reflecting the views of that individual when decisionally capable based on prior decisions. I think many people have recommended the best interest standard, but what that would do would simply be to outlaw research on people with disorders such as Alzheimer's disease since arguable the best interest is to leave that individual alone. And, therefore, in many cases we see individuals who expressed a prior desire to participate in research studies to see that their generation is the last that will have to suffer through this disease. But it seems that there is some risk that

individuals will have a right to say no but will not have a right to say yes.

In terms of assessment of capacity to consent, we are a long way from understanding how to properly address this. You've heard four different criteria. We came down in favor of a rather more strict criteria than is, I think, currently being used. We were concerned that some individuals can recite back a list of side effects or a list of facts about a given protocol, yet may be delusional about the study, delusional about their part in the study and how it might affect them, and therefore we believe that there should be priority given to developing instruments that can detect an individual's appreciation. Unfortunately, as we've heard in Los Angeles, that is arguably the most difficult of Dr. Appelbaum's criteria to formally address and we believe that NIH should prioritize this and the group recommended that the institutes do so.

It was also pointed out that comprehension for a person being capable of informed consent is not necessarily a yes-or-no, black-and-white decision. IRBs should also consider ways to enhance the individual's understanding and appreciation. You heard me talking all about giving small amounts of information repeatedly over time, about giving out a single sheet summary of the key aspects of the study every time the individual comes in to participate in part of the trial, and that may be considerably more valuable than having a six-page, single-spaced document in the individual's research file or lost in their home somewhere. Questions should obviously be encouraged. If we don't communicate better, we're just asking for additional problems in the future.

Conflicting roles, potential conflicts of interest--here we're talking about everything from financial to concern over mixing clinical roles and research roles, and I think these need to be addressed by the investigators and carefully considered by the IRBs since individuals with severe cognitive impairments may be more vulnerable to the therapeutic misconception.

Last, but not least, there was a view that this group felt that the common rule should apply to all human subject research involving individuals with questionable capacity for consent.

The implications--obviously the state of our knowledge concerning etiology is relatively primitive for severe mental disorders. Such research must involve individuals who are affected by these illnesses directly. Ethical research hinges upon informed consent, confidentiality protections, and adequate review.

We briefly considered issues such as placebo controls from washouts, etc., and decided that in order to really do that justice we would need another meeting and we are now planning such a meeting for the future to talk about research design and perhaps the talk following mine will lead into that.

In general it seemed that the advocacy groups understood the need for a better understanding of the underlying causes of these diseases, and they also understood that the biological vulnerabilities, as revealed by genetic studies for biochemical measures concerning who might best respond to a given treatment, might well not have direct benefits for that particular individual and in my attendance at these meetings it seems that research without the prospect of direct benefit of greater than minimal risk is of primary concern to some of the people who have spoken here in past sessions. We try to make clear that if we outlaw research that does not present the prospect of direct benefit and exceeds minimal risk, we may be making it extremely difficult to help the next generation of patients who will be admitted and the next generation of medications that will be used for their treatment.

Okay, I have three slides left, so I think I'm doing all right as time. Again, promising genetic paradigms. Designs intended to predict which individuals will benefit the most from which treatment generally involve either taking blood from an individual, finding a gene five years later which may or may not lead to understanding the etiology. We know that some individuals respond very well to certain treatments; others are troubled by side effects and don't respond very well. We would like to go back and understand the biological differences between people who respond very well to treatments and those who don't. Such studies would not be a direct benefit to those individuals, but they would potentially be of great benefit to the next group of patients who will come into the clinic with that same disorder. So, the concern was that we need to know why some people respond to treatment and others don't, and what genetic factors cause people to be vulnerable to the development of these severe disorders so that future generations of the same families do not continue to be at risk.

There was also a concern about--of the need to compare people who suffer from one particular type of mental disorder with individuals who have a different disorder or a different form. A childhood onset obsessive compulsive disorder vs. adult onset. There seems to be a trend toward narrowing the focus of distributive justice such that if we were studying a comparison population, that some people seem to be saying that research should be outlawed. If we go back to research of 30 years ago in which we compare chronically ill patients with healthy college students, we're not going to learn a great deal. We've discovered that until we can disentangle the effects of treatment of chronic illness, of hospitalization from the effects of the underlying illness, we are not going to be of the notion to understand the path of physiology.

And my final slide. Different degrees of research, risk, and decisional impairment should, the panel argued, lead to different levels of scrutiny and different levels of safeguards. Additional protections, everything from involving the family surrogates and independent monitoring may be quite advisable in high-risk protocols. But if we treat everyone who has a cognitive deficit as incapable of understanding research, that's really not accurate, and that's

really not respectful of those individuals. Scientific neglect of mental illness and substance abuse is not exactly beneficent and just and we, again, are trying to strike a balance maximizing the potential benefits, minimizing the risks, and comparing the risks of the experimental interventions with those that are intrinsic to the source being studied.

So, that is all I wanted to say. I left some time for questions. Oh, thank you very much.

DR. SHAPIRO: First of all, thank you for being here today and preparing this presentation for us, and thank you also for mobilizing the panel in the first place to consider these issues, which as you know we consider really quite important and very relevant to our work. So, we're very much the beneficiary of some of this and thank you very much for that. But let me move, now, to questions and let me turn to Dr. Childress so I know--I saw his arm up early in this discussion.

DR. CHILDRESS: First of all, I just want to echo the expression of gratitude to Dr. Shore and his colleagues for arranging the conferences our Chair has indicated, and also for giving NBAC members a chance to be at the conference to listen carefully to what was being said, and also to have an opportunity at the end of the conference to actually try to incorporate some of the suggestions into the evolving draft. So, we're very grateful for all of that, and also for the written statement now because some of the formulations here are illuminating in different ways, even than the earlier discussion.

One clarification, though, and then one question. The clarification has to do with the way in which some of the discussion in the work and some of your comments today seem to suggest that NBAC's drafts along the way and the discussion and the meetings have really put greater-than- minimal-risk research without the chance of direct benefit at risk of being outlawed. But really what we've done is actually said in most of the drafts that informed consent is required and if, for instance, as the document suggests, that you can have altruism combined with cognitive impairment, that is certainly true. But, we're suggesting that at least in the draft--we haven't voted on all this yet--that it may be very important to think about altruism in relation to people who can actually give voluntary informed consent. So that's a clarification, because as our drafts evolve we've not made efforts toward outlawing this, but rather setting certain kinds of limits on it.

The question that I have is this: I seem to hear in your comments today a little difference in tone from the conference, at least on the part of several speakers in the conference, regarding the question of possible regulations. There seemed to be at the conference a tendency to say no regulation unless they're mentioned in the guidelines. And yet in your remarks today there was much a more tentative approach and less distinguished strategy and tactics so it would

be difficult to bring about regulatory change, so let's go with guidelines. And then the recommendations we are considering--some would be for regulations; some would be for guidelines. But I guess what I was wondering is whether this document's maybe in contrast to some of the specialty conference, isn't now as opposed in principle the regulation, but rather as a more practical matter it'd be difficult, take time, etc. It'd more effective to go the direction of guidelines. Is that a shift in views?

DR. SHORE: The only one of our recommendations that I believe would require legislation is the last one, actually—of the application of the common rule to all research involving the cognitively impaired. None of the other seven, the other six recommendations would require regulation and then in effect all could be implemented now by IRBs around the country, and that's why we took that approach. Again, we're given a system which was intentionally decentralized and the ultimate authority was given to the local institution to citizens who live in that area to people who feel strongly about issues in that area, and we thought that in this current political trend brief

that it was relatively unlikely that a big-government solution was likely to soon be implemented and therefore we focused on what could be done now. I think that IRBs are having difficulty. The same protocol reviewed by three different IRBs might be considered acceptable, unacceptable, or in need of revision, and I think IRBs have been asking us questions, have been asking each other: How do you deal with this problem. And, that's why we brought together IRB members who have--we'll, when we tried this, this is what happened and this is what worked and when we tried this it was a disaster. So, again, we're trying to really provide more points to consider; that is, consider the risk, consider the degree of impairment, consider the prospect of benefit, and then bring in family members if you feel that the subjects are at risk or misunderstanding. Have an IRB representative present. You don't need legislation to require that. And again, the process can and should be visible throughout.

DR. CHILDRESS: I guess I'm unclear, then, would you have any objection if, for instance, through a change in regulations, IRBs would be required to include at least one voting member? I would say one could offer this guidance but one might also seek a change in regulation. DR. SHORE: IRBs are already required to include one voting member from outside the institution. It was our concern that of the five required members there is only one who is required to be from outside the institution at the present, and we now we see IRBs that consider a broad range of protocols and can take 20 or 30 members. And it was our viewpoint that the expression of views from outside the institution needs not to be deluded. One person has a hard time speaking and convincing 30 others and that people should be brought in with specific expertise when such protocols are considered. IRBs already have the authority to do that and they already have the requirement to have at least one person from outside. We emphasize there

be at least one.

DR. SHAPIRO: Thank you. I'm just conscious of the time, so with no disrespect to anyone I think we could try to keep questions and answers within three minutes or so; otherwise, they'll be considered speeches, which are out of order at this point in time. Mr. Capron?

PROF. CAPRON: I have several questions I wanted to ask you within the three-minute limit. Let me ask this one. The problems with certain kinds of psychiatric research in terms of design and informed consent have gotten a good deal of attention for a number of years. The UCLA study, the court opinions, and so forth. Has this led to changes in the protocols conducted or approved at NIMH? And if so, how do these factors that have drawn concern get flagged and taken into account in the decisionmaking process about which studies to conduct or fund? And how many protocols if any have been affected and disapproved because of such concerns?

DR. SHORE: Okay, I actually think I can answer that in three minutes. The answer is that yes, since 1994 we have changed things a great deal. In fact, we sent out between 200 and 300 copies of the OPRR report to all of our investigators who were doing research that might have might have anything to do with the kinds of designs that were used at UCLA. That was our first step. We have seen considerably more IRB comments and concerns coded on the peer review process as part of the outside scientific merit review. Studies cannot be funded with an IRB concern until that's resolved between NIMH staff and OPRR. IRB comments--we routinely require they be addressed if a study's going to be funded. The third part was how have we changed the way we do business. Since I guess I'm the person responsible for doing that, I can answer that fairly clearly. I think what we have tried to do in the last couple of years has been to identify protocols that raise this kind of issue: Taking people off medications to which they have previously been responsive; prolonged medication-free intervals, especially in outpatient settings. And we have in many cases required the consent documents. In some cases, frankly required changes in the protocol. I've gone over to Executive Boulevard on many occasions. And we wanted to make sure that the consent documents explain clearly the risks and the alternatives so that if people wanted to participate they could do so, but that those risks were adequately described. And, in some cases we wrote paragraphs describing certain kinds of risks for certain kinds of studies and they were adopted, so we've been a lot more active. I would say I look at probably one protocol a month of new studies in that way.

PROF. CAPRON: If I could just understand the process a little more clearly. There was a time when what I understood from OPRR was that study sections (if I am using the right term) didn't see this as part of their review of consent documents or the human subjects protection issues as such, but occasionally those issues emerged from the discussion but weren't

really seen as an assigned responsibility. So, if I could just ask: Have the changes that you described in NIMH been accompanied by some formal directive to study sections about their responsibility in this regard, or has this been more or less what you are regarding as a heightened sensitivity in the community; and, secondly, is it only in those cases in which you see something fall into the categories of research that you mentioned that you requested consent documents, or are those now routinely reviewed either by the study section or by your office for either all experiments or all categories that you've set out someplace where we could see a listing of them rather than just hearing it orally here?

DR. SHORE: I think I can answer those also. I think it is a misconception that IRBs, IRGs, or study sections--either term applies--did not look at human subject issues. At least for the last ten years as far as I'm aware since I've been sitting in on study sections, there's been a requirement and informed--pink sheets—at the end of a section that refers to human subjects and therefore the reviewers are required to address that. Often reviewers ask to see consent documents--not always, in certain kinds of studies more often than others. And, so, if the reviewers want to see the consent documents, they can ask for them. They can take them into account and decide whether they're satisfactory or not. And then they can decide whether to code an IRG comment or concern regarding human subjects. That's been the case for at least 10 years as far as I know.

In terms of routinely reviewing consent, we don't maintain a repository of consent documents because very often they change each year. The consent documents--well, these regulations haven't changed in 15 years. I think it's--most of us who have been involved in research are aware that the standards by which consent documents are judged have changed dramatically over the past 15 years and that's why we specifically tell people not to take an old consent document that was approved by your IRB and assume that it'll be okay now, because there's a very good chance that it would be considered inadequate now. But we do not routinely look at all informed consent documents. What we do is we look at specific kinds of what we consider to be potentially higher risk studies.

DR. SHAPIRO: Thank you. Steve, then we're going to have to go on to our next--.

MR. HOLTZMAN: As Jim Childress said, the draft in its current state does not recommend prohibiting nontherapeutic research involving greater than minimal risk per se. It only effectively prohibits it in the case in which the individual subject is incapable of giving informed consent. My question to you is: If you were to look at, on average, a 100 protocols involving nontherapeutic research involving greater than minimal risk, how many of them require individuals who are incapable of giving informed consent?

DR. SHORE: Well, let me give you a good example which will probably--.

MR. HOLTZMAN: I'm trying to get my arms around the magnitude of what is potentially being prohibited.

DR. SHORE: Let me give you what I think is one very accurate example: research on the genetics of Alzheimer's disease. The studies that have been conducted thus far that have identified or applied different genes that seem to confer a substantial vulnerability to Alzheimer's disease have typically involved the study of affected sibling pairs--an older brother, a younger sister, etc. In that case, given the progression of Alzheimer's disease, it is almost inevitable that by the time the younger sibling develops diagnosable Alzheimer's disease, the older sibling is probably not capable of providing informed consent.

PROF. CHARO: I'm sorry--excuse me, Dr. Shore, but since all you would need to do is venipuncture, which is minimal risk--.

MR. HOLTZMAN: Most people have said genetic studies involve more than greater than minimal risk.

PROF. CHARO: This is--no, this is exactly where the discussions are, but in this particular case you have the disease already. You're already symptomatic, you've already been diagnosed, it's not new information. So, it's just the venipuncture.

DR. SHORE: I would agree with you that in my view, as a former IRB member, I would see a study in which looking at medical records and taking a tube of blood as long as alarming information is not passed on to the individual or the family might meet minimal risk criteria, might qualify for a waiver of informed consent, but not all IRBs feel that way and many of the people who've testified before this group seem to oppose waivers of informed consent. And, it was my concern that certainly earlier versions of your document seem to make it very difficult for studies in which, for instance, insurance discrimination, employability discrimination based on confidentiality issues might cause this, as Mr. Holtzman was suggesting, to be greater than minimal risk.

PROF. CHARO: I'm sorry. We're going to be getting into this tomorrow, obviously, so it has slop-over to the definitions, what--the content of the meeting of minimal risk, but to the extent that people have argued that genetics research frequently is nonminimal risk, it's in the context of fishing expeditions, in which you're looking at asymptomatic individuals and looking for markers for things that you think might predispose. It's not in a situation in which somebody's already symptomatic where they've been diagnosed. Anything that's going to be found is already evident, so that the research is not creating a new risk except to the extent that you're doing the blood draw. So I'm still--I find Steve's question about the magnitude of

experimentation that might be somehow cut off by the recommendations of this report to be a very good question--I would love to understand the magnitude of what's at stake, and yet I find this particular example perhaps not the most persuasive one for getting at that category of experimentation.

DR. SHORE: I'll give you another example: Consider individuals with certain forms of rapid cycling bipolar disorder. Some people respond very well to lithium; some people respond very well to anticonvulsants; some people don't respond very well to any of those treatments. It may well be that they differ in receptor subtypes and that a spinal tap might be necessary to detect such differences to predict which individuals in the future would respond to which treatment, that spinal tap is not likely to help that individual because that individual has already either responded or not responded. It was my concern that a blanket outlawing or making it so difficult that one would have to go to the Secretary of Health and Human Services to get a waiver, would in effect make it impossible to do such studies, and presumably the next cohort of patients could benefit from that information.

MALE VOICE: All right, let's--if there are some questions--I'll turn to you, Eric, but let's not try to settle all the issues now because we don't have time.

DR. CASSELL: It's a 10-second response. The way the report is coming out, those would be permissible studies given certain protections that don't presently exist, but they would be permissible studies so it would not be ruling such a study out.

DR. SHORE: I'm glad to hear that. I was very alarmed by some of the earlier views--.

DR. CASSELL: Particularly in the example you used where the question of capacity of consent in that particular example of manic depressive or--bipolar rapidly cycling, the issue of impaired capacity of consent is not as great as it is, for example, in Alzheimer's or in schizophrenics and so forth.

DR. SHORE: A person with rapid cycling bipolar disorder can be quite psychotic.

DR. SHAPIRO: We will have an opportunity to return to this question.

DR. SHAPIRO: We'll return to this question.

DR. CASSELL: We appreciate the input and we'll be discussing it.

**Psychiatric Symptom Provoking Studies: Donald L. Rosenstein, Ph.D., National Institute of Mental Health**

DR. SHAPIRO: Correct. Thank you very much, Eric. I appreciate the comment. Dr. Shore thank you very much as well. I really appreciate it as well as you're help in previous

Commission meetings. I'd like now to turn to Dr. Rosenstein, who will talk about a subject which can be described in many ways--psychiatric symptom provoking studies is the way it's listed in your agenda. Dr. Rosenstein, thank you for coming.

DR. ROSENSTEIN: Well, thank you very much for this opportunity. It's truly a privilege for me to be here to talk with you about psychiatric symptom provoking studies. The reason this research strategy is so interesting and challenging to me is that it kind of commands our attention on the scientific and ethical questions that are really at the heart of research with vulnerable subjects. What justification is there for intentionally producing distress in research subjects? What are our standards for adequate informed consent? How are risk-benefit determinations made? What is the nature of the subject/investigator relationship? Psychiatric symptom provoking studies bring each of these issues into bold relief and I think it provides an opportunity to really understand what the issues are in a way that sometimes gets confused.

My main message today is that like so many of the complex issues that your Commission is considering, judgments about these studies depend critically on why they are done, when they are done, with which subjects, under what circumstances. In short, it's the context of this research paradigm that is most important in the evaluation of the ethical aspects of them.

Before I get into the body of my talk, what I'd like to is just mention very briefly what my history is with this, how I got interested in the area. And I also want to publicly credit Dr. Frank Miller for--if you'll excuse the pun--for provoking me into taking a more serious look at the bioethics of this research paradigm.

Dr. Miller is a bioethicist and a philosopher, and currently serves on the NIH Clinical Center Ethics Committee and the NIMH IRB with me, and I had a collaboration with him for the last six or seven years. About four years ago he came up to me and wanted to have a discussion about some of the studies that he had seen on the IRB that were troublesome to him. And to make a long story short what he was bothered by was the concept of the person in the white coat taking someone who was sick and making them feel worse. And I think it's important at the outset to acknowledge that for many people, upon first hearing about these studies, there is a similar emotional reaction to this, and so it's--I think that there are very legitimate ethical questions and my hope is to put these studies in some kind of perspective and to offer some suggestions about how to evaluate them. I believe that you've been given a copy of the manuscript that we wrote, and I believe that that's why I'm here today.

Let me begin with an overview of what I want to say. First I'll offer a definition of what psychiatric symptom provoking studies are, and then briefly mention some examples of challenge paradigms in other fields of medicine. I'll then address the scientific justifications for doing this type of research. Then I want to move on to what I mean by the contextual and timing influences and, in particular, how they impact on the ethical considerations. And then finally I

want to end with some specific recommendations to investigators, subjects, and IRBs.

So, one definition of psychiatric symptom provoking studies is as follows: The administration of a psychological, physiological, or pharmacological challenge to elicit psychiatric symptoms for the purpose of identifying their neurobiological causes and consequences. Now, I think it's particularly important to keep in mind that the point of these studies is to model psychiatric disorders so that we can learn more about them. There is not very much inherent value in demonstrating that you can make someone anxious, make someone sad, make someone psychotic or more psychotic. However, I think there is compelling scientific value in identifying relationships between symptom expression and underlying neurobiology.

A second point I want to underline is...these symptoms are not unintended side effects. I think a lot of people, including investigators, can get confused about that. Any time a drug or other intervention is presented, there's potential for both intended, usually beneficial effects and unintended adverse effects. In symptom provoking studies, the whole point is to elicit symptoms that are characteristic of the condition under study. In this respect, psychiatric symptom provoking studies really did extend out of a tradition in medicine, I believe, of turning on or stressing the system in order to learn more about that system under dynamic conditions.

Now, I'm aware that this next slide may be controversial because I've listed some of the other challenge paradigms in medicine. But I hope you'll give me an opportunity to at least offer my opinion about the goodness of fit and the limitations of such analogies.

Just very quickly--one you've, I'm sure, heard about is cardiac stress testing to uncover angina. We're all familiar with that. Glucose tolerance testing. Tests of new analgesics. Electrophysiologic stimulation. Instead of putting a sock around the heart and stimulating different areas of the heart in order to identify areas that--where there may be a focus of arrhythmia, and then trying out different antiarrhythmics to try to suppress that focus. Sometimes flashing lights in front of someone with a seizure disorder is used to identify an area in the brain where there's a seizure focus. Certain kinds of bronchodilators have been used in testing pulmonary function.

Clearly, some of these examples are very well- established, validated, and safe diagnostic tests that are used in clinical practice. I'm not going to suggest that the psychiatric symptom provoking studies are at that point yet. I understand that difference. Some of these have had profound benefits in terms of changing clinical practice. Some have had less--you know, or more modest clinical utility, and some of these are purely investigational. For instance, in the endocrinology world, the standard test to provoke the hypothalamic pituitary adrenal axis is CRH. Well, it looks like in the investigational setting interleukin 6, when administered, is a much more potent stimulus for the HPA. Now, I don't know whether it's going to develop into a clinical test

or not, but there are certainly other examples in medicine where provocation is used to learn more about the underlying condition, and hopefully we'll at some point have more direct clinical utility.

So, again, the point is not to represent nontherapeutic psychiatric symptom provoking studies in the same light as validated diagnostic tests. Some may or may not develop into that direction. The point is that this is the way of thinking—again, in the tradition of medicine, where you stimulate a system under dynamic conditions in order to learn more about it. It's not unique to psychiatry.

I think a reasonable question is: Is there something fundamentally unique about triggering psychic distress, and I think that's a debatable issue and I would argue that to do some of these studies, this is the only way you could do it, but I think that there are legitimate claims that there's something a little bit different about the psychiatric distress, although other people would argue that it's not fundamentally different than making somebody short of breath or having angina or some other symptom expression of what they suffer from. I'm sure there'll be discussion about that.

For returning to psychiatric challenges, the scientific literature contains a great variety of symptom provoking studies. Some employ purely psychological provocation such as public speaking or mood induction, but clearly the predominant paradigm is to use the medication to induce the symptoms of the disorder under investigation. For instance, intravenous infusion of lactate or inhalation of carbon dioxide has been used to precipitate panic attacks within the clinical research setting. Tryptophan depletion has been used in affective disorders and a number of other conditions. You've heard about amphetamine, methylphenidate, ketamine to probe perceptual or cognitive symptoms characteristic of psychosis. Interestingly, scopolamine is an anticholinergic agent that impairs memory and is currently being evaluated for its potential as an early predictor of dementia of the Alzheimer's type. This is, I think, a good example because--and we now have agents that can be used to delay the onset of the memory impairment in Alzheimer's disease, and I think that it would be wonderful to know who is at risk early on so that interventions could be started sooner rather than later.

I think it might be helpful to go over in some detail one symptom provoking paradigm, and that's the tryptophan depletion study. In this paradigm, which has been used in a number of different conditions, mostly in major depression, the basic procedure is that if someone presents with a major depression and then is treated successfully with a selective serotonin reuptake inhibitor, a type of antidepressant, SSRIs --and I name that because the proposed mechanism of action is thought to be modifying availability of the neurotransmitter serotonin in the central nervous system. Patients will--subjects will come in and be treated with an SSRI, and if there's a resolution of their symptoms then under double-blinded conditions with a placebo-controlled paradigm, an amino acid drink is given. Either a placebo, which is in the red line--it's

kind of hard to see where it doesn't change tryptophan levels—or a specific amino drink which is designed to acutely lower tryptophan in the blood and hence in the CSF. What the point is, is to see whether there is a time-limited and brief—I'll talk about the scale in a minute--increase in depressive symptoms that then might be correlated with a variety of different neurologic measures, either hormones that are measured or perhaps some kind of brain metabolism scan.

This is the Hamilton depression rating scale, and just to put this in perspective, you know, numbers in the teens are usually kind of consonant with what we might see in a mild to moderate depression. I should mention that the tryptophan depletion study, at least in depression, seems to be a fairly specific probe in that individuals who have responded to an SSRI are much more likely to have a temporary increase in their symptoms than individuals who have responded to an antidepressant that has a different mechanism of action such as dzipramene, which is a selective inhibitor of norepinephrine.

So, then, the next question is why do a study like this? And I think there are a number of important justifications to keep in mind. One is that one of the best ways to illustrate that a particular biological factor actually causes something is to block it. This paradigm allows in a sense one way to look at whether you can first elicit a symptom and then have a very specific way to block it, and I'll show you an example of another paradigm in just a moment where that was what was used. The tryptophan depletion paradigm is an example. Again, it's made tremendous contribution, I think, in our understanding of the surrogate nerve mechanisms and mood disorders as well its implications for treatment. Clearly, if we can identify some sensitive and specific diagnostic tests for a variety of different psychiatric disorders, it would pave the way for intervening much earlier under different treatment approaches. While I will acknowledge that we're not here yet with any of these psychiatric symptom provoking studies, this is a very reasonable hope that if someone comes to see a psychiatrist right now with a major psychotic episode or major depression, there's precious little information that we have to decide which of multiple agents are really better for that individual person. The ultimate goal, I think, for many of these approaches is individualized therapeutics to predict who's likely to respond and who's not and whether there are underlying biologic predictors of different response or even drug toxicity.

Let me give you an example of one challenge paradigm that at least starts to approach this condition and I'll try to run through this quickly. What you have here is a scale turned upside down of sadness, and these are self-ratings of--mood ratings of a woman who suffered from severe premenstrual syndrome. Every month just prior to and through her menses she had profound sadness with suicidal thinking, and this was predictable every month, right here. She was enrolled in a study at the Clinical Center in which she received--it was a clinical trial where received, in this bar here, lupron, which is a synthetic GRH analog. It essentially shuts down ovarian functions temporarily, and what you see then is that in the period after she received

the lupron her symptoms went away. And, here's where the provocation comes in. Under double-blind conditions, she received--and this was randomized--either estrogen or progesterone, and what you can see is an exacerbation of her symptoms. Again, this is under carefully monitored clinical setting. There was a brief increase of symptoms here--less so with progesterone. Clearly, the study was not designed as the diagnostic test for her; it was designed to learn about the role of reproductive hormones in a well-characterized patient population under carefully controlled and monitored conditions. Nonetheless, what happened with this individual was there were recommendations at the end of her participation to her gynecologist with respect to what reproductive oral contraceptive agent we tried and which concentrations of estrogen and progesterone. For other women who didn't have such a clear response to suppression of the ovarian cycle, there have been a number of women who had previously considered pherectomy as a treatment for this and then no longer considered that. And so at least it's possible to envision a time when there might be an individualized characterization of someone's response. Again, we're not there yet.

So, really, the question I think for this group is: Under what circumstances are psychiatric challenge studies acceptable or not? And, this is where I think context and timing become particularly important.

Some studies simply can't be done without doing symptom provoking studies. For example, the brain metabolism studies through looking at provocation and kind of the neurobiological effects of different drugs with suspected mechanism of action that are related to the underlying path of physiology require a symptom-free and on-symptom state. You spend a lot of time, I know, considering a clinical state of subjects in clinical research, and this is clearly one of the most important aspects because it goes directly to informed consent. And, it's obviously one thing to ask someone who's in remission from a syndrome if they're willing to do a study that may make them feel worse temporarily and quite another to approach someone who's in an acutely decompensated state with the same request.

This is something that Dr. Miller and I have been thinking more about lately, which is how are symptom provoking studies as individual protocols connected to a larger research program? I think that there's a lot of potential for blurring of some of the important distinctions, and I'll say something more about that in a minute. But the basic idea here is: Are these add-on challenge studies that are being done when someone is going to be in a drug washout phase for other reasons, or are there design aspects of the study that are put in place specifically to allow the possibility of symptom provoking study? I think that the fact that most of these studies can be best characterized as nontherapeutic makes it particularly important to keep the individual protocol distinct from how it fits in with an overall program, which may be fairly characterized as expected-benefit participation.

The last point here is one that I also think hasn't been given as much attention in the literature as certainly I think I should, and that is: What's the relationship with the investigator? Is this a longstanding relationship, or is this a brand new and somewhat anonymous relationship? Is the investigator asking someone that they've known for many years to do something that they believe is mild and short duration? Or, is this a request that is not taking place within the context of an ongoing relationship?

This notion of the quid pro quo--I hope there'll be some discussion about this because I think that there is essentially a more or less explicit quid pro quo in much of clinical research and I personally don't think that there's anything in and of itself that's wrong with that. And, I think that--my hope is that increasingly, the quid pro quo can be brought into the light of day and discussed in a more straightforward fashion, and subjects can make a decision about whether they're willing to do something knowing that it may make them feel worse temporarily and is not going to benefit in exchange for participation in an overall program that may in fact be to their benefit. I'm sure there'll be discussion about that.

Now, I know that this then kind of leads directly into what the fundamental ethical issues are, and we spend a lot of time talking about decisionmaking capacity in the role of how to assess informed consent. I'm not going to comment on that right now. I do want to mention, though, that it is important to highlight this notion of therapeutic misconception and certainly it is described by Appelbaum and his colleagues. This is a common and significant problem in research subjects. I would just like to make a point here that this is not a one-way street. Investigators are certainly susceptible to a therapeutic misconception, and within the context of research programs, it might be a considered expected benefit. I think it's possible to blur the distinctions between procedures done with the research study that are intended to benefit a subject vs. those procedures performed solely for the scientific information to be gained. So, I think that when any intervention of no expected benefit to an individual is considered, investigators, subjects, and IRBs must be crystal clear on that point.

With respect to risk-benefit assessment, here's another area I think that frequently gets blurred, which is, people talk about something being beneficial to society or to the field of medicine or psychiatry as opposed to beneficial to an individual and I think that point is clear enough but I think that the bottom line is that everyone involved in these studies really needs to understand two things: One is that the purpose of the study is not to help; the purpose is to learn more about the underlying condition. The second is that--and this is also different than saying that this study may not be of benefit to you, which is typically how the language reads in a number of different consent forms. There's different meaning there. And the second thing everyone needs to understand is this: The symptoms are expected; they're not unintended side effects.

So, let's then turn to kind of what some of the real risks are and I think that it's

fair to say from the overwhelming majority of published studies of symptom provoking paradigms is that symptoms have been experienced before on a number of occasions by subjects so that I think it's fair to say that there is less distress associated with the 750<sup>th</sup> panic attack than with the first one. Now, that may not always be true, but certainly that's been my experience as an investigator, that the familiarity somewhat offsets the magnitude of symptoms that are sometimes seen.

Again, the idea here is to model the primary disorder, not to precipitate a full-blown episode of illness or significant clinical decompensation. Nonetheless, there are clearly published reports here of severe and more prolonged reaction. To my knowledge--and I'd be curious if anyone has any other information--I'm not aware of any published reports of kind of catastrophic response to symptom provoking studies in a sense separate from some of the things you've heard about with respect to washout studies, but I'll be anxious to hear what you say about that.

I know that there's also been some concern about the possible negative effect on the longitudinal course of the primary illness, and I'd have to say that at least to my satisfaction, the data are simply not available. There has been a clinical analog that's been postulated for kindling sensitization with respect to repeated episodes of major affective disorders or depression. But, again, simply provoking studies are not intended to induce a full-blown major depressive episode or a relapse of a major psychotic episode. These are intended to be temporary and mild, for the most part.

I also just want to mention here that even though the intention is to induce the symptoms, there are unintended benefits that are frequently observed by subjects participating in studies. And, I've heard from many participants--for instance with panic disorder--that having a panic attack in a setting of a carefully monitored clinical research situation, is very validating, rather than carrying around a notion for many years that there is an inability to cope with anxiety or fundamental weakness in character. For some people to experience having a panic attack with lactate under blind conditions but not with saline can be reassuring that the fact there may be some underlying neurobiology to this. I won't belabor some of the indirect benefits that can happen, but I think it's important to note.

So then, what's a reasonable approach for evaluating whether a given study is ethically permissible or not. I would argue that the only way we can do this is to look at the overall context of the study and that there are better and worse ways to proceed, and I think that it's important to look at what happens when clinical research goes well, not just when it goes poorly. And, I've a better and worse case scenario here on the left side, on the left and right side. So, obviously, it depends on how things are done. Let's assume you have a capacitated subject who is approached with consent on the front end of the study who understands this is not

therapeutic and likely to induce brief distress. There's careful clinical observation and follow up. I'm much more comfortable with that than if someone with obviously compromised capacity who is recruited during the middle of a washout or when acutely symptomatic, that if the study is presented as beneficial; if there's some coercion involved but there's poor follow up. So it's really, in my opinion, not a question of the ethics of inducing symptoms but really the overall ethics.

So let me just finish up with some of the recommendations that Dr. Miller and I put in our paper, and kind of just run through these.

I think the first and foremost point I want to make here is that the science must be sound—without valuable information, obviously the protocol shouldn't go any further.

Here is where design issues come in and are particularly important. I think that whenever possible washout placebo phases should be minimized, but in many people's minds there are conditions where they're essential, and when they are necessary for clinical trials when those situations using provocations under drug-free states should be contemplated. I think that there would probably be agreement that performing psychiatric symptom provoking studies, to take someone who's been stable on medication and then take them off medication for the sole purpose of doing psychiatric symptom provoking studies, would be inappropriate.

The investigators and IRBs need to be more attentive to inclusion and exclusion criteria. Who are the subjects that are going to be recruited for the study? Are these going to be subjects who have a first episode of an illness, or just going to be subjects who are treatment-refractory. Those on meds of those off meds. Subjects with a strong history of suicide or violence should obviously be excluded for high-risk studies unless there are really compelling reasons and added protection. Obviously, decisional capacity is a critical factor here as well as any consideration of whether there would be surrogate decisionmaking in this setting.

A balance needs to be struck here between picking a challenge procedure that is going to give you measurable outcome variables, something that is strong enough to produce symptoms but not so strong as to induce more distress than is necessary, and that I think isn't in a sense looking at the least effective dose of something that I don't think IRBs are always thinking about when they review these studies. I've already talked about informed consent somewhat.

And, finally I just wanted to say that my feeling is that the standard of clinical care and clinical research just doesn't have to be up to speed; I think it has to be better. And I think in many of these studies more can be done to provide for added protections, subject monitoring, follow up. And, my hope is that what we can do is we can devise a way to continue in what in my opinion is an important approach to research but in a way that pays attention to the issues and takes what we're doing right and can do better and minimizes what we could--what we're falling

short of. So, thank you very much.

DR. SHAPIRO: Well, thank you very much. We're very much appreciative. Eric?

DR. CASSELL: Well, I have a number of comments. The challenge study that you used as examples in managing although short-lived. There are therapeutic actions that can be taken if they get out of control, there all meant to lead to a treatment. It's an effective treatment, and they are physical symptoms. The symptom that you're provoking is not quantitatively the same as angina, for example. And if you don't--if you've worked with it so long that you don't know that anymore, that would be a distressing thing in and of itself. That happens sometimes, but those are different in tone, they're different in severity, they're different in the endpoint, and they're different in the point of the whole thing. So that's the first thing.

I want to pick up on quid pro quo for just a moment. It certainly indicates that a patient that you've cared for a long time is more willing to work with you in new ways than a patient you don't know. And they do that out of trust. I can remember a patient that we wanted to put in an experimental protocol who wouldn't even consent. "I know you wouldn't let anything happen to me doc." And that's quid pro quo. But the quid pro quo goes both ways, in fact. You can't let anything happen because the longer the relationship, the more responsible you are to that person that nothing happen to them.

And then, finally, you've given an impression of a degree of control. You don't say the probability is the symptom will be short; the probability is the reaction will be damped down. That's all you could really say, isn't it. You can't say absolutely. So, in each one of these things you give the impression that the symptom will be short; it won't be severe. That's not the case. The probability is.

DR. ROSENSTEIN: In the overwhelming majority of cases that is the case.

DR. CASSELL: Well--but "overwhelming" is a funny word. I don't know what that means numerically, but I do know what probability means. Probability means that sometimes it's not the case.

DR. ROSENSTEIN: That's true, but we have data on it.

DR. CASSELL: Exactly right. And when you set up ethical guidelines and things, they're not for when everything goes well; that's for when things go badly. We know everybody's good and true. It's, "Have they protected their subjects should things go badly?" So on at least three counts, your argument, for me at least, I find unpersuasive. I understand why you want to do it--it's the protection of human subjects that's the question.

DR. SHAPIRO: David?

DR. COX: I would like to applaud a point in your presentation and that's the first one, which is talking about the importance of the scientific design. I don't know a whole lot about ethics, but I know a lot about science, and to simply have a hypothesis isn't in my view sufficient measure for good science. To have a hypothesis that then has follow up consequences to it and things that you can do subsequently, that's a good scientific design. Now, I'm being vague, but I think you get my drift. It's an example of I wonder how a car runs so I'll go in and I'll hit it with a hammer. Yep, it doesn't run anymore. That doesn't tell me a lot about the engine. And, so that--that in situations like this where you can't actually predict what's going to happen, and sometimes it really screws people up. Looking at what the scientific validity of the design is extremely important. So, tell me about that. Who does that? Is it the people that do that kind of research? Is it independent review? Because this I think is a key, key point. I hear what you're saying. You're saying sometimes it's really important to do this. So, who decides when it's important on a scientific basis?

DR. ROSENSTEIN: I think it's a very important question, and I can only speak to what happens at the Clinical Center. That's my only direct experience. And, what happens at the Clinical Center is that the IRB considers that. And, in response to a question that was asked earlier, there has been a shift in the last few years in terms of the scrutiny of the science in the IRB. I think for a long time the only considerations were with respect to subject protections; and certainly there's been a culture change recently, which is, this needs to be very compelling to all of the scientists and laypeople around the table before we're going to go ahead with this. And there have been numerous suggestions about design changes, and about collapsing different phases so as to minimize placebo phases.

DR. COX: Well, I'll just say that while I see that as plausible, having the IRB make these kinds of scientific decisions—I am not very enthusiastic. I'm just trying to be supportive of what you're trying to do, which is to have some vehicle open for this kind of research in really critical situations. It would seem like to have a special group of people who weren't necessarily invested in that kind of research themselves, that this would be a very helpful thing without new regulations, but really paying careful attention to scientific design.

DR. ROSENSTEIN: I think that's fair. I wasn't quite finished. There's also a separate scientific review of each of the protocols that goes on. Now, I can't say that that's an independent group. It's certainly at the clinical center, and I take that point there. The scientific group you is not solely contemplated in the IRB.

DR. COX: I in no way mean this to be disrespectful, and if it comes out that way I don't want it to be, but often times in different fields, when other people don't agree with what

you do you start your own journals and have your own people do the reviews. And I think that particularly in situations like this--and it's true in genetics, it's true in psychiatry, it's true in a lot of things--to have, particularly in scientific evaluations for this purpose to have broad-based input I think is extremely important, and I think in many of these areas we tend just toward the opposite because it's very critical, and so it's very easy to get people who think like we do that to convince ourselves that this is really good science. So, those are my comments.

DR. SHAPIRO: Thank you. Alex....

PROF. CAPRON: I first wanted to get some clarification from you as to why you're talking about symptom provoking studies. You excluded washout studies. Because looking in terms of most of the points you made about having to have a group of subjects who are manifesting the particular symptom in order to study it and to see what levels and so forth and so on, the argument that we've heard from people who do that kind of work sounds very much like your argument. Is there an a priori for making this distinction between drug challenge and washout?

DR. ROSENSTEIN: I think there are a number of them. I mean, I kept them separate because I think they are separate, and part of the problem is that they get blended together because the challenge studies that in my opinion invoke the strongest responses and concern are those that are done in drug washout states, but that is far from the universe of symptom provoking studies, and so I wanted to--I think it's important for this group as well as for IRBs and investigators to keep separate what the specific protocol is.

PROF. CAPRON: Well, let me come around to my endpoint. At the end of your presentation I thought I saw the reason why you made the distinction. It's precisely because the greatest criticisms have been named at washout studies and washout studies have involved long-term consequences and suicide. And you're--so, your distinction didn't seem to me it was driven by an initial set of scientific characteristics but rather by trying to distinguish a subset of this field by provoking systems through drug challenges with people who perhaps aren't the ones that are controls--you felt it was a better form of research.

DR. ROSENSTEIN: No, I didn't mean to imply that. Obviously there are greater concerns with respect to informed consent and risk in some circumstances than others. I don't think one can make global statements about whether a given research paradigm is justifiable or not in a washout setting. I think there are a number of valid scientific justifications for learning and doing imaging studies when receptor occupancy is none as opposed to fully occupied.

PROF. CAPRON: You and I aren't communicating. I fully accept the notion that just as you could provide scientific rationale for saying, "We can learn good things, important things, and maybe even things that would satisfy scientists from outside your immediate field," as

being well designed to answer the question. By doing challenge studies, I think we would hear the same thing from people who “provoke symptoms” or provoke the states that you can image by washing out. I reached the conclusion that you would base your distinction based on severity; that is to say, looking at this range of things which you think have been lumped together you said, “Well, if I say I’m only talking about this part,” then I don’t have to worry about certain severe consequences, which leads me to my next question for you which is: Would you set any limits on research aimed at answering important questions about diseases that had otherwise frustrated scientists’ ability to offer understanding what’s going on and methods for treatment, and if so how would you set those limits?

DR. ROSENSTEIN: It’s such a vague question it’s hard to answer.

PROF. CAPRON: Well, I don’t think it’s so vague. Obviously one thing I’m getting to is do you think that there should be limits on washout studies? You’ve excluded them from your definition of symptom provocation.

DR. ROSENSTEIN: It’s a complicated, interesting area. I wasn’t asked to talk about the justification of washout studies and we could do that at another time. Some washout studies--I think there are very compelling scientific justifications for them, others not. Depends on the specific study. There are certainly some regulations that I think would be reasonable, and I mentioned one of them in this context during the study, which is I think that it doesn’t make sense to take someone who’s stable off of medicines for the purpose of provoking symptoms to learn more about it. It just doesn’t--you know, there are other examples, but I guess my point is you have to look at what’s the study, who are the subjects that are going to be recruited, what are the protections, what’s the level of informed consent, are these treatment-refractory subjects or first-episode subjects. You can’t make a judgment about whether they’re acceptable or not outside of the overall context; it’s not just severity of symptoms.

PROF. CAPRON: May I ask one more question? In part you answered one of your own questions, which I took to be a real question, not purely rhetorical. Does anyone know of any indications that there have been any long-term adverse consequences? Would you say that if we looked at--you’re at NIMH, is that right?

DR. ROSENSTEIN: Yes, sir.

PROF. CAPRON: If we looked at NIMH sponsored or conducted studies in the last decade, we would see as a uniform part of such studies a process for long-term evaluation of the subjects of those studies, because an absence of data is significant only if the data has been collected and you don’t find something...not if you don’t look for it.

DR. ROSENSTEIN: I think that’s a fair question. I’m aware of one study in

normal volunteers looking at one-year follow up after CO<sub>2</sub> inhalation in triggering panic attacks to see whether there were subsequent panic attacks and there were none, but I think you have a fair point. I don't think that--.

PROF. CAPRON: You don't think this has been a uniform part of all study design.

DR. ROSENSTEIN: I don't think it is, but I don't know the answer to that question.

PROF. CAPRON: Perhaps Dr. Shore could answer that?

DR. SHORE: I was just thinking in terms of drug washouts, that is going to be one subject of meetings that we're planning now. I agree with Dr. Rosenstein that it depends on how well a person's doing, on how long they're going to be off medication. Are they going to be an in-patient in the hospital? Or are they going to be at home? How much supervision do you have? How well have you explained to family and clinicians involved? That's why there are yes or no answer to that. I think the field has changed within the past five or ten years and that studies that might have been on an outpatient basis or in-patient studies that might have involved two-month washouts are now talking about two-week washouts and that, as I say, I think that there are some times—for example, when you start a new medication—when you need to be off the medication you were taking previously because we have no clue as to drug interaction when you start the medication that's just recently been approved.

PROF. CAPRON: I was restricting myself not to the washout studies but just to the challenge studies, and that was partly what you addressed in your panel, and I just wondered whether your panel--I didn't hear you recite it now. You said that one of the criteria that you were aware was important in looking at past examples, because you were clearly responding in part to problems that have arisen in the past. One failure to follow up with those normal volunteers or those psychiatric patients or children who were given challenges with various drugs to see what not just physiologically what's happening with that but what their behavioral response has been over the subsequent years and how they interpret that advance a year or a number of years later. Was it something you looked at? Were you satisfied that this was being well done?

DR. SHORE: Actually, there is some literature on that, but it's fairly limited. There have been some suggestions that exacerbation of symptoms may have long-term problems. It is certainly apparent that the longer a person remains--with schizophrenia, to which I'm referring--that the longer that a person initially remains psychotic before the person receives adequate treatment, the poorer the long-term outcome. That's why you don't see studies anymore that are doing long-term psychotherapy for years comparing that to medication. We already know the answer to that question. The answer is those people do not do well. There

have been studies that look at the question of whether somebody with chronic schizophrenia, having a fourth or six episode makes any difference to clinical reports five years later. The answer to that, to the best of my knowledge, is no. I'll send you the reference to that.

PROF. CAPRON: And how about with the normal subjects?

DR. SHORE: I don't know systematically that's been determined. I know that, for instance, one of the reasons that we're bringing together the meeting is that in the past, when the medications with which we were dealing were things like haloperidol that produces tardive dyskinesia or imipramine or elavil that has severe antipulmonergic effects, it was easier to justify balancing the risk of continuing on the medication with the desire to come off the medication and risk increased symptoms. As you probably know, 70 percent of patients who develop schizophrenia stop medications on their own within one to two years because they don't like the side effects. We are now re-evaluating it because we have new medications. We have this surge in urgent specific reuptake inhibitors. We have now the agent for antipsychotics. Later this summer, we'll have an additional one for that category, and that's why we want to look at the risk/benefit ratio because some people, myself and my institute director included, see that the risk/benefit is now changing for medication discontinuation studies. When the only drugs that we had were quite toxic and not tolerated well by most people, then it was a lot easier to justify discontinuing medication since patients were probably going to do that anyway. Now that we have better medications that people are willing to take for longer periods of time and don't, as far as we know, produce long-term toxicity-like problems with tardive dyskinesia or other movement disorders, I would agree with you that that equation is changing. That's why we're bringing together this meeting.

DR. SHAPIRO: Thank you. Rhetaugh and that last question.

DR. DUMAS: This raises a number of questions in my mind. One is, are we implying that it's unethical to do symptom provoking studies or wash out studies, and if so how do you rationalize that? Is it possible to assess precisely risk/benefit ratio and if you can't, under what conditions do you proceed with your research? There are a number of issues, I think, surrounding the studies that are being done with people who are mentally ill and I have a sneaking suspicion that we tend to look at them differently. If a person is able to give their consent—and I'd ask to think you about that because there are a number of studies that are done where the long-term outcome is unknown. You might say that about many of the studies that are done, that the long-term consequence is really unknown. It cannot be assessed really precisely a priori. So what is it about the symptoms provoking studies in psychiatric patients that gives us more concern about their protection, even if they--is it because by virtue of their psychiatric diagnosis we fear that they may not really be giving informed consent?

DR. SHAPIRO: Were you addressing that question to everyone here?

DR. DUMAS: Well, I was raising that question--I think that's one that we need to address. We either do it now or we may need to do it later, but it just occurred to me that our dialog and debate changes depending upon the category of patients that we're talking about. Now, we started out--we had been talking about people who have some impairment in decisionmaking, but not all psychiatric patients have the impairment in decisionmaking and yet we tend to discuss these issues as if they did.

DR. SHAPIRO: Well, I think, at least the staff tries to be very careful about that. That we can't just paint them all with one brush. Let's see if there's any response. I really want to get on to the report itself in a few minutes.

PROF. CHARO: I'll tell you, Rhetaugh, briefly for myself. The reason why I view this differently than other areas of research is that in most areas of research there's the possibility of harm. And your question is simply is the harm that you're intending to create within tolerable limits based on the scientific goals you have in light of their ability to participate in the decisionmaking to make it a voluntary experience.

That, to me, is somewhat different. It's on the same spectrum but it's somewhat different than the possibility of harm. It's unusual for us to deliberately do harm to people. And that is why I approach these differently.

DR. SHAPIRO: Other comments now? Because if not, we are running atypically late today, and with apologies to Alex, I'm going to suggest, one, that we take a five minute break—at least our break is on time—but then I want to go directly to a discussion of the report on the session involving persons with mental disorders, et cetera, because we just can't postpone that any longer. We'll get to the others as soon as we can and when we can.

Let's take a five minute break. Let's try to reassemble here precisely at 3:00.  
Thank you.

**Discussion of Staff Draft Report on Research Involving Persons with Mental Disorders Affecting Decision Making Capacity: James Childress, Ph.D., Jonathan Moreno, Ph.D., and Commissioners**

DR. CHILDRESS: [Request for names to add to list of readers of Commission draft report on research involving persons with mental disorders affecting decision making capacity - inaudible]

DR. MESLIN: We have the staff up and letters going out.

DR. CHILDRESS: Okay. Are there any questions for Eric on that topic?

It's presumably the sort of thing that we could incorporate results not only into a staff draft but even into a Commission draft, if we reach that point in our deliberations during this session.

You have on the first page of the memorandum several general items. Be sure to mention that to staff so that we can make sure we get the appropriate materials. The flowchart that's mentioned has now been updated and made, what shall we say, more complicated.

DR. CHILDRESS: I haven't had a chance to look at it yet. But we can come to that in the course of the discussion. Jonathan and staff have prepared that and we also have it available on an overhead so we can walk through that as need be.

The new section in the report on ethics in study design is obviously important and has already played some role in our discussions today. And then the other major change had to do with six and seven being merged.

DR. DUMAS: I don't know whether this should be on our list or not but it emerged just a few minutes ago, and that is the ethics of the purpose of the study, the type of study, not just the design but the purpose of the study.

DR. CHILDRESS: Good. I think that should come into play in relation to the issue of design justification and so forth, at least given the categories we have here, though it could be done in other ways. Let's make sure we get it in.

Okay. If we look at page two at the points for discussion, let's keep one other thing in mind as we work on this, and that is some of the recommendations we're making actually would call for changes in regulations, others would simply call for additional guidance for IRBs, and then there are still other levels of recommendation as well. So part of what is a matter of our discussion and special discussion with other groups, as came out in Dr. Shore's report from the conference in early December, has to do with even if we agree that something might be good, advisable to have, where do we want it to play into our process? Do we want it as a matter of regulation, or do we want it simply as a matter of guidance?

I would also note that the staff did a good job in identifying a number of the pages where particular topics are discussed, but there are also others, and so I'll try to mention some of those along the way if we need those for discussion.

I'll try to move us through this in a reasonable way. We want to spend as much time discussing any particular topic as that topic merits in our collective and individual judgment. But we also want to think about trying to move the report along.

Let's start with the topic that came up at the very end and then turn to the topic

that occupied most of our attention during the last session. The topic that came at the very end is the population this report addresses, and then, of course, the research design topic is the one we spent most of our time on.

The population this report addresses. That's already appeared, obviously, in the title which we have discussed several times. We have language addressing this in the text on page 2 and I guess we have a revised page 2 before us, do we?

DR. MESLIN: Let me just say a word. Alex was kind enough to jot his suggestions for revision down on a separate two-page document which has been distributed to you. Three-page document, I'm sorry. It says Chapter 1 and it's stapled and it was just recently handed out.

PROF. CAPRON: I would suggest that we try to be responsive to this question that Jim raises and we can get to that later.

DR. CHILDRESS: Thank you. But on page 2, on pages 12 and following, and then on the pages listed here, we have discussion in this draft of the population. And the question posed is are we satisfied with the description of this population? Keeping in mind that we are talking largely about mental disorders affecting decisionmaking capacity, that does not mean that those disorders affect any particular individual's decisionmaking capacity. That's a separate determination. But the presence of the mental disorders would trigger closer examination.

But are we satisfied that we have indicated in the title and in the description in the text the population we want these recommendations to address?

DR. DUMAS: I'm satisfied with it.

DR. CHILDRESS: Any discussion?

DR. BRITO: Well, Trish made a comment about the mention of delirium in here. I'm satisfied with it, but I'm not sure if we should address that right now because I'm not sure if that doesn't confuse it a little bit, on page 13 and 14.

DR. DUMAS: It says somewhere in here that although our primary focus is people with mental disorders, that we're not ignoring the fact that there are other conditions that can affect decisional capacity. So I think it takes care of your concern.

DR. CHILDRESS: On page 2 in the draft, we note that persons with mental disorders are not, of course, unique in being at risk for loss of decisionmaking capacity, et cetera, et cetera. And we also talk about children and why they're different from the group we're talking about here.

Perhaps we ought to pursue that one with Trish. I don't think she can hear us this

morning.

DR. DUMAS: Is her concern that delirium does or does not follow the rubric of mental disorders; it does or doesn't?

DR. BRITO: Her concern is that it shouldn't be separated out like this.

DR. SHAPIRO: Not directly relevant to this, but I thought the materials included in this particular draft which points to the fact that people suffering from other kinds of disorders altogether could have some problems in this area, really responsive to Eric's comments that he made last time, really improve this quite a lot. I feel pretty good about where that is right now.

PROF. CAPRON: I guess what's important to me is a concise statement of the interaction of the different factors that are going to be present to different extents with any particular patient, but which in a cumulative fashion are likely to cause problems. One is the kinds of illnesses that marginalize people in society, which make them difficult to deal with, which make them frustrating for physicians and others to treat, which often lead to their institutionalization, and where the kinds of research that we're concerned about are studies on their mental status itself, about their mental condition. And in this sense, they are different from patients whose physical conditions render them less able to make fully informed judgements than a person with no medical stresses in their life because of the very thing that's under study is their psychiatric condition.

When you have any one of these factors, you have a problem. For many of the patients who are most likely to be vulnerable to well-meaning or otherwise abuses, it's where these things come together—where they are institutionalized, where their condition is progressive, where their families and others are either absent or are not able to deal with them, or society is annoyed by their presence or takes no interest because they're no longer productive members of society, et cetera, et cetera.

I don't see that our report finally pulls these different strands—whether it's schizophrenia, dementias, deliriums, other conditions—together and ties them into what I would say is more the sociological as opposed to the medical context that has led to the long lists of problems that provoked this report. And that's still what doesn't quite come through for me. And you're right, as to that extent, there's a little bit of language in these pages that I drafted to try to get at that. But I don't want to get into those.

And it seems to me, even back in the introduction on pages 12 and 13 to the different categories, we are at great pains to say not everybody with schizophrenia is unable to make decisions about their medical care. And we say that point over and over again, I agree with you. But we don't seem to pull together why this group is particularly a vulnerable population.

DR. CHILDRESS: I think if I've heard our discussion over time, I think there would be general agreement that we ought to do that and that there are places, for example on 65, where we deal with institutionalization and so forth. But your point about pulling it together and getting everything out and seeing how the different variables may be relevant for decisionmaking, that would be very good to get that up front.

DR. MORENO: Could I just ask, Alex, maybe at some point, and I could focus on pages 22 to 25, which do attempt to do what you've suggested, but maybe we could see together how we need to improve those, beef up that section.

DR. DUMAS: I think it's very good to be as clear as we can be about what it is that makes this group vulnerable and give us concern about protections. But I caution that we not get into too much detail on specific aspects of this because my feeling about the document as it is, is that our salient points often are embedded in a lot of verbiage. So if you can keep that in mind, that we don't surround the whole thing with circumstances and miss the major points.

DR. MESLIN: Just as a point of procedure. Alex, is it your sense that the strands that you're referring to are here in the report but they are just not brought together early on?

PROF. CAPRON: Yes. It's a way of saying what Rhetaugh has said.

DR. MESLIN: Okay. Because I think the strands, if we look at 2, 13, 64, 22 to 25, and 149 to 151, they're there but they are strung out. And you'd like to bundle them, to use a computer term.

DR. CHILDRESS: That's an important editorial point. Good.

I'm just going to go through and assume that silence means acquiescence. So if anyone has any strong objections as we move along, be sure to express that.

If there is nothing else on population, let's turn to the topic on which we had the very important discussion earlier this afternoon. I think it was actually one of the most fruitful discussions we've had on this particular draft report. The big question that's being raised here is where we want to set the presumption in terms of challenge studies, and how those compare with what we want to say about washout studies and/or placebo controlled, and then a few pages are given there where we discuss these matters in the text and I would just add also pages 10, 148 and following, and some others where there's some discussion. But, of course, the critical ones are on ethics of research design. And also keep in mind Rhetaugh's question that the purpose also is important, and any issues about that we can work into this.

DR. DUMAS: I had a concern that we make sure to address the purpose of the study. But I note under this topic of Research Design the concerns that I have are here, they

would be treated under this topic. And it has to do with wash-out studies, and what do they call those others? Symptom provoking studies.

DR. CHILDRESS: Alta?

PROF. CHARO: Although I'm certainly open to an alteration of these views, it strikes me that the way in which we generally assess any kind of study, that is looking at the magnitude of the harms that could occur and the likelihood that they will occur, which is what we generally understand as risk, as measured against the need for this study, is a perfectly acceptable way of handling all these different formats, whether it's placebo controlled, standard therapy controlled, washout, or challenge.

I think that in a context of challenge studies it's fair to say that the likelihood that somebody is going to experience a disturbing event is pretty high, because that's the whole point of the study, but the actual magnitude of the harm that that represents is going to be quite variable depending upon what kind of challenge study you're doing and the kind of person you're working with and their familiarity with those symptoms. And that would be part of the kind of discussion you'd expect from a sophisticated review body in the course of figuring out how to assess the risk and then look at whether or not these studies are genuinely needed or if there are less risky alternatives to achieve your goals.

For that reason, my instinct is that rather than create more categories, we would want to subsume this under the more traditional risk-benefit, risk-necessity balancing, and we would want to perhaps in the form of guidance—and we'll talk later about guidance versus regs versus both tracks—use these as examples of the kinds of studies that go on and the elements of the discussion that are necessary in assessing the risk of the study.

PROF. CAPRON: I think that I take a stronger view on the washout studies. I recognize the wisdom of what Alta says when she says that things are going to end up being contextual. If you're washing out someone who has migraine headaches or something and the risk is another migraine headache, it's different than washing out someone who has schizophrenia or some other psychosis and the risk is a full-blown florid episode of psychosis.

What I noticed, however, in Dr. Shore's answer to these questions as we were asking him, was the problem that I think seems to be unavoidable in this area, which is when you get to do something that seems as adverse to the interests of the person you're doing it with, you begin to develop rationales. His argument today to us was that he would be more reluctant to engage in, or approve, or think it was all right to do a washout study now that there are drugs which have fewer adverse side effects.

Now, when you think about the logic of that, what that was, as far as I could see,

is that it wasn't necessarily without benefit to a person in the old days of those other drugs to go into a washout study because the adverse effects of the drugs were such. But that's simply the researcher buying into the therapeutic misconception.

People were not being put into those studies because of an individualized assessment that in your case the side effects and so forth from the drugs were such that you would be better off on a lower dose, or no dose, or let's see if you overcome your schizophrenia and you don't need this drug anymore, or whatever the rationale would be for doing it. It was simply that we need patients who are in this episode to see how we intervene to pull them back from it, how quickly we can do that, or what their brains look like, or what their blood levels look like when they are in this, whatever the rationale was. It was the scientific rationale, not for the benefit. But it was darn hard for an experienced investigator to own up to that.

Which then to me, on a research subject side would say, why would anyone in their right mind who is being successfully treated for psychosis agree to go off and become psychotic again. Given everything that anybody has said about what it's like to be in that condition, particularly if you've been brought out of it and can view your behavior then and what it was like and how distressing it was for you and everybody else, it —

PROF. BACKLAR: Trish Backlar has her hand up.

PROF. CAPRON: Well, let me pause and let Trish intervene.

PROF. BACKLAR: Okay. When you finish.

PROF. CAPRON: No, no. Trish, I defer to you. I'm so glad that you're with us.

PROF. BACKLAR: It's hard to hear it. It's as though it's a transatlantic call in the 1940s. Are you going on speaking?

PROF. CAPRON: Go ahead, yes. We're all hanging on your words.

PROF. BACKLAR: I'm afraid I couldn't hear what was just said.

DR. CHILDRESS: We're waiting for you to speak.

PROF. BACKLAR: It's just that you brought up something that I wasn't sure, I missed the conversation with Dr. Shore and Dr. Rosenstein, and that was I would like to know is, other than the usual methods they use, how they could persuade anyone to be in such a study, in a challenge study? How could one be persuaded? I could not be persuaded. And therefore I'm concerned that the people that you are persuading really do not understand what is going to go on.

PROF. CAPRON: I'm glad you said that because that's exactly the point, Trish.

And, therefore, I would say, given Alta's comment that this isn't totally black and white and there may be some situations in which you would think that the harm would be de minimis or something, I would like us to directly confront this issue.

And if it's appropriate to move, I would say our report should say that it requires an overwhelming burden of persuasion for an IRB to approve any study removing a subject from an effective treatment for their mental disorder in order to study their underlying condition. I would have said they should simply be forbidden. But in light of Alta's comment, perhaps that flat-footed way of putting it is too strong. Because I cannot understand, as Trish said, what you could say to a person that would honestly convey to them what they're going to face that would have anyone who has decisional capacity agreeing to go ahead in those circumstances.

DR. CHILDRESS: Go ahead and respond and then I have four others on the list. I have Rhetaugh, Alta, David, and then Eric.

DR. SHORE: I was just going to say, I'm sorry if it was not clear, that people who are doing well on medications would not ordinarily be invited to participate. People who are not doing well under current medication. For instance, during 1978 through 1985 when I was in the intramural program, people came to the inpatient unit at St. Elizabeth's for the study of schizophrenia. We never made any attempt to recruit people who were doing well for exactly the reasons you describe. What would they have to gain from going off these medications as opposed to what they would have to risk.

PROF. CAPRON: In other words, you would not object to the standard that I just put forward because you think you were following it. And that may be the case, but we know that research studies have been carried on which haven't followed that.

DR. SHORE: Well, could you give me some examples?

PROF. CAPRON: Yes. I've read the research description of the UCLA study and it did not limit itself to people who were failing medication.

DR. SHORE: Well, what it did was to take people who had been able to tolerate three months previously off medications and did well and offered them the opportunity on an open basis to go medication-free for eighteen months. And only if they agreed to that while they were well did the study proceed. I've heard a great deal of misinformation about that particular study come from this group and others. But since I, in fact, was the project officer and was present at site visits in 1986 and 1989, I am convinced that I am one of the people who actually knows what took place in that study. It has been, I think, unfairly mischaracterized.

But individuals who consented to be in that study presumably didn't want to continue to take the medication for the rest of their lives after having one schizophrenic episode.

Remember, this was not people who had five or six episodes every time they stopped their medication. This was first onset. This was 1985, we had no idea, we believed that a third of the people who developed schizophrenia would get better and never need to take medication again, that another third might have another episode, and that another third would continue to be psychotic. So the people who did well presumably had a 50-50 chance of not needing to take the medication. Therefore, it seemed a valid research question at the time to offer people an opportunity to get off medications that produced a 5 percent per year risk of tardive dyskinesia.

PROF. CAPRON: I don't really want to spend a lot of time. We don't have the protocol in front of us. But when those studies were done and the results were published, the researchers stated that the advantage of their research design over other people who were asking similar questions about the effects of treatment on these patients was that they were dealing with patients who had been brought to a relapse, a full relapse. So they intended some of the patients in that study on the predictive basis you were just describing, I don't remember that it was a third, were people who would fully relapse and who could, therefore, be studied in that condition.

DR. CHILDRESS: Just a very brief response so we can move on to the other questioners.

DR. SHORE: If you read that paper carefully, and, believe me, I have, most of the people who relapsed in that study were on medications. And not all of the people who were taken off medications showed a relapse. And in point of fact, what they did was simply look at the people who deteriorated very rapidly and went to the point of relapse during the two week interval between the follow up visits. They did not, despite allegations to the contrary, they did not allow people to show clinically significant deterioration without recommending that they go back on medications. That's another fallacy of the study that's been repeated so many times that people believe it. But if you read that study carefully, you will see that most of the people who went to relapse were, in fact, continued on medication. And that was not the design of the study to produce relapse.

PROF. BACKLAR: May I say something? I apologize if this has been discussed, but it seems to me, David Shore—David, was that you speaking just now?

DR. SHORE: I'm here.

PROF. BACKLAR: Was that you speaking just before?

DR. SHORE: Yes.

PROF. BACKLAR: I'm a little concerned about something that I think I heard you say, which was that you only invited people in to a challenge or a washout study who were not doing well on their medication, and that if they were doing well, you didn't approach them.

And if they were not doing well, it seems to me you would come to confusion there because it would appear that maybe you're developing a kind of therapeutic misconception as though they were going to be helped being in a study. Am I missing that?

DR. CHILDRESS: Trish, in order to move it forward, I think this is helpful, but we're going to have to move away from the UCLA study and really address the two kinds of questions that we have before us. We have Alta's proposal to treat this the way we do any risk-benefit analysis, just make our judgments within that context. And then Alex's proposal that, no, we come down with a much stronger presumption in this area.

I have Rhetaugh, then Alta, and then David, and then Eric.

DR. DUMAS: I would like to speak for the possibility of those patients who can give consent to have the opportunity to participate in those studies if they choose to, even though I myself might not choose to do that. And I think that we need to be very clear about the kind of protections we would want to propose to take care of the concerns that people have rather than eliminating the option for the person to participate in the study.

PROF. CHARO: I think the question of why anybody would volunteer for this is a very good one. It goes to the heart though of all people who go into research experiments where there is little or no prospect of personal benefit, medically speaking.

I speak now out of the experience of having been a research subject many, many times. A lot of times people go in because of ancillary benefits. Some are financial, some are the opportunity to be seen and interviewed by physicians other than the ones they usually deal with, sometimes it's because they simply feel they're going to get more frequent attention, and some do it because no matter how many times it's explained that there is little or no prospect of therapeutic benefit, there's a secret deeply held belief that their really is a therapeutic benefit out there for them somehow.

It's this last concern that I think is rife through the entire area. It is particularly rife in this area, as we've seen. And I am thoroughly and genuinely concerned by it. I still feel that it's possible that a well operating IRB, and that's an important condition, can take this into account when they look very hard at a study design, look very hard at the particular population that is being recruited and ask not only what is the magnitude of the harm and the likelihood of its occurrence, but look at harm not only in absolute terms but as the difference between where somebody is and where they'll be if it comes to pass, which really does make the picture look different when you looking at somebody who is doing well who might now crash versus somebody who is doing poorly and might crash.

This may not be a happy thing though that people who are doing poorly should be

more easily exposed to an even more miserable experience. But this can be part of I think a good discussion. In some ways a realistic question here is whether we think that IRBs, with examples and explanations, can handle this, or if there's so much skepticism about the ability of IRBs across the country in every possible institutional setting to manage this that one wants to draw brighter line rules.

That may be the way to go at this is to incorporate how much you trust IRBs to be able to handle this. Because I agree that, in large part, these are going to be the most difficult kinds of studies to justify for these populations, even if analytically I think they do still fall along a spectrum.

DR. COX: I'm in favor of a brighter line for the reason that I said earlier. I really do care about the therapeutic misconception, but I care about the benefit to research misconception. It's very easy for someone to say that this is outstanding research when it's garbage, and to have vehicles to really adjudicate that issue is very difficult under the best of circumstances. So I think that if we don't really make a bright line on this, it's just going to fall by the wayside like so many things do. The therapeutic misconception is bad enough, but the research misconception is even worse for me personally.

That's not to say, though, I would feel extremely uncomfortable about saying that we, however well-meaning we are around this table, could decide for other people whether they should do something or not. I'm extremely uncomfortable with that. So I'm with Rhetaugh on that. But for the two reasons, both the research and the therapeutic misconception, I'd like a bright line on this one.

DR. CHILDRESS: Eric, and then I'll get Harold in on this issue.

DR. CASSELL: There are patients who want to be off their medication because they really believe that they don't need medication and, yet, it's not clear whether they do or they don't. I think that they should be permitted to come off medication if they can give consent, but with the extra protections that we have given elsewhere—informed consent, plus a representative, I want to discuss the word “legal” another time, plus a representative, plus the physician from outside the unit—so that they're protected to the degree possible. I think if that's what they want to do and the research has been looked at, they ought to be able to do that.

DR. CHILDRESS: Harold, and then Larry.

DR. SHAPIRO: I had a series of comments on this and let me just try to keep it very short. I think we should specify once, and perhaps not have to repeat it over and over again, that we are going to have a very strong section on study design. Everybody agrees. I think I've not heard any disagreement about it. And that's going to have to inform this perhaps in a more

thorough way than currently exists in the report.

With respect to the issue of drawing a bright line or not, I guess, as I listen to the comments, I think people have different idea what that bright line is. So, for example, I would be against prohibiting this or outlawing it, as someone suggested before, and I didn't interpret Alex's statement as suggesting that either. And so it's really a question of whether we think this deserves some special notice because of the concerns that swirl around these studies. And I sense that we all think it deserves some special focus here in some way and that it's just a question of fashioning language which is not so restrictive as to put people in a straightjacket but would highlight it in some way, that would draw the attention of the IRBs and others to their responsibilities.

I'm somewhat unsure, although I find, Alta, when you made your comment, I found it really quite persuasive as it went along. I kept saying, yes, that sounds very sensible and so on. But then I took a step back and said, well, but this is what they should be doing in every study there is, there's no exception from that. And so that I think if we could find some language that would highlight this in some way that is not overly restrictive that would be very helpful. I don't have any language proposed, I haven't set down.

Alex, I couldn't quite decide whether I approved of the language or his enthusiasm was getting in the way, because somehow I felt he was going too far but it may have been his enthusiasm as opposed to the language. I didn't quite get all the language, so I would have to see it. But that's where I feel we ought to be.

DR. CHILDRESS: Larry, then Eric Meslin.

DR. MIIKE: I think I'm awake now so I guess I can say something.

DR. SHAPIRO: Welcome, then. We'll ask you again when you're sleeping later.

DR. MIIKE: My comments are going to be similar to Harold's. I'm interested in what we're talking about a bright line. If bright line is absolute prohibition, then I couldn't agree with that. I guess it boils down to what some of the presenters were—I think there was one slide up there where the intent was to cause a harmful effect versus a high probability of a harmful effect in a study design. And so if the intent is to cause a harmful effect, then we obviously need more safeguards.

But I think the spectrum that we've been talking about should be able to handle that. I don't think we should be getting into individual instances or individual examples to carve those kinds of things out. We need an approach that handles everything.

DR. CHILDRESS: I would just say in addition to that, it seems to me that there

have been different perceptions of harm, not only in our discussion today with our two previous presenters but in some earlier sessions as well. I take it that many on the Commission are willing to refer to, to use Joel Feinberg's language, to setback the interest that occurs when one becomes very distressed and the like as a harm, whereas some other discussions have tried to look at something other than that, seeing that as not quite counting as a harm. But I hear much of the discussion on the Commission at least as including that as a harm.

Eric?

DR. MESLIN: As a suggestion for moving forward with language, I just want to draw the Commissioners' attention to page 30 and 31, where this issue is raised and offer a proposal. The staff report mentions line 6, for example, on page 31, deciding which design will best answer the research question, what procedures will be used, et cetera, have both scientific and ethical justifications. What I've heard from Harold is that that's the right direction and it's the degree of specificity or the burden of expectation that an IRB would have of an investigator who provided such a design in a protocol, that that would be appropriate.

If the phrase, the two options we've given in the memo that challenge studies are, in general, ethically problematic but under exceptional circumstances permitted. And we phrased it in an extreme sense. It sounds like Commissioners might like to see that IRBs should be especially careful in scrutinizing those proposals in which the designs raise profound ethical questions, and we should not be shy in saying, for all of the reasons that have been indicated, that this set of designs raises particular questions. Alta's suggestion that the scrutiny of IRBs in the risk role I think is entirely consistent with that proposal. But if you are asking us, I would propose that we flesh out lines 6 to 8 along this direction.

DR. CHILDRESS: I guess the question before we do that is whether there is general agreement that we want to say that challenge studies are, in general, ethically problematic but under exceptional circumstances permitted. If that's the direction. Now, here we may get the tension between Alta's formulation and Alex.

It's sort of where you set the presumption here that seems to me to be the critical matter, and that the bright line really is once this appears, then look at it very, very carefully, and you have to have very strong, maybe overwhelming, but you have got to have a very strong justification for going forward with the research of that sort.

DR. COX: Jim, Larry and Harold were right, when I was using the word bright line, most of the time people mean that that's like a prohibition. For myself, that's not what I meant. What I meant is it should be able to go ahead, as Rhetaugh said, but I believe that it's special, not just because it's a challenge test, but because of something that Alta said earlier that I thought articulated it beautifully; that is, that it was either an intent or a high likelihood of a harm.

Now, that's an unusual way to do experiments. That's what makes it unusual for me, not that it's evil, or not that it's always going to do a harm, but that that's the reason to highlight it. That's what makes it different.

So, without sort of turning that whole line of scientific inquiry into an evil, which I wouldn't be keen on doing, it gives an ethical reason why to distinguish it from other things, and not to prohibit it, but to say that people better look very carefully at it. And then it strikes me that that is hitting what everybody is saying. Maybe not, Howard. Maybe it's too wishy, too wimpy.

DR. CHILDRESS: Okay. I have Steve, then Alex.

MR. HOLTZMAN: I can imagine a challenge experiment in which I'm provoking a physiological adverse reaction in a normal subject, one in which I'm provoking a psychological adverse reaction in a normal subject, and one in which I'm provoking a psychological adverse reaction in a person with limited mental capacity. When we're talking in this discussion about challenge, are we talking about all of those cases, just the last two, or just the last one?

DR. CHILDRESS: Alex, then Rhetaugh.

PROF. CAPRON: The focus of what I was saying about triggering special concern was actually the wash-out study. As to these different challenge studies, I think Dr. Rosenstein was provocative. Eric answered why he thought it wasn't a sufficient response, but he kept saying there are circumstances where for diagnostic reasons, for example, one provokes a physical symptom.

MR. HOLTZMAN: No, see, I was very moved by Alta's point about it's in the nature of this to produce —

PROF. CAPRON: Well you put someone through a cardiac stress test that can do them harm but you're doing it in the context of diagnosing and treating their condition. What I just see as a thread running through this is a therapeutic misconception. And I ask myself, it isn't just subjects who are befuddled and desperate or whatever, it's time after time that the consent forms themselves slide into suggesting ways in which this will be of benefit to you. Because I think it is just so hard for people to face up to the fact that they're putting someone at direct risk for scientific purposes. And if this were a person who was under no obligation, psychological or medical, to participate in this study and so forth and you said you had the astronaut willing to take off into space at the risk of never coming back or something, you might at some point say, sure, it's okay for two people to reach that agreement. But we know with this population or many members of this population there is a history of abuse of that misconception.

And I just want IRBs, with language, Eric, we're looking at the transcript to get this, language that is stronger and more direct than the language you suggested to be told that the

need for scrutiny, the need for monitors, the need for second opinions and outside doctors making sure the person—look, if you want to go off, we can get you off your drug without you going into this research project. Just so that that's really clear. If a person says, no, I have schizophrenia, a lot of people have schizophrenia, I really want to be the person who helps to contribute to understanding this disease, and I know I'm in a lot of risk, and I know I'm going to get nothing out of this, but I'm just the most altruistic person in the world, I want to do it. They've gone through everything and the research is really going to show something, David, I wouldn't make it absolute, I'm with Alta, I think it shouldn't be absolute, but it should be harder.

And frankly, Alta, to answer your question, I'm a lot more comfortable with a committee that has David Shore on it who has looked at this subject inside and out than the IRB at Podunk Hospital, which happens to have a mental unit, when somebody comes in with some idea they're going to do some research and (a) David says it's not going to be scientifically as good as what goes on at NIMH; and (b) that IRB, unless this has already been waived to them because this is a special concern, they're not going to know it's a special concern and they may approve it without the scrutiny it deserves.

So I want us to say this is something which in the regulations you are required to do special review for this — I'm sorry if my enthusiasm diminishes the effectiveness or persuasiveness of my point here.

DR. CHILDRESS: I think we're pretty close and it may just require now that we actually get wording worked out, staff to do it.

Let me take three quick comments and then see if we can move on to another topic. I have Rhetaugh, Alta, and —

DR. DUMAS: I'll pass.

DR. CHILDRESS: You pass. Okay. I have Alta, then Eric.

PROF. CHARO: I think Eric was actually ahead of me. So, go ahead.

DR. CASSELL: To be very short about it, I want to just underline what Alex said, but in my usual quiet, calm way. And I want to also point out that in the discussion in the report the history has to be mentioned so that people understand this isn't just an arbitrary, oh, they didn't like that kind of, that this has a history and that is part of the reason for the strictness with which we have dealt with this topic in general. Understanding that, then IRBs will be put on notice, and they should be.

MS. CHARO: I have no problem with the idea of a guidance to IRBs that says that as a whole washout placebo and challenge studies with this particular population tend to

represent—tend to represent—the most extreme examples of every ethical problem that has been associated with these areas of research to begin with. And that on that basis that every tool in the tool kit for special protection should be considered and that the scientific merit should be given the greatest possible scrutiny in order to make sure that we have a reason to be doing this at all.

I do still have a problem with the idea of trying to carve out a subset of these things and call them ethically problematic in a way that is substantively different from all the others, partly because of what I said before about them being on the spectrum, but also because as soon as we do that I think then we're going to have to negotiate very closely on is it only wash-outs, is it wash-outs and challenge, wash-out and challenge of placebo, is it all of them, some of them.

The more that you try to get specific about carving things out and saying you must do these things for this particular category, the more important it is that you've carefully defined the category. The more that you're simply pointing IRBs in the right direction, the more flexibility there is in your description of those circumstances that should be noted for them.

And so for that pragmatic reason, I would prefer something that avoids classification but simply identifies these and says, "We've seen every problem imaginable in context with these and they deserve your extra attention above and beyond the extra attention in general."

DR. SHAPIRO: I think we're getting close enough here, Jim— I'm sorry, I didn't mean to interrupt.

PROF. CHARO: That was it.

DR. SHAPIRO: I think we're close enough to move on. We do need to redraft the language along the lines that reflect some of these ideas here. As I look at the memo itself, as opposed to language in the report, I think the report is not strong enough, this language may be too strong. But I think we're close enough to produce a reasonable draft that reflects these concerns.

DR. CHILDRESS: Eric was suggesting that maybe some people who are particularly interested in this—Alta, Alex, Rhetaugh, or anyone else who's interested—might actually want to try their hands, even tonight, and see about getting something drafted, a kind of direction for the staff that could then be amplified. Is that agreeable? If there's nothing else on research design, let's turn to the other topics. I think it was important that we spend a fair amount of time on that one since it's the one that has bothered us for a while and we had some good discussion on today.

Capacity assessment instruments. We require investigators in this, IRBs — page 2

of the memo. Investigators are required to justify their chosen manner of capacity assessment in the protocol and that will then be reviewed by the IRB. Does that go far enough? This is discussed in the text at 170, at 71 and following, as well as 72.

DR. CASSELL: It seems to me a reasonable thing to do, you know how I feel, because I think there's so often impairment. But on another side, we're trying to get further research on the instruments to measure impairment and this helps do that and it ought to keep that pot boiling. It doesn't rule out instruments, but it keeps it going.

DR. CHILDRESS: Eric?

DR. MESLIN: Just very quickly. In the second flow chart that was handed out to you just moments ago, we can go through it another time, but this may be just a point to flag for you. If you see this, I don't know whether we need to put it on the overhead if everyone has one in their hand, but the audience might not. All I want to point out is an issue that Jonathan raised to all of you in an E-mail, and that is the capacity assessment activity could occur in two places. The first place that it can occur is in determining whether or not individuals are capable with respect to informed consent to join the trial in the first place. But the second place is that individuals who are capable may, during the course of a trial or the course of a study, become relatively or completely incapable, in which case the question arises, "Should some other type of ongoing capacity assessment activity occur?"

The staff and Jonathan were sort of struggling with this. I confess that we weren't able to solve the problem. You see in that very complicated flow chart the middle two boxes, approve the investigator's justification for assessing capacity, that's the IRB's job. They can't approve an instrument, as we know there aren't instruments that have been validated. But I just raise this as you discuss out loud that there are possibly two places at which assessment of capacity will occur.

Jonathan, do you want to add anything?

DR. CHILDRESS: Are we satisfied the way the report goes on this with the amplification in the flowchart?

DR. CASSELL: Well, we're sort of left with the problem of fluctuating impairment, aren't we.

PROF. CAPRON: I have one question, and it's not on the pages identified in the memo, but on the pages beginning at page 79 in the draft. That is the substantive issues. It seems to me that the question that we don't fully grapple with is whether, again, we expect IRBs or somebody to evaluate the appropriateness of the method that is going to be used. And if so, what questions we would have them use, particularly, again, an IRB that may not spend a lot of time in

this field, in making their evaluation.

And perhaps you won't be surprised to know that I'm somewhat of the view that some good questions were raised by Professor Elyn Saks in her presentation, the gist of which, putting aside a lot of questions that arose about some of her particular arguments, is that there are certain normative expectations that are to a certain extent implicit in and to a certain extent even buried in instruments which an IRB may regard as "scientifically validated" and not be aware that in the process they are, in effect, answering what I would call a fulcrum question in our flow charts and in our whole conception, which is, the person who is found to have impaired capacity and not be able to make the decisions for him or herself is one who in certain circumstances is going to have the decisions made on their behalf by somebody else.

And the gist of that is that if you're applying an instrument that equates lack of capacity with particular responses on the instrument, you are in effect embedding in those responses the sense that this is a person who deserves to have their decisions taken out of their own hands. In other words, it's not simply a protective description of the person, it's a presumptive or taking over of the person by an outside, beneficent perhaps, but outside process.

And if I were on an IRB that hadn't spent any time on this, I would want to be able to read this report and see that issue flagged more clearly. That the reason that you care about this is that the instrument that's going to be used is going to have real effects on what people can decide for themselves and what others can decide for them. And some of the questions that are asked may presuppose, most obviously, the question of do you know you have this psychiatric illness, may presuppose correct answers that this is normative for the correct answer when the person may be equally as capable as someone else in making decisions but just rejects that rubric as being something that's being imposed on them from the outside.

And it's important that IRBs say we're still comfortable having that done, or we don't want that part of the instrument used, or something. I would like to see us be a little clearer why this is an important issue.

DR. CHILDRESS: Eric?

DR. MESLIN: Can I just ask Alex whether the paragraphs beginning on line 13, page 69, preceding —

PROF. BACKLAR: Can you speak up louder?

DR. MESLIN: Sorry, Trish. I'm just asking Alex and the others to turn their attention to page 69, in fact the lines before then which try to flesh out some of those reasons. Are you thinking that we need to identify another section that sort of highlights for IRBs here are the things that you really need to be thinking about, given that we can't tell them to assess a

particular instrument?

PROF. CAPRON: Yes, Eric, that's the question. Are we in a situation where it's just going to be catch as catch can, that the real thing that IRBs are going to say to people is simply use some recognized instrument and they're not going to care whether the instrument is full of presuppositions which they're never going to be told about and they're in no position to do anything about therefore. And the answer is no.

The stuff on page 69-70, as I read it, has to do with the notion of either progressive or intermittent impairments of capacity. That's not what I'm talking about. What I'm talking about is the fact that the questions you ask, which we rather blandly describe as performance—

DR. CHILDRESS: Performance capacity.

PROF. CAPRON: Page 73, line 3, any assessment tool measures capacity indirectly through manifest performance and our performance does not always reflect our capacity or potential. That's one problem, which is you can take a test and do poorly on it when you really know something. I'm talking about the judgment that whether or not you answer a question a certain way indicates that you ought to be judged incapable of making decisions for yourself, not because it doesn't accurately reflect, it perfectly accurately reflects the answer you want to give and the answer you believe to be correct. It's not that you're wavering or that you're under pressure and you're not taking the test well, it's just that that's an answer.

If I ask you, "In what year did Columbus discover America," I gather that there's an agreed upon answer to that and if you say something else, you're wrong. If I ask you whether or not you have paranoid schizophrenia and you say, no, I don't, but if I ask you, "Do you do the following things," and you were to say, "Yes, I do," what's the difference? You reject the label paranoid schizophrenia. Now should that mean, as it does in the Appelbaum-MacArthur instrument, does that mean that you are judged one count against you on your capacity.

Now if you're on an IRB and you don't know that that's one of the ways that that's calculated, you won't know that autonomy is being undermined by that instrument.

DR. MORENO: Can I just make a couple of comments?

DR. CHILDRESS: Jonathan, then Steve, then Harold.

DR. MORENO: First of all, you know, Alex, that Columbus didn't discover America, but never mind. I have also been concerned about this question. It's something like the general problem that IRB members have, that they don't necessarily have expertise in the methodology that's being used in the study or that's being proposed as use in the study. And yet,

again, it's different because capacity, as we agree, is a different and threshold issue for participation, particularly for this population.

I don't know how to make much headway with that issue except to note that there are other protections here that help perhaps with your concern; namely, the additional membership which should include at least one individual who is professionally competent to evaluate the instrument or the process for assessing capacity. And another, which I think is not unimportant, is that this requires investigators to go on record and, perhaps by going on record, to be more aware about what they're doing and how they're doing it. And for a third point, should as well, as somebody mentioned before, stimulate further research in the development of instruments like Appelbaum-MacArthur and others.

PROF. CAPRON: Right. But do you think that the first two points you made I've missed in this report?

DR. MORENO: I hope not.

PROF. CAPRON: Can you point me to them?

DR. MORENO: To those points?

PROF. CAPRON: Yes.

DR. MORENO: Well, Columbus is not one of the first two. You mean the additional membership in the IRB, which —

PROF. CAPRON: And the self-scrutiny of the investigator by having —

DR. MORENO: Is not mentioned, no. Good example —

PROF. CAPRON: Those would be steps in the right direction.

DR. MORENO: Good. Thank you.

PROF. CAPRON: Now let me just finish the loop of my thinking. One thing could be to say we don't realistically expect IRBs to do anything about this. In which case, rather than simply say we hope there will be more research in this area and we ought to stimulate the research, we might say as a recommendation, not for regulation but for NIH responsibility, that NIH should have a task force that looks at this issue and puts forth for IRBs an evaluation of different instruments so someone doesn't come along and say, well, I'm using the Capron Scale that he published in the Hastings Center Report or something about how to do assessments of capacity when the people in the field say that's garbage. The IRB doesn't know it.

DR. MORENO: We do have a recommendation to the NIH to sponsor more research on the general question of consent. But we can more specify it along those lines.

PROF. CAPRON: Right. If we concluded that IRBs are not going to do the function well, is the function going to be not done by anyone, or is it going to be done by some other body that might have enough expertise to provide a guidebook to IRBs about this or a three-page pamphlet, in which they would be told what the issues are.

DR. CHILDRESS: Okay. I have Steve, Harold, Larry, and Eric. And then perhaps we should move on to the roles of other decisionmakers.

DR. SHAPIRO: I think this issue is an important one because of the impact it has to take away decisionmaking capacity from someone. Therefore, it is, as Jonathan or someone said here a moment ago, a threshold issue. My own recollection of the Saks paper is that she did raise a number of very interesting points there which are relevant and not reflected in here.

I would support going back and thinking about that carefully and seeing what we might want to include here as a way of making people sensitive to this issue so they might at least have a chance to think about it. I would also support some guidance to NIH on this of the type that Alex, some of it is in the back of this report and you may want to change that some. But I think some move in both those directions I would support.

DR. CHILDRESS: Eric has reminded me that Elyn Saks is still revising the paper and we'll be getting another draft.

Larry?

DR. MIKE: I just have two contradictory statements to make. My first is, and it's a constant spiel that I make, is that we're getting to discussions where it's the cookbook approach. We want to give so much detail when I think we're a policy guiding Commission. And so I get frustrated when we get into these very detailed discussions.

On the other hand, I hear Eric saying, well, that point is on page 69 on line 7. And so if there are important points, then they're buried somewhere all around in the report. So I'm listening to this and I guess what I'd like to see the staff do is that those points that the Commission raises as important be given more visibility, and maybe not in the sense of redrafting the whole report, but those are the kinds of points that have got to be pulled and summarized in the executive summary.

So those are my two contradictory statements.

DR. CHILDRESS: Eric, and this will be the final one.

DR. CASSELL: Well, all this raises once again, though I don't expect us to settle it, it raises two questions; one, of the consent monitor in certain circumstances, and the other one is the training of investigators on obtaining consent. It always comes around, the same set of

issues, and somehow or other we have to, I think in this report or separately, address the fact that investigators must be specifically trained and/or that there will be monitors. That ought to motivate them.

DR. CHILDRESS: That leads us then, if there's no objection to the next question, but keeping in mind the —

PROF. CAPRON: I do have an objection. Eric, the problem with that is this is not a consent issue. This is whether or not we deal with consent or we deal with permission from a legal representative. If you go down the chart that was passed out today, and you're over here on, even on the beneficial research —

DR. CASSELL: I understand that.

PROF. CAPRON: The subject doesn't have capacity. The subject's consent isn't even in the picture.

DR. CASSELL: I understand that. But by knowing that the monitor and the consent part are more rigorously dealt with, it pushes the importance of finding out whether that person have the capacity to consent, that's why.

DR. CHILDRESS: Okay. So staff will follow the discussion and change when they contradictory or amplify the draft. The next set of questions will focus on other decisionmakers. In the draft or proposed recommendations we have legally authorized representatives, independent physician advisors, and consent monitors. So the question being raised here, and there are several other pages for the legally authorized representatives, 74, 77, 114, 133, 195 —

PROF. BACKLAR: Can you speak louder.

DR. CHILDRESS: Sorry, Trish. I was just mentioning additional pages, I won't run through them for you, where some of these are discussed. We can talk about those pages later. But the big question here is whether the roles of these three decisionmakers are clearly described in the current draft, and whether commissioners agree with the proposals for each of these, their use and their function.

Here, again, you may want to look at the flowchart or at the recommendations. Here you might even find the simplified, the earlier flow chart useful for identifying pretty clearly. Eric?

DR. CASSELL: I raise the question I raised in the E-mail about what about states in which the family is not a legal representative, does that exclude the family from this process? Why does it have to be a legal representative rather than a family, first degree relative, or legal

representative, and/or, so that we don't exclude the family.

DR. MORENO: I'm not a lawyer, but my understanding is that this is not a prescriptive term, Eric, but a descriptive term. That is that as a matter of practice anybody who has the authority to do this in a jurisdiction is going to be legally authorized. Now that's not necessarily going to be recognized by statute, it will be part of the common law, through the case law of that State. I don't think we have any way to avoid that.

DR. CASSELL: Well, in New York State until just recently the mother and father, for example, were not legally surrogates.

PROF. CAPRON: No, Eric. The situation varies from State to State. For a long time there was simply no statutory law and actually no decisional law that recognized the common practice, for example, of having spouses consent for each other when one of them was in surgery and you have to get someone's consent, or one of them is in an accident and you have to get someone's consent. Minor children, yes, it was quite explicit the parents were the natural guardians of the children. But that practice went on.

In twenty-some States I believe now, maybe slightly more than that, there are these family decision acts which allow a specified rank ordering of people to step in and decide in the absence of direct directions. In some states, like New York, people without explicit authorization from a court, as I understand it, are not going to be allowed to make certain categories of decisions, however.

DR. CASSELL: They couldn't make a DNR decision.

PROF. CAPRON: They could not. And in many States there are particular restrictions on people making judgments about mental treatments or enrollment in research, and the generally drafted surrogate decisionmaking statutes, like durable powers of attorney for health care and so forth, explicitly exclude in most States, I believe, treatment for mental illness, or shock therapy, or institutionalization. Those are not things which you can consent to without going to court and being appointed a committee or guardian of the other person.

So it's going to vary all over the place. But Jonathan is right that there will be people who are regarded as the legal representative and can sign off on a lot of things who haven't gone to court to be approved just because the State has allowed that as a practice and no one has ever challenged it. It's a kettle of fish though.

PROF. BACKLAR: On the other hand, it would be quite dangerous. I would be very concerned if a public guardian could make decisions like this.

PROF. CAPRON: Public guardian? This is for a person who lacks a family

member, right?

DR. MORENO: We try to manage this problem in the recommendations by including some suggestion to state legislatures, at our peril, that they devise statutes that include specifically family members as representatives of this kind. Obviously, the Federal system being what it is, we can't do this for the states.

PROF. CAPRON: On page 175, what about Trish's concern about the public guardian who are legally authorized to make treatment decisions. At the bottom of our chart, should they be the legal representative who can consent, as it were, give permission if there's no apparent dissent from the mental patient?

DR. MORENO: Good question. It's not one we considered.

PROF. CAPRON: Among the most vulnerable people, again, are those who are not befriended, as it were, those who have to rely on the so-called public guardian.

DR. CHILDRESS: Do you have a recommendation on this?

PROF. CAPRON: I would say that the public guardian should not be in a position to act as the legal representative to enroll people in the research.

PROF. BACKLAR: It varies, you see, from State to State.

DR. SHAPIRO: I just ask a question of information. There are, unfortunately, increasing number of people who are legally giving up the guardianship of their children really to make them eligible to enter state institutions and to come under State guardianship. Is that the group we're talking about here? If not, how does that group fit into what we're discussing?

MS. CHARO: Harold, that's not actually the group we're talking about, but it does give one an idea for guidance because the same question is going to be coming up with children. What are the residuals of decisionmakers when parents are not around? What are the rules that govern with regard to things like public guardians for children? And it may be that there are a set of workable rules that we could parallel, or it may be that we'll discover there are no rules there either, but either way actually it might be valuable for this discussion to see what's happening in that analogous area.

DR. SHAPIRO: The population I was thinking of, although I didn't describe it very well, were children and/or people, primarily teenagers, who have very severe psychiatric symptoms which require extensive treatment of very expensive kind. And just for good or ill, in a lot of those cases parents are giving over guardianship to the State, who then takes over their care. That's, unfortunately, common. I just don't know how that fits in here. I guess you're saying we haven't worked that out yet, is that right, Jonathan?

DR. MORENO: You're right about that.

DR. SHAPIRO: Okay. Then that's something we've got to think about.

DR. DUMAS: I'm going on to another question that I had. In this group where there are not potential benefits, down on the right-hand column, indicating informed consent and legal representative and physician. Can somebody tell me why the health care provider is limited to the physician when in these settings there are other therapists?

DR. CHILDRESS: On the first draft, we have in the text where we had the flow chart, actually it says health care professional monitor. The question was why we had only physician on this draft you cannot see because it was just handed out today when on the previous flow chart we actually had health care professional monitor.

DR. CASSELL: I'll tell you why. It's a question of power politics in the research unit. If there is a physician available, that physician will have more power vis a vis the people running the research than the psychiatric social worker will. If there isn't a physician, then it should be another caregiver. But that's the only reason. It was really to give that patient more crunch on his or her side.

DR. DUMAS: Well, I don't think we ought to continue to reinforce it.

DR. SHAPIRO: I don't think you can change it in this.

DR. DUMAS: And because there are some units now the directors of the units may be a psychologist or a social worker or even a nurse.

DR. CHILDRESS: Trish, do you want to get in?

PROF. BACKLAR: Well, it's very hard for me to tell exactly what you're talking about. But if you are talking about what it sounds like, I also am concerned, and Eric, I think you and I have talked about this. Many people have psychiatric disorders who hardly know their physician, their prescriber. They're much more likely to know their caseworker.

DR. DUMAS: That's right. Caseworker.

DR. CHILDRESS: So, if Eric Cassell doesn't object, we'll go with health care professional monitor?

DR. DUMAS: Yes. Even if he objects.

DR. CASSELL: I do object. I do, because what will happen, by doing it that way, remember that the team goes to pick this person, it isn't the patient that picks this person, the research team picks this person. They will pick the weakest one they can get.

PROF. CAPRON: An IRB could designate the person.

DR. CASSELL: Well, then make it physician or, if not available, other health care worker. Or primary health care worker.

DR. DUMAS: Primary health care worker I'll agree to.

DR. CASSELL: Physician or primary health care worker.

DR. DUMAS: No, not physician.

PROF. BACKLAR: You know, Eric, I think you're absolutely right. I think you're right not only in the sense these people have more power, but also because I think all these people should have at least some acquaintance with somebody who is prescribing their medication. So I'm not going to argue with you about having it there because I think it's good. I do think it's going to be a problem.

DR. DUMAS: We said therapist is fine with me, but I don't think it should be limited to physician. They're not the only therapist.

DR. CASSELL: It isn't limited to a physician.

DR. DUMAS: The responsible therapist would seem to me to be the case.

DR. CHILDRESS: Should we say instead of this the responsible health care provider, whoever it is.

DR. CASSELL: Well, it may not be a health care provider. They may have no outside health care provider.

DR. CHILDRESS: But we're requiring that on this.

DR. CASSELL: No, we're requiring a physician. The physician did not have to be a health care provider.

DR. CHILDRESS: Larry is trying to get in, then Harold, then Alta.

DR. MIKE: Just a little aside thing just getting back to the term "legal representative." It is confusing when in the recommendation there is a recommendation to State legislatures to legislate legal representation, including family, et cetera. So we're using legal representation both in a general term and in a legal term. And because legal representation—by the way, I'm one of those legal guardians in a state that deals with children and adults that you talk about. And if there are questions about who you exactly want to be able to make these decisions in the mental health area, maybe we should just find another word, "authorized representative" or something, just so that there's no confusion about the term "legal."

DR. CHILDRESS: Could several of you, particularly those with legal background and experience, such as Larry, and concerns about power, Eric, get together over some of these categories and make sure we get the ones right?

DR. DUMAS: The power struggle is here, that's where it is.

PROF. CHARO: I'd like to talk to this because I fear that if we continue debating this we're debating something that gets down, as Larry has said before, to a level of specificity that almost obscures our goal. If what we're doing is creating a tool box for IRBs and we say to the IRB that when you've got certain kinds of red flags we want you to use these tools, it's probably sufficient to say to the IRB we want you to have an independent consent monitor.

And in the discussion, in the more elaborated form, not the short form, we would be acknowledging probably the way this is going to happen is that the research team is going to propose somebody, their name is going to be mentioned to the IRB, members will have a chance to see if that name raises any red flags, but otherwise they're going to pass on it. But point out to the IRBs that the purpose of this consent monitor is to give, as you put it, crunch to the patient, and that they should keep in mind the effect of professional hierarchies in the effectiveness of this monitor but also the actual personal knowledge of the patient's situation, preferences, and patterns of behavior in the past.

And, again, it will be on an individualized basis that this whole thing gets reviewed. But the point is that you're signaling to the IRBs that there are all these things that go into the consideration, please take note of it. I doubt that we can come up with a word or a rule here that governs every situation equally well, nor do I think we're trying to draft regulatory language that attempts to do that.

DR. COX: You just said it. Write it down.

DR. CHILDRESS: That's right. You've already taken the discussion forward.

PROF. CHARO: But we've got all these transcribers here for \$10,000 a day.

DR. CHILDRESS: Harold?

DR. SHAPIRO: I had a comment similar to the one that Alta, a suggestion that was similar to the one Alta made. If I understood Eric's suggestion, it seems it was that you wanted physicians to be in the list, that is you said "physician, or something of that nature." So it wasn't—and you just don't like physicians on the list?

DR. DUMAS: No, he said only if there is not a physician, then somebody else.

DR. CASSELL: Just that way, physician, or, or, or. We're trying to solve your whole group's power problem that's as passé as anything could be.

DR. DUMAS: No. My problem is already solved, Eric.

DR. CASSELL: Not yours. You're powerful.

DR. DUMAS: I agree with Alta. I don't think we should be so specific. And she said it really beautifully. And I would be glad to go along with that.

DR. CASSELL: I'm happy with her language.

DR. DUMAS: So that takes care of it.

DR. CHILDRESS: We have consensus. I'll let Harold finish, and then Steve.

DR. SHAPIRO: I'm through.

DR. CHILDRESS: Steve? Could we try to move on to do something about risk next.

MR. HOLTZMAN: Just an endorsement of what Alta said. That does happen on occasion, Alta. It goes to the further question of the form of the report. For it to be effective in giving our IRBs that kind of guidance, what is it about the way we've written this thing that—if you look at your question, it was are these rules clearly prescribed in the current draft. We've just spent 15 minutes trying in some measure to figure out what do we say and do we agree. That can't be very good guidance. So somehow we have to get a step back from what's an enormous amount of important stuff that's in here and say how do we put it into a format where, in fact, there will be a response to it.

DR. MORENO: We've already talked about an executive summary and introductory section that can boil the important points down. And it clear from what people have said that needs to be done.

DR. CHILDRESS: We'll take Alex, and the perhaps we can move on to risk.

PROF. CAPRON: Alta, the only question I have about the description you gave was you said at one point the IRB would look at the person and decide is this a good person to play that role. I understand the that the thrust of what had been said is they're going to have an approval for a research project, there are patients at this institution, my understanding was, our hope was this would be the health care professional who is knowledgeable about that patient and in a therapeutic relationship with them who could maintain that therapeutic relationship and help advise and evaluate what the researcher is bringing in. That's going to be Dr. Jones here, Nurse Smith here, therapist so and so. There's not going to be one person. But if we look at the transcript, Alta, and we wrote down what you've said, it would have been that they were approving a person. It seems to me what we're talking about is a category of people which will include many potentially different professionals, some of whom may be milksop doctors who

won't stand up to their colleagues, and others of whom may be dynamite nurses who won't let a doctor hurt a patient because they're holding a club over his head. Who knows what. But it's going to be a whole variety not defined by profession. It's a category, right?

DR. DUMAS: That's what I thought Alta was saying.

PROF. CHARO: But for a given person it's a specific person.

PROF. CAPRON: But it's not a specific person, because the research protocols, for the most part, are going to say we want to recruit 20 patients with the following conditions, we don't know which ones are going to agree to be in, and who are going to have the conditions of this project. So which ones of the staff at this hospital or outside doctors who have seen them before?

PROF. CHARO: I suspect that unless we get even more specific, and remember, nothing that we suggest is going to be required absent a regulatory change, which won't happen even if it did happen for ten years, so at best we're talking guidelines, right? Unless we were to specify, I suspect there would be variable ways in which this kind of thing would be implemented, as is true for everything with IRBs. Some IRBs would ask that the protocol come in with a generic descriptor like we will use the primary care physician, or we will use the doctor who runs the ward, depending on the context. In other cases, IRBs would approve this conditional upon having for each recruited patient notification of who it is that's going to be the independent monitor, and the IRB will not allow you to begin actual work with that subject until they've seen who the monitor is and they've had a chance to see whether or not it raises any red flags.

It will depend on exactly which IRB you're working with, and they run the gamut. Now we could decide we want to get into that level of detail.

PROF. CAPRON: Don't we have any minimal floor here, Alta?

PROF. CHARO: I wasn't saying that as a challenge. We could decide if we want to get into that level of detail or not.

PROF. CAPRON: I understand that. This is a broader question—which Jim posed to one of our afternoon witnesses—which is when we talk about the IRB may, and the IRB may, present guidelines already allow IRBs to place all sorts of conditions that are way above the federal requirements, right?

PROF. CHARO: Right.

PROF. CAPRON: They can already insist that you have three independent doctors. The question is do we want to say that an IRB should not allow certain categories of research to go forward until it has ensured that a person with the following qualifications, as a

minimum, shall be appointed to work with the potential subject in a therapeutic, protective, whatever role that they want to describe it as. Or, are we going to say this is something IRBs can pick out of the tool chest? Aren't we saying then, in fact, the NIH Common Rule should be modified in this regard to say that this is required that the IRBs ensure that such a person is in place.

PROF. CHARO: First, let's remember that this particular tool, the independent monitor, was never in our recommendations required for any category of research. It was always an optional addition for IRBs above and beyond even what the recommendations say should be the new regs, the theoretical new regs. It was never required. It was an additional —

DR. CHILDRESS: Which are you talking about? Are you talking about in the past?

PROF. CHARO: Yes.

DR. CASSELL: Consent monitor is different.

PROF. CAPRON: That's not consent monitor. This is physician advisor.

DR. CHILDRESS: Right. But she was speaking about consent monitor.

PROF. CAPRON: Non-beneficial research.

PROF. CHARO: Oh, excuse me. Sorry. Okay. I confused myself for a moment. Right. Right. Right.

PROF. CAPRON: But this was just a generic question of which this is an example. Aren't we talking about here that one outcome, not ten years from now, but before research should go forward is that our report would come in, NIH would publish, take the report and put forward modifications in the regulations in a special subpart.

PROF. CHARO: You mean in 2010?

DR. CHILDRESS: I think they're to be offered as guidance.

PROF. CHARO: Even as guidance.

PROF. CAPRON: Guidance before that. But the objective is to say that there are minimum requirements.

DR. CHILDRESS: I would note that even in the recommendation part we've revised this to say "should" not merely "may." The earlier draft had "may," "The IRB may consider...." And this one does actually change it. So it tried to strengthen that a little bit.

PROF. CHARO: But the minimum requirements you're talking about are the

minimum requirements for the professional, that it should be somebody with personal knowledge of the patient. Well, what minimal requirements are you talking about? Those?

PROF. CAPRON: The minimal requirement is that the IRB should ensure that it exists as opposed to the IRB might have such a primary care person involved in a certain category. I'm saying that the IRB should have. It's just what Jim just said, IRBs should have. Then we could say conscientious IRBs will do it now, others will wait until the Federal Government tells them they really have to do it and they can stop thumbing their nose at NBAC.

DR. SHAPIRO: This latter statement I think is really quite important. The issue of how long it would take to make any change in the Common Rule take hold is speculative, but the evidence says a very long time. And we would aspire for changes to take place faster than that, that some IRBs, at least many, would listen to some of our advice or other advice. NIH, of course, could adopt its own rules any time governing itself.

DR. CHILDRESS: I think we may have said enough on all that to provide the kind of guidance to staff, Jonathan and Eric and others, to work this out.

DR. BRITO: Really it's more of a clarification. When I read the flowchart, and when Rhetaugh was making her comments, I'm reading this word "physician" here as the person representing the subject in the research. When I go back through the text, though, and I'm reading the description of independent physician advisor, I'm not reading that as the same. Are we talking about the same?

DR. MORENO: Same.

DR. BRITO: We are talking about the same.

DR. MORENO: Independent of the researchers.

DR. BRITO: Because that changes.... Nonbeneficial, nonbeneficial, greater minimal risk research, right?

DR. MORENO: Right. And it could be a non-physician primary care professional.

PROF. BACKLAR: Somebody tell me the page you're on.

DR. BRITO: You have a chart you can't see and I'm comparing it to page 174, where it's discussing independent physician advisors.

DR. CHILDRESS: And you don't have the other chart that we're talking about. It was handed out today. Okay, can we turn to question of risks and we have, this is chapter 4, also discussed in various places along the way in some detail. And we have Laurie's proposal. Everyone received a memorandum today in which she raised questions as she has before about

our deletion of the category “minor increment over minimal risk.” And she’s arguing for the three rather than the two categories.

DR. MORENO: Can I just speak to that, Jim? I think we addressed this last time. We are not, so that everybody’s on the same wavelength here, we are not eliminating anything. You can have as many categories above minimal risk as you like. And you can have as many categories below minimal risk as you like. We’re only specifying in this draft the minimal, the minimum requirements if one is above that threshold of minimal risk. IRB can impose or apply, introduce whatever other protections it likes. So this is not eliminating a category. And the category as I understand it...

DR. CHILDRESS: Of particular concern is that we are eliminating it as a standard for classifying research protocol.

DR. MORENO: You’re not.

DR. CHILDRESS: In our recommendation.

DR. MORENO: No, we’re not, though. We’re eliminating it as a basis for developing incremental protections. We haven’t seen a reasonable way to do that.

DR. DUMAS: I understand, and I like that.

DR. SHAPIRO: What do you like, Rhetaugh?

DR. DUMAS: I like the idea of designing protections according to minimum level of risk, whether it’s minimum or whether it’s above it. And that, to me, eliminates a lot of confusion on the gradations in between. Anything above minimum level is what we’re talking about protecting.

DR. CHILDRESS: Other discussion?

DR. BRITO: But I can also understand Laurie’s concern because depending on the IRB, depending on how much time is spent, I could see how some research that is just that grade above minimal risk could be prevented—some beneficial research. So I can understand the concern. So I think maybe if we define it the way it’s defined is fine, but maybe just a little bit more explanation somewhere in there about that it really needs to be looked at very carefully when there are just levels above minor or minimal risk, etc. Some gradation.

DR. DUMAS: Then you get into the distinctions with the variation among people on what they call “just above minimal risk.”

DR. CHILDRESS: Alta, then Eric Meslin.

PROF. CHARO: I continue to believe that simpler is better in this area. And that

an additional category with separate procedures for “minor increment over minimal risk” is an invitation to confusion at the IRBs. However, in light of Laurie’s continued concern that the absence of this category is going to mean that there are a fair number of people who can no longer give informed consent, who will then become ineligible for important research that is a minor increment over minimal risk and nonbeneficial, I’d like to suggest that this report go out to the public in a way that highlights that question for reactions from the public and particularly asks for some examples of the kind of research that would be affected and the magnitude of the research that would be lost. But as we continue to debate this particular issue, we will know exactly what’s at stake.

DR. MESLIN: Just very quickly. When the writing bucket, and this is for the benefit of the Commissioners who weren’t participating in that conference call, discussed this issue, two points were raised that I think bear repeating. The first is that the issue is only relevant if the “minimal risk” bar is set at a particular place which either is overly inclusive or overly exclusive. The worry of the writing bucket was that if the bar for minimal risk is set so high that everyone would be in minimal-risk research and only incredibly risky research was above minimal risk, that would clearly be inappropriate because no one would be afforded protections. If, conversely, the bar was set so low that virtually anyone could jump over it and be therefore in a category of greater-than-minimal risk, that too would be worrisome. So the issue was where to set the level of minimal risk, which is a judgment call, and I think the writing bucket agreed that examples would be helpful.

The other point that the writing bucket discussed but doesn’t come out in the report, except for an additional staff suggestion, was in the absence of any data or evidence that IRBs can make the distinction, the fine distinction, between slight increment over minimal, even greater slight increment over minimal, etc., that it would not be doing them a service to make those distinctions. And besides, the regs permit us to have these two levels anyway with the exception of the childrens’ regs. So it was suggested that one prospective recommendation might be to evaluate this particular recommendation in the field after we implement it.

PROF. CHARO: But Eric, one thing in B response confuses me. We are not in control of the definition of minimal risk. It is a definition controlled by the regs.

DR. MESLIN: I understand. Well yes and no. We could .... I don’t want to do the Larry worry, but the definition of minimal risk in the regs is sufficiently vague for purposes of this discussion; that we could have, the writing bucket could have that discussion and ask where the bar would be set. Eric Cassell asked whether we should be adding a new word to the minimal risk definition to include treatment, a particular type of treatment. So you’re right, we are limited by what the regs say, but the definition is flexible to have this point still be on the table.

PROF. CHARO: Okay.

DR. MESLIN: And we included the regs in everyone's briefing book if you wanted to...

DR. CHILDRESS: Alex, just a suggestion to make sure we had a debate in clear form. Are there other thoughts on the question of risk?

DR. CASSELL: I hate to do it, but ...Trish's concern that risk is different to this population than it is to another population is really not addressed. And yet she's correct about it. That something may seem like minimal risk to somebody else but to somebody in this population feel very risky. We haven't addressed that, and one way to address it was to try and just eliminate too many categories. But in fact we have not addressed that.

DR. CHILDRESS: But we have addressed it in the text, though, right?

DR. SHAPIRO: Yes.

DR. CHILDRESS: But not in the recommendations.

DR. SHAPIRO: Yes.

DR. CHILDRESS: Harold, sorry, Harold was first, sorry.

DR. SHAPIRO: The issue of what research is going to be discouraged by this approach as opposed to, let me just call it Laurie's approach... The issue of what research is going to be discouraged or what useful research we will no longer pursue because of having these two categories rather than three, as far as I can tell so far remains an assertion. And I would feel much better about this if we had something more than an assertion on this matter. Otherwise, I think the logic takes either the minimum versus not minimum. But there may be something real here, which I don't know about, and quite willing, even likely that that's the case. But I really don't want to move that way; I'm happy with all the suggestions, wait for some feedback, but I wouldn't want to move that way without something beyond an assertion in this area. And perhaps get some data on this, I just don't know what's available.

DR. CHILDRESS: Tom?

DR. MURRAY: It would seem to me that some progress was made in this discussion of the last several minutes, but it's not clear to me where we came out on it, and I wondered if anybody would be willing just to state where we think we are in terms of a shared agreement about this so we can come back to it next week in writing and have people say no, that's not what we agreed to. Why don't we try to nail it now?

DR. CHILDRESS: It's late in the day, we may not have many volunteers.

DR. SHAPIRO: The suggestion, the only actual suggestion I heard was Alta's suggestion, that namely we keep it in this form as it goes out for comment. But we find some way to encourage response on the issue—that we focus attention on the issue here from other investigators, other people who know things, just what they feel on this issue. We know how Laurie feels, and she's a thoughtful person, very experienced in this area. But let's hear from others. That was the suggestion that Alta made, which seemed entirely reasonable.

DR. MIIKE: Yes. If we're going to have definitional problems of what is minimal risk, I'd have an even greater definitional problem of what is a minor increment.

DR. SHAPIRO: I completely agree with that.

MR. HOLTZMAN: I assume we all agree with that because in the beginning was the action of the word, and what Laurie cares about here is the action here. The implication that no box...that says there is a class of research which will not be able to be done. So the issue is whether or not we're going to, in terms of our simple bimodal classification, now change that to a yes or leave it as a no and look at the implications. We talked about an empirical question, that how much research should be excluded. I think the little interchange between you and Dr. Shore and myself really went to the point of what is the interpretation under the reg of what is minimal risk. And are we in a situation, in fact sociologically, where people are being broader in their interpretation of what is risk than they used to be. And so therefore the class of research that would be excluded under this proposal is in fact getting broader. If anything, I think those are the issues that are at stake. And I don't think we have the consensus on whether even going with the bimodal scheme should be a yes or a no.

DR. BRITO: We've previously had quite a discussion on defining minimal risk from experts and from within ourselves, etc. And no one's been able to come up with a conclusion. At first I thought Alta's idea was a great idea putting this out for the public, but I'm not sure we're going to end up coming to a conclusion with that either. The way the Federal regulations are written, they're written vaguely in this area and there must be a reason for that. And I think it's because past commissions haven't been able to define minimal risk. And I think there's a lot of variation of what is—we've talked about this before—what is minimal risk to one may not be minimal risk to others, whether it's the investigator or the subjects in the research. What I was suggesting earlier is, and I don't know if I made myself clear, is that I think in the body of the text we discuss what Laurie's concerns are. And she gives one clear example of the PET scans etc. in her letter about what is just above minimal risk. But in our recommendations, we make it just the two categories where we make it very clear it is up to the IRB to determine what is greater than minimal risk, because that is in the end what we're entrusting the IRBs to do to determine that. I'm not sure, I think we're going to get such a varied response from putting this out.

DR. SHAPIRO: Well in the way I think about this, Arturo, it's hard to define "minimal risk."

DR. BRITO: Right.

DR. SHAPIRO: It doesn't get easier by defining "minor increment over minimal risk." It doesn't change anything. It just gives you some leeway to figure out what minimal is. That's all it does, it's just another way of defining minimal.

DR. BRITO: But shouldn't we leave it up to the IRB to define what is above?

DR. SHAPIRO: Well, my only point is you don't need two categories to leave it up to them. If you're going to leave it up to them, you can leave it up to them in one category. Either it's minimal or it's not. And that's just how I think about it. I'm not an experienced investigator in this area and maybe there's something quite bad about that.

DR. CHILDRESS: Larry and Diane.

DR. MIKE: I think the answer is whatever we've been trying to do as a decisional pathways. The more decision points you give them, the more comfortable they would feel in erring on the side of caution because you still don't block it just by saying it's greater than minimal risk. You just have more safeguards built into the process.

PROF. SCOTT-JONES: Another problem that occurs when you have minimal risk and then minor increase over minimal risk is that minimal risk is defined in terms of an ordinary, everyday person. And then minor increase over minimal risk is defined in terms of the individual research participant, and then the logic is used to justify higher level of risk to that individual participant than you would to an everyday person who doesn't have the problems of that potential participant. And it is then used to justify even greater risk to the individual participant, and I think that's a problem with using the two categories and defining them very, very differently from one another.

DR. CHILDRESS: That discussion is on 92 in the text.

PROF. SCOTT-JONES: Right, on 92 and 93.

DR. CHILDRESS: Okay, I have Bette and then David.

MS. KRAMER: It's late in the day, but it seems to me that maybe where the problem lies is in trying to define specific procedures as minimal risk or greater minimal risk, when in fact it depends on the context. So would it be possible to incorporate in the report that to capture that notion, citing for instance, Laurie's concern that this certain population not be automatically excluded by the use of a procedure that might in some context be considered greater than minimal risk; but then for people of another context, could possibly render great

knowledge. I don't know if that just confuses it more.

DR. COX: That was going to be my point. I mean we have something here, we have a distinction we want to make as an example. We don't make a whole new class. Make the class, which we're talking about and put in the distinctions, saying that by doing this we don't want to screw up and turn this into a complicated deal. I think here's one example of something you don't want to shut down. So you could just use this as an example and you don't have to make a whole new class about it. So I do agree with Bette.

DR. CHILDRESS: Alex, Jonathan, and Rhetaugh.

PROF. CAPRON: I have two points. One is I agree with the notion of staying with the minimal risk definition and then flagging for public response examples of research that would become problematic. Not forbidden, but potentially delayed and made more difficult under our charter. The problem I have is in reading the present sections on page 90 to page 100 based, I can't figure out what we're saying, because we mix two...to follow up on Diane's point, we mix two different issues. One is the question which was addressed by the national commission and then dropped in the language of the regulations. And we heard from Gary Ellis a while ago, very interesting discussion of that history and how OPRR looks at it now, which I don't think actually merges that clearly. I think we can go back to the transcript and get that position more clearly stated. Which is whether or not the bar is set by reference to things in the lives of people who have the diseases under study or the general population. That overlaid onto that is the observation that any particular procedure may be of higher or lower risk, particularly in terms of psychological reaction, for people who are in this special population than for people in the general population. As Bette said, that would be relevant if we were saying PET scanning or venous punctures or spinal taps are or are not on one side of the line. You have to say wait a second, something that's okay for you is not okay for someone else in this other category. So, but that's not really what this is about. This is about how you define that reference group, and then you may come back to the reference group and say, now when we evaluated a particular procedure, let's keep this other insight in mind that the IRB should ask investigators and ask non-investigators or experts on the population, are they going to react differently? Is there some reason why this is lower risk for them because they're so familiar with it, or higher risk because they're more disturbed by this? And this discussion, I don't know where we come out. If you look at the top of page 100, it sounds as though we're getting to our point. "For persons with mental disorders that may affect decisionmaking capacity, the risks that are minimal for general population may pose special psychological burdens, even with regard to interventions the person may be familiar with," and so forth, and we just ... it sort of peters out. I expected us to finally tell us that we expect people to use the general population standard or the specific population standard. I would like to know where we come out on that. Because otherwise our whole notion that we're setting a bar and

saying if you're over that bar, particular requirements click in doesn't mean anything.

DR. CHILDRESS: Okay, I have Jonathan, Rhetaugh, Diane, Alta, and Eric.

DR. SHAPIRO: Just after that long list is announced, we have about ten minutes, okay, before we have to turn to Tom. We'll take a half hour more tomorrow to try and ...

DR. MORENO: Briefly, we do have a box on the graph for exactly the contextualization of risks that you guys are talking about. And it is supposed to fall in this box that reads IRBs assess the investigator's determination of risk in light of the specific subject population, does this risk involve greater than minimal risk. And it's addressed in the recommendations in 171-172. But I agree with Alex that we need to indicate exactly where we come down on this earlier in the text, in the dicta portion and not only in the recommendations.

DR. DUMAS: Am I next? The concern that I have is not that we are eliminating anybody from the possibility of participating in the research. What we are doing is only classifying those people who need additional protections. And I would rather err on the side of more protections than fewer.

DR. CHILDRESS: Alta?

PROF. CHARO: I share Rhetaugh's presumptive directions. I know that's exactly where this source of disagreement is with Laurie. Perhaps for the agenda for tomorrow, I think it's possible that we would be well served if in conjunction with this report we were to try and produce a document as short as the *Belmont Report* and as influential for the ages, which focuses a little bit less on some of these details and little bit more on the thrust of why these details are being fought over. Such as, the coalescence of factors that leads to special vulnerability, the presumption in favor of excess protection at the risk of losing certain areas of research rather than in favor of research at the risk of exploitation, and why that particular presumption is being chosen. And examples of these tools with a focus on their purpose as much as their operation, including the retention of a minimal risk category that's defined by reference to the Federal regs, which do in fact talk about a general population that is an average of healthy and ill, which is one of the reasons why it is so difficult to understand because it includes both in its own existing interpretations. But that very deliberately does not try to redefine minimal risk by definition with this subject population. The only purpose for doing that, of course, would be to expand the number of people who can be researched upon without consent, without giving their own consent. And that's not our thrust. But if we were to try to produce something really short that highlighted the underlying goals, that might be a very important part, a most important part, of all of this exercise. Just one last thing in defense of staff, one of the reasons why this has gotten to be a hundred and so odd pages is that every minor thing that any of us ever mentioned as being of interest has now been incorporated. So we are collectively responsible for how difficult it is to

find the salient points.

DR. CHILDRESS: In some ways, it seems to me, you may be proposing a special executive summary, that is, a document that really says why this is very important, not quite an executive summary.

PROF. CHARO: It's not exactly an executive summary.

DR. CHILDRESS: But it's something that will play that kind of role. Diane?

DR. SCOTT-JONES: I just wanted to say that now that Jonathan has pointed out what the flowchart says, it does put this in a different light. But I would really strongly urge what Alex has said, that we do need to clean up the language in the text, or it is very, very confusing. And then also, I read really carefully what Laurie has said, and I know that she said that many times before, and I think that somehow we ought to acknowledge her position. If we agree ... if the rest of the Commission decides differently than Laurie's position, I think we really should acknowledge her strongly-held views.

DR. CHILDRESS: Anyone has a right to file a dissent if we end up ever finishing a report. It would be possible to have a dissent. Chair, we're at 5:15.

DR. SHAPIRO: Okay, thank you.

PROF. CAPRON: I just urge that if we're comfortable with the current Federal position which as I said, Alta, I believe Gary told us very nicely to just go back to the transcript, then we ought to have that in place of the discussion page 90 to 100 and just say, "Minimal risk means the present thing," and then maybe a footnote explaining the Canadian trial and the this and the that and all the different groups that have talked about it. And then come to this question which is the assessment of the risks of this research are compared against that metric.

PROF. CHARO: Right. And then emphasize again that IRBs are always welcome to say that although the research is generally considered minimal risk, to this research population it's not and we are choosing to treat it as nonminimal. That is always within their purview.

PROF. CAPRON: Exactly, but that's the standard.

DR. SHAPIRO: Okay. Jim has a comment. I want to make a comment, and Tom will be back and give us instructions.

DR. CHILDRESS: I notice that we have a few items left over for tomorrow. Harold said we could have about 30 minutes tomorrow. I think some of these won't take us very long. I would note in addition to the report here that Laurie also raised a question about our requirement of necessity to look at that as well. And then Trish has raised issues and a question about whether we have adequately dealt here with the question of conflict of interest. We sort of

mentioned it several times in passing, and it's implicit in some of the recommendations we make that what we're trying to do is really avoid conflict of interests, but we need to be more specific about that.

DR. SHAPIRO: Thank you. I'm going to turn to Tom in just a minute. With respect to the comment not that Jim made but the discussion that ended with Alex's comment, that is are we satisfied or do we get to be satisfied with the Federal regulation, which as Alta described as some kind of average, that may be a good to start. That bothered me a little bit when I went through this, frankly, and I tried to come to a formulation in my own mind which said something like the following, and I don't have this well articulated yet, but just give you the notion maybe we can talk about it tomorrow or another time: that we did allow ourselves to look specially at this population, but never and whatever we adopted would never exceed the Federal regulations, that is, you can only go away from the Federal regulations and that is to be more protective. And I was trying to formulate that effectively and I never really quite succeeded, but maybe somebody here might think about how we could formulate that and if it's a good idea altogether. So that eliminated the possibility that you would exploit this population by defining something which allowed greater leeway. But you would allow yourself to move in the other direction. That may or may not be a useful thing to think about, we can come back to that. There are two other tools which I came away with after reading this report, thinking that might be very useful in this area which we don't seem to ever discuss; as far as I can see others don't discuss it either. And I just want to mention them here. I've already mentioned it to Jim earlier today, and I mentioned it not to cause any discussion now—we don't have time—but to see if any of you might think about this and we could review it another time whether they're useful or not. The two tools I have in mind are audit and disclosure. In all these areas where we're struggling, whether IRBs are overworked or not overworked or whether we can define a regulation or not define a regulation, whether we want all IRBs to have the same rule or and so on, a lot of those, it seems to me, could be at least resolved in some respect either by a disclosure document where the IRB just indicated what it does and published it and people could look at it, and that's a certain amount of accountability. And/or whether audit of IRB procedures is something that's appropriate for us to consider. Not to audit every IRB every year, but whether IRBs on some basis might be subject to audit just to see how things are going. Because time and time and again we've come up with the issue that we're not quite sure just how the IRBs are doing and what they're doing. And it seems to me that those are two tools which may or may not be appropriate. I've not thought about it carefully enough, but they aren't used and are very widely used in other contexts for exactly this purpose. And so that's something I would just ask the Commissioners to think about as to whether that is even any conceivable way that those tools might be useful and simplified. The purpose would be to simplify yet sustain the effectiveness of what we're proposing. If it complicates it, I'm not so sure we want to think about it very long. So that's just

something to think about, but let me now try to adjourn the meeting by turning to Tom to give us some instructions and then it's tomorrow morning, what time do we convene? Eight o'clock tomorrow morning. Tom?

PROF. BACKLAR: Are you going to start with this in the morning?

DR. SHAPIRO: Yes, we're going to start with this.

DR. MURRAY: [Administrative details].

PROF. BACKLAR: If Jim has any time to call me this evening, he's welcome.

DR. CHILDRESS: I'll call you.

[End of discussions of Day 1)