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I N D E X

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

PUBLIC COMMENT

PROFESSOR CHARO: I would like to introduce myself. I am Alta Charo.

While we get Trish Backlar and Rhetaugh Dumas reconnected, and while the remaining Commissioners get back from lunch, let me just note that there were no people who appeared to testify during the public comment session but let me just check again if there was anybody that did want to testify during the public comment period.

If there had been, this would be a great time to identify yourself.

Great. Okay. If you would please come forward to one of the microphones, sir.

PROFESSOR CAPRON: He is for the next panel.

PROFESSOR CHARO: He is -- that is Dr. Kahn, who is going to be speaking on our next panel. So, please, if you would come forward to a microphone, give us your name, and if you have an affiliation, give us your affiliation as well for the transcript, please.

And if I can just remind you, although there is not a crush here, the usual rule is that we ask people to limit their remarks to five minutes and we ask you to present anything you like in writing at any

length.

DR. WEINBERG: I came here as a spectator and a person with many years of experience as a chairman of an institutional review board for a major hospital in Southern California.

My name is Dr. Weinberg and I came as a Chairman of the Glendale Adventist Medical Center.

The thing -- I was very impressed with the deliberations today and I did not know what to expect and it was a very impressive demonstration.

The thing that disturbed me, though, with apologies to you, and the comment that this gentleman made is that I find it difficult to tie biomedical ethics to women's liberation. I think it complicates it unduly. If you are going to tie -- and I am for women's liberation. Ask my wife.

But there are places in the world with -- where regardless of how you personally feel about it and regardless of how the educated element in that society presents their stance, women are chattel. Their husband effectively owns them. In those areas often the medical and biological problems are most apparent and certainly deserve to be an area of research and to be an area which is gender-free research.

However, I do not feel that the research organizations should be required to predicate their entry into that area with a philosophical idea of a respect for person. Respect for person has many meanings.

I could not be more against the idea of an institution or an organization or a drug firm going into an area and approaching the owner of the ladies, and many times it is plural, and telling him that if he supplies the subjects he will be rewarded for them. That to me is a form of soliciting prostitution.

On the other hand, with respect for their situation, it seems only appropriate that the husband or the spouse or the village elder, whoever it is, be included into the decision making. They should be informed but they should be promised nothing. In other words, the restriction on research in that area rather than gender associated should be spelled out so that no -- there would be no reason for them to accept or proffer their chattel for remuneration. That should be spelled out. Companies should not go in there and say to the husband or the head man I will pay you so much if you deliver your wives. That would be wrong and I think that is more important a consideration than forwarding the cause of women's lib. It reminds me of

a rider on a tax bill that has nothing to do with taxes.

Thank you for your time.

PROFESSOR CHARO: Thank you.

Are there any people -- before you leave, Dr. Weinberg, any members of the Commission who would like to direct comments to Dr. Weinberg?

Okay. Thank you very much. We appreciate it.

DR. WEINBERG: Thank you.

ETHICAL ISSUES IN INTERNATIONAL RESEARCH

CHAPTER 2 - INFORMED CONSENT (continued)

PROFESSOR CHARO: Next -- although it is not on the schedule, we are going to return briefly to Chapter 2 from the International Report. Dr. Capron -- Professor Capron will continue the discussion on that before we then move on to the scheduled business for the afternoon.

PROFESSOR CAPRON: Just so that we can provide staff with a further input, I wanted to see whether the sense that Recommendations 9 and 10, which suggest first that it would be useful to consult with community representatives for learning creative and innovative ways to communicate necessary information and then, second, Number 10, that researchers should devise means to ensure that participants do, in fact, understand the

information, that those are unexceptionable from our viewpoint. They are ways of elaborating on the requirement of getting informed consent.

Does anybody have any amendments or disagreements with those recommendations?

All right.

Recommendation 11 is the one --

(Technical difficulties.)

PROFESSOR CAPRON: Eric said that having had a conversation he would fill us in on what that comment means.

DR. MESLIN: Just very briefly, the -- I do not have my text in front of me or even my notes to -- someone has 11 -- do you have a -- yes.

The phrase "researchers should develop and implement a process of community education and consultation to take place before, during and after the research" struck Harold as potentially being a very large obligation, the scope of which was undefined. So his question was one of scope rather than of substance.

What would that involve? How long would it occur and the like?

Now, of course, in Ruth's absence, she cannot speak to this directly but others --

PROFESSOR CAPRON: No, but she said she was

going to listen to the tape or the transcript.

Steve?

MR. HOLTZMAN: I had a very similar concern because I found myself writing "researchers should, if necessary and useful, to engender," and then I found myself with a blank.

And then, of course, if we fill that in appropriately, we will be fine and we will all agree with it.

(Laughter.)

PROFESSOR CAPRON: So where do you want to go with that observation? Do we want -- is it a matter of refining it more as to a process -- such process as is necessary to enable potential subjects to make choices or is that too broad? Or is that at least some of a restriction from a general language about education and consultation? Is this an important point or is this just sort of a commentary on another point?

Bill?

MR. OLDAKER: I did not -- if this is additive to the consultation that has to be done with the subjects themselves then I am not sure we really need it. It seems to me that there is an ethical responsibility to consult with the subjects and to explain during, before and after certain things to

them.

I do not know what in addition one would be telling the community leaders other than what one would be telling the subjects themselves.

And so, you know, if that is what we are doing and we are saying this is additive and you have to tell the community leaders what you are telling the subjects, then my question would be, you know, as to the rights of privacy and in some areas as to the subjects, and how far we want to go with that.

And so that is why I was a little perplexed by it.

PROFESSOR CAPRON: Yes, I did not understand this to be community leaders but the community from whom subjects would be drawn is I think the idea.

MR. OLDAKER: And I am not sure who that is if it is not the community leader. Now if it was the health minister, I can understand us saying that you had to consult --

PROFESSOR CAPRON: Oh, I see. It is the word "consultation."

MR. OLDAKER: Right.

PROFESSOR CAPRON: Yes.

MR. OLDAKER: Exactly.

PROFESSOR CAPRON: Okay. So education and

consultation. Maybe if we were speaking here of education, that is to say before you start recruiting people in the community you do some education about the research process, that there is some group that has come into the community, that has met with the community leaders, they will be through clinics or otherwise looking for subjects. This is what the research is about. This is the process of asking for consent that will be gone through and so forth. I mean, just -- in other words, I think that is probably what is in mind. Whether it is a good idea or not or should be a requirement or should simply be an example to follow on Recommendation 7 that out of that process of getting community leaders' consent you might then have a community education program.

We have examples in the testimony we heard of people doing exactly this but whether that is a requirement or simply an illustration of a good way of going about things --

MR. OLDAKER: And I understand prior to. I am not sure what you would be doing during and what the responsibilities would be afterwards if we do not spell them out in some way because I am not -- in a lot of the tests -- a lot of the trials there will not be any information to communicate afterwards, I would think.

PROFESSOR CAPRON: Okay. Those of you who have not spoken, the sense conveyed by both Bill and Harold is that this is too vague a requirement, that if -- the should is a strong one. It is too onerous and if the should is a very weak one it does not amount to much. Is that a fair statement?

MR. OLDAKER: Mm-hum.

PROFESSOR CAPRON: Where do other people come out on this last recommendation? Jim?

DR. CHILDRESS: I would be in favor of deleting it.

MS. KRAMER: I would, too.

PROFESSOR CAPRON: Bette says she would too. Arturo says he would. David?

DR. COX: The same.

PROFESSOR CAPRON: The same. Yes?

MR. HOLTZMAN: The question is --

PROFESSOR CAPRON: Steven?

MR. HOLTZMAN: The question is that if you look at Recommendation 9 where we have the consultation with the community leaders, I suppose 11 adds something in addition in the second sentence certainly that would say that you should outline in your protocol to the IRB what your process is going to be.

So maybe there is a way of tying those two

together because it is not clear to me that 9 in some respects is any less vague. Or if we think it is less vague when it says "necessary information" that may be the handled for the education and consultation.

PROFESSOR CAPRON: Well, with that recommendation then perhaps we can put this to bed. As I understand it then, probably as to 9 and 10 the notion that the protocol that is approved by an IRB should include information about how these steps are going to be carried out. And as to 9, recognition that in consulting with community representatives you may be able to get advice about how to carry out individual education as part of the consent process and there may be also some advice about means of collective education and the idea would be, depending on the circumstances of the particular research and the particular community and so forth, different mixtures of those may turn out to be appropriate in different circumstances.

And we would fold in any thought of community education as an illustration or as a point to be considered in the explanatory material that follows the recommendation.

PROFESSOR BACKLAR: Alex?

PROFESSOR CAPRON: Yes. Go ahead. Is that Trish?

PROFESSOR BACKLAR: It is Trish.

PROFESSOR CAPRON: Yes, go ahead, Trish.

PROFESSOR BACKLAR: And I was thinking there was somewhere some explanatory material and I do not know if it was in this chapter. We had a researcher who came who talked about precisely doing this over a some kind of radio program and so on and so forth.

PROFESSOR CAPRON: Yes.

PROFESSOR BACKLAR: Ruth -- is Ruth still there?

PROFESSOR CAPRON: Ruth is not there but I think it was the man from Haiti.

PROFESSOR CHARO: Jean Paul.

PROFESSOR BACKLAR: It was not just in Haiti. There was somebody else who -- from another place, whose name I do not recollect. And which they did a considerable amount of education through whatever media was available.

PROFESSOR CAPRON: Okay. We will remind Ruth of that as material. This recommendation would probably spring from a discussion of that material.

PROFESSOR BACKLAR: Correct.

PROFESSOR CAPRON: Yes, Bernie?

DR. LO: I know there is pressure to move on, I just wanted to say two quick things. First, around

lunch Alice, Ruth and I tried to draft some alternative language for the discussion we had this morning and maybe I can give that to one of the staff and see if we can get it typed up into something that is legible.

Secondly, I think we are missing some recommendations here on first the therapeutic misconception and, secondly, the need for NIH to sponsor research on how to do informed consent in different cultural contexts and to have some form by which researchers can sort of share best practices.

I wrote some specific language. I actually gave it to Ruth and Alice who are not here but maybe we could -- I could bring it in tomorrow and we could xerox it and look at it or e-mail or something. I know we cannot do it today but those are just two things to sort of mark on the agenda for more discussion.

PROFESSOR CAPRON: Alta?

PROFESSOR CHARO: Just a friendly amendment, I hope, Bernie, because my understanding is that NIH in the last few years has, in fact, put out requests for proposals for a number of studies on the informed consent process, including a variety of cultural settings so that I think to first look at what has already come in and what is in the works first before a recommendation that formally calls for further study

might be a wise thing to do and then revisit it.

PROFESSOR CAPRON: I also want to put on the record something that I hope we will be seeing tomorrow or subsequently from Ruth and Alice as a result of a helpful intervention by Jim Childress suggesting that there is a middle way between the alternative (a) and the alternative (c), which uses the notion of presumptions that people will be independently approached but recognizing that there may be circumstances where that presumption might be overcome and I suppose the kinds of circumstances may relate to whether or not if the research is not done there it will be impossible to do it anywhere would be an example of the kind of justification that would have to be spelled out and further considered by the IRB.

So we will see what they come up with there but I think he suggests that one of the reasons he did not vote on the alternatives we had before us was that he felt there was a need for yet a fourth alternative somewhere in there.

So I think what we -- all I was trying to do -- and I realize I was pressing people to vote on something where they thought that the vote did not fully summarize all the discussion -- was that there have been a number of times when we have looked at

something that came out of a previous meeting and there have been cries of distress.

And I think if we trace it back to the previous meeting, at least in some of those cases, it was because a number of people were making points which really were not compatible with each other and it was hard for the staff to know where the Commission as a whole on balance would come out.

And clearly the discussion on this issue of husbands and wives this morning left us with a lot of conflicting ideas but also some substantial division and we will have to see how that is spelled out with the recognition that it may be a circumstance in which we have some separate or minority statements on a particular conclusion.

And with that I turn it back over to Alta for the afternoon discussion.

Thank you.

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS RESEARCH

PROFESSOR CHARO: Thank you, Alex.

Okay. It is now 1:50. We are about 20 minutes behind schedule. We will see if we can pick up any time during the afternoon.

I would like to begin with a brief overview of

work to date by Dr. Marjorie Speers on the Domestic Human Subjects Research Oversight Project.

OVERVIEW OF WORK TO DATE

DR. SPEERS: Okay. Thank you.

Over the next three to four months we will be drafting chapters for the Oversight Report. By September you should be able to see drafts. At this meeting and at the July meeting we will continue to hear testimony and discuss potential recommendations. However, we are moving as quickly as we can to have written material for you to review and discuss. We realize that it is much easier for you to have a discussion about recommendations when you have written materials in front of you.

Following the May meeting, we revised the recommendations regarding the definition of human subjects research. The draft recommendations were distributed to you via e-mail. Based on the comments we received, we revised the draft recommendations. The current draft recommendations were included in your materials for this meeting.

Most of the concerns about the definitions deal with issues that are better addressed, I believe, by other recommendations such as those that are likely to deal with types of reviews, that is full board

review, expedited review, exemptions, or waiver of consent.

These types of issues will be addressed in upcoming meetings and what we would like to do is to revisit the draft research definition recommendations when you are able to review them in the context of other recommendations related to IRB review.

If you have written comments on the draft recommendations, please give them to me. Alta has given me her comments and if anyone else has comments on the draft that was circulated to you, please give me those comments. Otherwise, we will come back for another discussion on the research definition recommendations later.

This afternoon we will be discussing informed consent. Dr. Jeffrey Kahn will make a presentation based on what will appear in his paper.

Because this topic is of great interest to you, we have allowed an hour for discussion today. This is an opportunity for you to bring up issues that you would like to bring up around informed consent and also to revisit some of the discussion that we have had via e-mail regarding informed consent.

You may want to have the discussion today with a thought of identifying areas where you will wish to

make recommendations or even to suggest recommendations that we will then discuss more fully at the July meeting.

The second panel is a round table discussion with representatives from the private sector.

The Commission, as you know, but I will say this for the audience, voted unanimously in 1997 to adopt a resolution that all persons who participate in research should have the protections afforded by an IRB review.

If federal protections were expanded to the private sector it wold include industries beyond the pharmaceutical and biotechnology industries.

Today you will be having a discussion with representatives from the auto and food industries.

We will end the day with a discussion on alternative models to the U.S. system. Our plan is to link Professor Donald Chalmers via the telephone from Malaysia. If the link fails it is likely that we will adjourn early today.

Tomorrow we will begin with a presentation on independent IRBs. This will be an opportunity for you to ask questions you have about the independent IRB system. A second panel will discuss the purpose of regulations.

Alta or I will have more to say about these panels in the morning.

Our main task tomorrow will be to consider options for improving the current regulatory framework. We will not be dealing with the substance of regulation but rather with regulatory structure.

Options were sent to you by Federal Express. I hope that you will have a chance to review them by tomorrow so that we are able to conclude the morning with one or two recommendations.

Finally, when you have raised questions with presenters or even for the staff that have not been answered during the course of a meeting, we have followed up to get answers for you to those questions. And included in the materials that were sent to you are the responses that we have received to date and we will continue to do that as we receive responses or additional questions are raised.

Yes?

DR. BRITO: A quick question because there are so many papers and I am not sure what I downloaded and what I have got here.

The recommendations they were talking about, initially there were two recommendations on one page. Is that dated May 24th? Is that the latest version?

DR. MESLIN: Yes.

DR. BRITO: Is that correct?

DR. SPEERS: Yes. So it is dated May 24th.

DR. BRITO: Thank you.

PROFESSOR CHARO: Marjorie, two questions by way of clarification. You said there were options sent to us by Federal Express. Can you identify what in the packet is an option that you want us to be -- these colored charts?

DR. SPEERS: Yes.

PROFESSOR CHARO: But when you say "options," I am thinking you want us to be voting on something. You just want --

DR. SPEERS: We are going to --

PROFESSOR CHARO: -- to present --

DR. SPEERS: We are going to present those tomorrow to you and --

PROFESSOR CHARO: Thank you.

DR. SPEERS: -- I just want you to familiarize yourself with them so that we could move to recommendations.

PROFESSOR CHARO: Okay. Thank you.

One other remark with regard to the material. The definition of human subject that Marjorie referred to and for which she requested comments was the single

sheet all in bold type.

I just want to highlight for people's attention that it embodies the latest thinking on a discussion about the way in which we will handle third parties about whom information has been developed by intervention with a first party. So it is research on a cadaver that yields information about family members, which is specifically contemplated in there.

What is not contemplated in there but has been the subject of controversy around the country is intervention with an individual, a living individual that yields information about that living individual's family members. And that is no longer present in the definition so I would urge people to take a look, decide how they want to come out on each of those issues, if they want them to be the same, different, and please send in your comments to Marjorie in writing so that she can get everybody's feedback.

Steve?

MR. HOLTZMAN: Can we ask questions about this?

PROFESSOR CHARO: Sure.

MR. HOLTZMAN: Not -- just for clarification.

PROFESSOR CHARO: Sure.

MR. HOLTZMAN: The last part of the definition

of human subject, Marjorie, are you saying human subjects include living individuals who provide data about others where -- and then it goes to the end, real risk to the individual providing the data? So we are not trying to say that the people with respect to whom information is provided are the subject. It is rather the individual who is providing information about others wherein that information about others comes back and affects the first individual.

PROFESSOR CHARO: Right.

DR. SPEERS: That is correct.

PROFESSOR CHARO: Any other questions before we move on to the presentations this afternoon?

Okay. With that I would like to welcome Dr. Jeffrey Kahn, who is the Director at the Center for Bioethics at the University of Minnesota. You have an annotated outline of his contract paper on informed consent.

Dr. Kahn, thank you very much for coming.

PANEL I: INFORMED CONSENT

JEFFREY P. KAHN, Ph.D., M.P.H.,

DIRECTOR, CENTER FOR BIOETHICS,

UNIVERSITY OF MINNESOTA

COMMISSIONED PAPER: INFORMED CONSENT

IN THE POST-BELMONT ERA

DR. KAHN: It is my pleasure to be here.

I think before I launch into my presentation I want to say one thing about a comment that Alta just made about the NIH and funding research on informed consent in the research context, if I may.

I serve on the Study Section that has reviewed now three rounds of proposals in response exactly to that initiative and I will tell you that of the three rounds that have come through so far, I think there may be 15 or 20 that have been funded, none of which deal with cross-cultural issues unless you think about diverse populations within the United States as being cross-cultural. So nothing outside of the U.S. context.

So if the Commission felt a recommendation along those lines was appropriate, I think that might be welcome.

The last time we met to review, which was only in March, there was a real sense that there was a lack of high quality proposals and I think that you have identified a gap in that area so I would encourage that.

What you have before you, as Alta mentioned, is an annotated, a fairly heavily annotated outline around issues in the informed consent post-Belmont.

What I thought I would do with you today is take a few minutes, not terribly long, and walk through my thinking along the lines of this outline in an effort to talk about the shortcomings in informed consent because we have staked so much of the ethical weight in research to the concept and process of informed consent, and I think it will help identify where the recommendations ought to go if we have a good sense of what is wrong with the way the system now works.

So the outline you have before you is laid out in four large Roman Numerals and I thought I would just walk through for maybe 10 or 15 minutes what you have here before you.

I think we all know, and I will not dwell on a lot of these things because it is so well known to all of you and to those who work in the context of research but let me just identify a few of the highlights so that we are all on the same page.

I think we know that the informed consent process is flawed, both in the way it is carried out and in the way that subjects perceive that process and that experience.

We know that the short-comings lie in areas like the quality of informed consent. You have seen in

the outline that I have identified a few of the studies that have shown this. I worked on the study that the Advisory Committee on Human Radiation Experiments undertook to examine the informed consent process. In 1995 we looked at informed consent forms that had been approved by IRBs and found what will be not surprising to anybody in the room or to people who do research that the consent forms were nearly universally difficult to understand, that they had reading levels that were too high, that the language was very technical and the detail was often overwhelming, leading to a problem, I think we would all agree, in whether informed consent was really achieved.

I think that we know sort of where the process has broken down but I think it is not just about the way we have implemented informed consent. It is also about the way research has developed since the Belmont Commission did its -- the Belmont Report primarily was written by the National Commission in the mid-1970s.

So I think what I would like to sort of say now are a few things about the challenges that clinical research poses in the post-Belmont era.

I think you will hear more about the notion of the shifting emphasis towards the benefits of research and away from protections from other contract papers

but I think it is an important part of the context about how informed consent works in the current world.

I have laid out, I think, a short argument about where that shift in emphasis has occurred and why, and it is a relatively recent change in the way we think about research.

So when the Belmont Report was written we were really emphasizing or interested in emphasizing justice as protection from the harms that research carries and since the mid-1990s, if not before, we have really started to talk much more about access to the benefits that research has to offer, which changes the way people ought to think or people will think about what research means to them as potential subjects. And, therefore, raises challenges for how we do informed consent in that context.

I think this is an issue that is through going. It is not something that is particularly important for one area of research versus another. We can point to things like HIV/AIDS research and clamoring for access to those clinical trials in that research area as one example. We can point to the work of the Institute of Medicine on women in clinical research as advocating for inclusion in that context.

But I think it goes all the way through the

system now and I, in fact, was just reading in the New York Times the day before yesterday that Vice-President Gore has said that we ought to double the amount of money going to cancer research so that more people can participate as research subjects. There should be no barriers to research based on money, for instance.

So when we are seeing all the way through our system up through the highest levels of our government admonitions that we have to do better about making access to research available to people, I think you can see where it puts pressure on the process of consent to make sure people really understand what they are getting into.

In addition to the sort of shifting of emphasis, I think we have known for a long time that there is an important problem or an important issue in the way research and therapy have long been entwined with each other and are now only becoming much more so leading to often misperceptions of research subjects and potential research subjects.

So we have a pretty strong sense, I think, from the empirical literature that people are confused and that confusion, I think, lives at two different places. There was interesting discussion this morning and mention of the area known as the "therapeutic

misconception" but I think actually that there are two things going on in what we often term the "therapeutic misconception."

And one is a confusion not about seeing benefit or experiencing benefit when one is a research subject but actually not understanding the difference between what is research and what is actually therapy, which is, I think, a different problem than therapeutic misconception.

And we know, not from terribly much empirical research but at least from some research done by again the Advisory Committee on Human Radiation Experiments, that there is a significant number of people who misunderstand what they are engaged in. They either think that they are in research when they are not or, more problematic, think that they are not in research when they are.

So the first case is sort of the wannabe research subjects, which is an interesting problem in and of itself. But the second case is more problematic, which people have turned the unwitting research subjects, and that is certainly a problem for informed consent.

If people sign pieces of paper or go through a process in which they are supposed to be informed and

consenting in a voluntary way to participate in research and then do not understand that they are in research and not getting clinical care, that is problematic. That undermines the very notion of what we think about as informed consent in the research context.

So that perception, the confusion between research and therapy, really challenges whether we are doing informed consent at all.

And then, as you have talked about already today and I am sure in other meetings as well, the concept of the therapeutic misconception is one that challenges whether people really understand as well. That being the idea that even though I know I am in research, I also know that I am going to get some medical benefit from my research participation.

And it has been shown that, even in the context of placebo controlled trials, people really believe they are going to get active agent that will really help them based upon their diagnosis and medical needs. That is a somewhat different issue, I would argue, than this confusion between research and therapy but certainly no less a problem or a challenge for how we do informed consent.

The third area that I think that undermines or

challenges informed consent in this area of clinical research is the, I think, increasing blurring of the roles of physicians and researchers. We see this, in particular, in areas like cancer research. In particular, pediatric cancer research where physicians are not only caring for patients but are also often investigators, if not principal investigators, of the studies in which their patients are being enrolled.

And that dual role problem or two hat problem really challenges how well people could, let alone do, understand informed -- have informed consent and understand what they are getting into in the context of research when the same person who is caring for them as their physician is also an investigator trying to recruit them into his or her clinical trials.

I think all of this is true historically and continues to be problematic as we move ahead into the future. And if you sort of bundle this together with what I have labeled here as the evolution of areas of research, sort of moving from the kinds of research that was being done in the immediate post-Belmont era to what we see today, the things are really quite different in the research enterprise. It is not that the people are different or that the challenges might not be that different but that the kinds of research

certainly are, and that challenges the way we think about how consent ought to be sought and, hopefully, achieved.

In my -- the final paper that I will submit to you, I will try my best to lay out in tabular form if it will work, sort of the kinds of challenges that arise in different research populations, in different research types, and in the places where research is done.

I have made a first stab at this in the annotated outline you have before you and I think just by looking at the way the X's line up in the boxes you see that different kinds of research, different research populations and different research settings raise different kinds of ethical concerns, which means we ought to do informed consent at least in different focused ways in those various populations, research areas or research settings.

And I think that is just instructive for how research is really different in different areas, and I will certainly do the best job I can in laying out what those differences will -- do look like and will look like in the future.

An important area that I hope you will agree has to be addressed is a practice that many IRBs engage

in, which is to apply what is often boilerplate kinds of language or approaches to informed consent in research. The idea that I have labeled here in Roman Numeral III as the problem of one size fits all informed consent.

And as the chart, the table that I have presented to you here in rough forms, shows not all research is the same. It raises different issues. It is different kinds of research and it includes different kinds of subjects. And I think, therefore, we ought to rethink how informed consent ought to proceed to reflect those differences.

We have focused in large part in creating our regulations and the informed consent process that grows from it on biomedical research and often to the exclusion of other areas of biomedical research, even clinical research, which obviously is an important area but not the only area in which ethical issues in the protection of human subjects arises.

In addition, I think we have done a rather poor job of distinguishing the issues that arise in Phase II and Phase III clinical trials when we are talking about clinical research, when we are outside the context of clinical research, social science research and the particular issues that arise in that

context, along with other nonbiomedical research, what we ought to be thinking in terms of informed consent related to research on healthy subjects, and sort of conceptually how to "rejigger" that, if that is the right term, to better reflect the concepts of informed consent and the oversight process in which we all try to do our research.

Lastly in that Roman area is an issue that I think is not going to be surprising or new to anybody here, and that is that we ought not focus as much on the process of informed consent -- pardon me -- on the forms that we use in the informed consent process and ought to focus more on the process itself.

Informed consent, of course, is a relationship between subject and investigators and those that work on the research and not about pieces of paper with signatures on them, and we have to get away from that over reliance on pieces of paper and the boilerplate language that often gets included in them.

Just to sort of wrap up, all of this identification of short-comings will not really amount to a hill of beans unless we have some discussion of the implications for how we ought to improve the process and the practice of informed consent.

And I would like to sort of leave you in terms

of how we start our discussion with six areas, which actually are not reflected in this outline because it is sort of the where does this all come out. The answer to the question about where this all comes out.

And I would suggest that there are six particular kinds of recommendations that I would offer you for your consideration around two categories: The process of informed consent and the information contained in it.

In terms of the process, I think we have to first of all focus on education for investigators and physicians and others in the research community. Coming down from the Public Health Service, we are already going to see requirements for researchers to receive education and training in the responsible conduct of research. That, I believe, will be a sort of empty -- not content rich recommendation or requirement from PHS/HHS and this Commission, I think, stands in a good position to tell -- to give direction, pardon me, to recommend what kinds of content areas ought to be addressed in that education and training.

So there is an opportunity to make sure investigators understand what the short-comings in informed consent are and how to overcome them. I think we have to go outside of investigators in that

context as well and talk about education of the physicians who refer their patients into clinical trials and to those who work in the research context outside of the clinical area so that they understand what does not work in informed consent and how we ought to improve it.

Secondly, in terms of the informed consent process, I think we need to consider the addition of additional parties to the process of informed consent. There is lots of debate and discussion at the IRB level about whether it is appropriate for only the investigator to be doing informed consent or whether it ought to be somebody other than the investigator, anybody other than the investigator, because of the power differentials that occur between subjects and researchers.

But I think that is too narrow a debate and that we ought to think about who ought to be in the room in addition to the investigator and/or research staff:

To include people like ombudsmen or ombudspeople, whatever the gender-neutral term is for that, as a way of getting an objective non-affiliated individual into the process. Not just to make sure that there is an advocate say for patients or subjects

on the IRB but in the process of informed consent in an ongoing way. This individual could be a part of the IRB or not, and I think goes to the possibility, if not the recommendation, of ongoing audits of the informed consent process in research.

In addition, I think that there is some validity in ideas like including subjects, existing subjects, in discussions with prospective subjects about what research participation actually means.

This has not been done, although it has been proposed by a few people, and I think it is an interesting idea whereby the power differences between researchers and subjects is in a way addressed by allowing subjects who are in trials or in research to sit alone with prospective subjects and have a frank conversation about what that research actually is like.

I think, in particular, we need ongoing audit and these sort of third party advocates or ombudsmen in the context of research where there is proxy consent given or waivers of consent. I think those sort of raise the stakes of how we ought to make sure consent takes place in acceptable ways.

A third area related to the process of informed consent is that we have to do -- find other ways to achieve informed consent other than pieces of

paper that people read and this is not new and I am not unique in suggesting some of these options but I think we have to look hard.

And the kinds of research that is being funded by NIH now actually speak to a few of these areas, the research that I mentioned at the beginning of my remarks, whereby individuals may watch a video or use an interactive CD to go through the consent process or have individuals other than the investigator in the room and discussing the research with prospective subjects.

So expanding outside of the typical pieces of paper that subjects are asked to read and then sign as a way of achieving informed consent.

Some of these things are staked to the IRB process and so maybe it is appropriate to talk about them in the context of how IRBs do their work and how oversight works and others, I think, are really specific to the process of informed consent.

The last three recommendations that I would sort of put forward in a general way relate to what the content of the consent process ought to include. You have heard me say that I think it is very important that we do a better job of distinguishing research from therapy and I think that is at the top of my list

certainly for clinical research issues.

We have to do a much better job of helping potential subjects understand that research is not therapy and how it will be different for them to participate in research than it would be if they went to "standard therapy" for whatever their disease or illness might be.

Second, I think that we have to do a better job of helping IRBs and researchers identify the particular areas in which they ought to focus in their consent processes for different kinds of research. So we have now ten points that IRBs look at for what constitutes valid informed consent and those are quite general kinds of information.

If we look at the kinds of research that are being done, genetic research, research that involves pregnant women and fetuses, we have to think quite differently about what ought to be in consent processes, not just consent forms, and we have to do a better job and be able to do a better job of directing researchers and IRBs towards what they ought to include outside the standard boilerplate kinds of language.

And then, lastly, I think we have to do a better job of making it clear to potential subjects the ties that researchers have, both financial and

otherwise, to the research that they are carrying out so that it is clear when there is role overlap between physicians potentially in the clinical research area and the research that they carry out or the funding for research that subjects are being asked to participate in.

The last thing, which you have already said and which I have spoken to as well, is that I think there needs to be ongoing research on informed consent in the research context. That has begun with the recent NIH RFP and the few studies that have been funded and are ongoing. No results have come out yet but I think it is important that that be encouraged to continue.

So with that I think I will stop and engage you all in conversation if we can do that.

PROFESSOR CHARO: Thank you very much, Dr. Kahn.

Alex, Bernie. Anybody else already want to get on the -- and Jim.

PROFESSOR CAPRON: Jeff, I know it is going to be very helpful to have your paper because you have already done a nice job in the outline of teasing apart some of the distinctions.

I wanted to take you back to the first set of

distinctions that you were making about the challenges to the idea of informed consent and I have a comment and a question for you in talking about has research outpaced the Belmont era, as you put it, approach to informed consent.

The comment is that under the heading of the "Shifting emphasis towards the benefit of research participation," I see you lumping in there something which, I think, is a distinct, though not irrelevant topic, and that is the benefits to the categories of people.

For example, women, who would benefit by systematic research being carried out on their population rather than what happens now with research being carried out on males and then applied on the clinical level willy nilly to females without careful research on the potential differences.

That seems to me a very different phenomenon where we say that we are now more concerned with the benefits of research and making sure that those benefits are available to a category of people who are the beneficiaries after the completion of the research from the other idea, which you have here, is the benefit to subjects from participating in research where the research offers a potential means of

addressing a medical problem they have for which there are apparently no other satisfactory, in terms of side effects or outcome or cost or whatever, not adequately satisfactory alternatives.

And certainly the AIDS example, the HIV example, I think, has led people widely to say that by the 1980's this paradigm shift had begun to occur and with that impetus was more broadly perceived.

I think it is important to keep those two things distinct because they have different effects.

Now my question for you is what does all of this have to do with informed consent?

Now there are several answers that I have been -- maybe I should just let you answer it but let me give you a couple of alternatives.

One is that -- one would be -- well, it has to do with consent because the emphasis on protecting subjects meant that we wanted a very high standard of consent with the recognition that telling people certain kinds of information about risks and insisting that they get educated about a lot of stuff would be a barrier and would keep some people from participating, and that was okay because the main thing we did not want to have happen was someone participating in research where they were not fully informed and fully

voluntary in doing so.

A second alternative, I suppose, is that the way in which this paradigm shift arises is that the groups of people who we would consider suitable subjects for research in terms of so-called vulnerable populations would change, that where we thought in the past that we were very concerned that people whose illness meant that they really were either not able to deal with a lot of facts, there was some impairment because of their mental condition, or they were just so desperate, and we often think in this case actually more of parents who are desperate for a cure for their child or something, that the consent side -- not the informed side but the consent side is undermined and that these vulnerable populations were, therefore, people that we wanted to sort of keep from being used in too much research.

And maybe the women's example snuck in that way because we thought, well, women are vulnerable because of their medical conditions or if they are pregnant or whatever. I do not know. I mean, I do not know where exactly that came from.

But neither of these, it seems to me, go to the heart -- I mean, you could have a recognition that benefits -- the benefits model is now a major part of

the consent process instead of just the vulnerability and risk and protection model, and you would still have basically the same consent process.

It would just be that where researchers want to describe the benefits of research they are either given more encouragement to do so or more liberality in doing so if those can be made palpable but it does not really change the model of informed consent.

So that I have thought that the shift in the paradigm has had more to do with the types of research that people think is acceptable to carry out or the populations that one might go to, to do it, rather than the consent process.

So can you both respond to my first point about being clear about where the paradigm shift originates and maybe putting to one side the orphan populations as the idea goes that women are an orphan population, and then respond to this question of what does this really have to do with consent?

DR. KAHN: So the first point is the difference between benefit to groups and benefit to individuals, which I think you are right about, and it is obviously not the same thing. That is your first --

PROFESSOR CAPRON: Well, and I would almost exclude -- I mean, if I were writing this, my

inclination would be to note the recognition that certain groups -- I mean, the idea from the IOM study and then the NIH declarations that we have to have more women involved in research as well as more studies that look at women's illnesses but that does not -- that is not this paradigm shift.

DR. KAHN: Well, I think it goes -- I think they are all of a piece, and I will tell you why. I think that we do know from some of the empirical work that there is a tendency anyway, independent of the shift, to -- in the process of informed consent, if you think the paper is anything like a stand in for the process,to underestimate the risk and over emphasize or over estimate the potential benefits in clinical research at least.

So if you couple that with the swinging of the pendulum towards more emphasis on the benefits that research has to offer then you see, I think, it sort of pushes the consent process even further out of whack towards an over emphasis on the benefits and under estimation of the risks.

So I do not know that it means we should change the consent process so much as it means we have to think hard about how to make sure that the information that is portrayed in our consent process is

accurate and objective, and it gives people the right sense of what we are asking them to do. Because, you know, I think we always say this but it bears saying again, research is about uncertainty. We do not call it research if we know that it is going to work and we have to give people a strong sense that that is true.

And if we start saying "and there is all this benefit to you and all these benefits to you and to the group that you belong to," I think we tend to shade it even further away from how we want to in terms of objective information about risk and benefit.

PROFESSOR CAPRON: Yes. I agree with what you are saying. I just do not see that as outpacing the Belmont era. I mean, to the extent that the Belmont era is associated, I guess is your way of putting a research review process that worries about people being brought into research where they do not really understand what they are getting into and where the risks are too great, and they really ought -- either no one ought to be involved or only people who are very highly informed of what the risks are ought to be involved.

I do not see that that is -- that any of this changes that. Are you just simply saying it reminds us of the need to be vigilant?

DR. KAHN: Well, it certainly does that. I think it is more than that, though. I think that the way that -- immediately post-Belmont or the post-National Commission era, we thought of justice as making sure that mostly the risks were fairly distributed amongst subjects.

Now we are talking about not only a fair distribution of risk but a fair distribution of benefits and I agree it does not change the sort of framework in which we do consent, maybe that is the point you are trying to make. If you are asking that question, does this change the framework of the general process, I would say, "No, it does not change it." But it challenges the way we achieve success within that framework.

PROFESSOR CAPRON: Okay. Because -- all right.

DR. KAHN: Is that helpful? I do not know that we are --

PROFESSOR CAPRON: It is helpful. Maybe it is the way you have framed it initially that I thought you were -- there are -- put it this way: There are some people, it seems to me, who say that Belmont by its emphasis on individual choice and fully informed consent led to people raising barriers to research,

which ought not to be there.

And that as people say, "Gee, it ought to be easier to get into research because research is where you get benefits," that would be a reason for saying that Belmont's emphasis or that Belmont version if you are -- it may be a mischaracterization of Belmont but the Belmont era version -- was wrong.

DR. KAHN: Right.

PROFESSOR CAPRON: And that we really ought to be less concerned and more liberal. So what if people get in without full understanding, they are getting into something good. We should be happy for that. A beneficence view that research is where the goods are.

And I -- now I understand you to be saying, "No," that is not what you are saying. Is that right?

DR. KAHN: Yes. No, that is right and I would say that the -- if you play that out that research is a good that people ought to have access to that the issues are not about consent but about recruitment and what we do not know is why certain groups do not get into research or why the rates are different amongst different populations. So I think that is not about consent. I think that is about something else.

However, to sort of pick up on your point, I do think that, to push aside your point and go to

another one, that the categories of research do challenge us to do consent in a different way. So it is not so much about the shifting paradigm that drives that but rather the Belmont approach really did not foresee some of the kinds of research that we are now doing and will be doing in the future.

So it causes us to think hard about whether that process is adequate for what is coming down the pike or has already come down the pike.

PROFESSOR CHARO: Bernie?

DR. LO: Jeff, I was hoping that in your final paper you would be able to sort of address the question of to what extent are recommendations that others and we are likely to make on how to improve the informed consent process empirically driven or not.

I mean, there are a lot of things that people like to say would be good to improve informed consent. Third party monitors, ombudsmen, using video tapes, audio tapes, and that sort of stuff.

What is the empirical evidence that that really enhances consent if we even understand what the question means because there may be a -- there certainly is a cost in terms of requiring more resources to do some of these things.

How convinced are we or how solid is the

evidence that this really promotes what we consider informed consent? Do we know how to even study that question empirically? Is there data already to support it? Or are these things that sort of seem like obvious good things to do and so we say do them without really kind of rigorous evidence that they are, in fact, going to achieve the goals we want at a price we are willing to pay?

DR. KAHN: I think we do not actually know whether they work. However, for 18 months now there have been a few studies ongoing, again funded by this NIH RFP, on informed consent in the research context, which are looking at things like video tape and other interactive media as a method of improving the informed consent process with evaluative components in their proposals.

That research has not yielded is results yet so I think we are probably another year away before we know and these are only the very first sort of toes in the water in terms of measuring whether these novel approaches actually improve the outcomes of informed consent so I do not think we know yet.

At least there is some research going on that may actually yield answers to that question. Unsatisfying, I know, but that is I think -- I think

that is where we are unless other people have more information than I do.

PROFESSOR CHARO: Jim?

DR. CHILDRESS: Mine builds on Bernie's because in some ways our recommendations about improving the consent process will be awfully speculative without the kind of information that we are talking about. And you have identified a few studies that are underway that may help to fill in some of the gaps but probably we will not have that -- the data, conclusions and results from those studies until long after the time we would need them.

And I guess perhaps one recommendation that we will -- could end up making has to do with increased research on the informed consent process.

But many of the studies that I have seen focus a lot on the question, and probably when we talk about informed consent, on disclosure, understanding, comprehension, and often in inadequate ways, like focusing mainly on how much subjects recall from their initial presentation of data.

But are -- I am looking at a side that we tend to think less about in terms of the voluntariness of the consent.

Is there much research going on there? Are

there things that you could tell us? That really does not play a role in the way you have sketched out here -- it may just not be enough to say anything about that.

DR. KAHN: Yes. And I do not know of any great amount of information that answers the question that you raised but I think it is obviously a good one.

I think we do know just sort of by way of extrapolating that paper tends not to be a very good approach. For instance, we know that if you talk to people about -- in the clinical context about informed consent and ask them did you sign a consent form they will say, "Yes, I am sure I signed that form with a lot of other forms that I signed."

It does not stick with them as having been particular to research and so I think if we just take it out of the context of signing pieces of paper in the whole stack of paper that you sign that has a chance of going towards helping them remember that they actually participated in something different.

That is not sort of empirical evidence but I think that that is -- it is hard to argue that that would make a difference, at least differentiate it from signing a waiver for surgery or something. You know, it is outside of the regular clinical context of health care delivery.

I do not know how satisfying that is to you as an answer but I think that is the only kind of evidence that we actually have until some of these studies yield their results.

PROFESSOR CHARO: David?

DR. COX: So first of all I would like to thank you very much because the -- your views are completely consistent with my own, which means that you must be right.

DR. KAHN: I am glad to know that.

(Laughter.)

DR. COX: And with that aside, I actually think they are pretty reflective of the reality of the situation of researchers out there in the trenches trying to do their research and trying to convince people that they should do it.

So I really like your layout but I have two questions for you and the first is why do you think it is that we have switched in this format from protecting people to everyone clamoring for the benefits. So like where are those benefits and why has that come about? I have my own views but I would be very interested in your's.

Keeping -- I do not ask that many questions, Alta, so this is like a two-part question.

PROFESSOR CHARO: No problem, David.

DR. COX: And the sort of second one is really if this is more in the context of explaining to people that they are partaking in a risky situation, which I actually think that that is exactly what the process is about, then why would anybody want to do it?

DR. KAHN: If we were really honest with them, why would they participate?

DR. COX: Exactly.

DR. KAHN: Well, to answer that second question first, you know, people have said -- people who I respect who are researchers have said "We ought to put at the top of each consent form big bold letter boilerplate language that says, 'This is not for you. Participate in it because you are wanting to be altruistic more or less,' and that should be the only value that we actually want to pull out of people. Everything else is sort of wrong headed."

I do not subscribe to that view. I think that should be part of what people -- what motivates people to participate.

So to answer your question, it ought to be to help other people. That is why we ask you to put yourself in harm's way, to benefit others but this is a segue to answering your first question.

DR. COX: Exactly.

DR. KAHN: I think that it is true that there are benefits to be had in research potentially for you as a subject and that is more true today than it was 30 years ago. There is probably a -- there is a greater likelihood that you will benefit medically from research participation.

Now it gets complicated when you think about, for instance, people who do not have great access to health care who we know participate in research trials partly because that is how they can get health care. I mean, that is not a good reason. We do not want that to be their motivation. That is problematic. Not because of consent, though. It is problematic because they do not have access to health care.

So we do not want people to have those kinds of motivations.

Why do we get this swinging in the pendulum, I would say, is that it is a complicated story but you can go back to HIV/AIDS and the first trials for AZT when ACT-UP and its predecessor organization would have rallies in the large cities in our country with placards that said "Clinical Trials are Health Care Too."

And if you say that you have conflated the --

you have done the job that we have been talking about, right. So now it is not just beneficial. It is health care to be in the clinical trial. So that, I think, sticks a little bit.

And then I think we did a bad job of making sure that populations did receive the benefits of being researched on. So the point that Alex was making before. I think that is real that we excluded women to death as people have argued. You know, we lost information about the health care needs of certain parts of our population, in a way a misguided effort, to protect them.

So it is, I think, all -- in a very short answer to your question -- it is all mixed together and once that cocktail is all -- is mixed up, we get the sort of sense that, you know, there are real benefits to be had in research and that is part of why it makes sense to be a research participant, rightly or wrongly.

DR. COX: In fact, that is very helpful.

DR. KAHN: Okay.

DR. COX: Because my sort of -- what I would have said from my perspective --

PROFESSOR CHARO: I am sorry. David, can you speak more closely to the microphone?

DR. COX: Yes. So, I do not disagree with any

of those things. I would have added one other thing, is that I think over the past 10 years the research community has become extremely adapt at their own public relations.

DR. KAHN: Well, that --

DR. COX: And so that to the point --

DR. KAHN: -- is fair.

DR. COX: -- where even they believe it. Right?

DR. KAHN: Yes.

DR. COX: Yes.

DR. KAHN: And that is actually a very good point.

DR. COX: So that the -- given that, right, the -- and -- because there is some truth to it but not on the time scale that it is represented. So it is long-term gains, not short-term gains. It is like the stock market. We should have some stock people actually doing this for us so that -- so I really think that things have changed in my view.

I think you are right but not because the process of consent has changed but because the players have changed and gotten -- have changed sort of what the game is to get people to enroll.

So anyway that is -- but I think that this --

understanding that, okay, goes a long way then to coming up with the things that you want to fix.

And I must agree with some things that Bernie and others said, though, is that although these are really great ideas, in my view, is that coming up with practical solutions to implement them, I would hope, would be an important part of your paper.

DR. KAHN: Well, and I think, you know, a lot of these would be rightly perceived as unfunded mandates and that is always of course, difficult to sell institutionally or to the government. So I am sensitive to that.

To pick up on one of your points, and I think someone said this earlier today, I do not remember who, I am sorry, but therapeutic misconception is not just about subjects, it is also about researchers and about physicians because there is actually interesting empirical evidence about that.

Why did you refer your patient into this particular clinical trial? Because I thought it would benefit them medically.

DR. COX: Exactly.

DR. KAHN: Well, do you know what the chance of that actually is? And the disparity between what they answer and what is the case is often quite large.

So that goes to the point you are trying to make.

I think it is very important for us to get to the researchers themselves. I talk a lot to researchers in my own institution and I often will talk about some of the things that I have laid out here and that we have been talking about, and they are always quite amazed that this is actually true.

So they are very adept and they know a lot about what they do but they do not specifically step back and have that bigger picture, which I think is important to give people a better sense of how to do this right.

PROFESSOR CHARO: Jeff, if I may ask that when you deliver the final paper, if you could highlight the references for that information about therapeutic misconception by investigators and physicians.

DR. KAHN: Sure.

PROFESSOR CHARO: That would be handy.

I have on my list Steve, Diane, Bernie, Eric Cassell, I put myself on the list toward the end.

Trish, you are out there on the phone?

PROFESSOR BACKLAR: Yes, I am.

PROFESSOR CHARO: Did you want --

PROFESSOR BACKLAR: I am having to come and go

unfortunately.

PROFESSOR CHARO: I understand. I just wanted to ask if you had wanted to intervene at any point because you had been so active on e-mail talking about audio taped --

PROFESSOR BACKLAR: Right.

PROFESSOR CHARO: -- consent.

PROFESSOR BACKLAR: But I think it would be useful to listen to what others have to say.

PROFESSOR CHARO: Just give a shout whenever you would like to intervene.

PROFESSOR BACKLAR: Thank you.

PROFESSOR CHARO: Okay. Anybody else who would like to be on the list?

Steve.

MR. HOLTZMAN: One of the things I really like about your approach is the recognition that one size does not fit all because this is an area where there is a tremendous amount of texture.

So what I find a little inconsistent with that is then when we come to the discussion of the therapeutic misconception and its quotes about what researchers find and think, there does not seem to me the same attention to texture.

What I mean by that is you do reference the

fact that if a well educated health care consumer comes down with an incurable cancer -- I am going to sort of play out what you said -- and goes out on the web searching for where are the clinical trials that might be able to save their life, that is not a therapeutic misconception. That is a very, very well informed health care consumer and we are moving into an era where things like referrals to clinical trial are being viewed as benefits to come out of health care plans precisely for those sorts of cases.

So I am somewhat surprised after that attention to texture is that you drew, even though you sort of point in that direction, there is a difference between going into a Phase I without knowing anything versus that kind of case. You then said we need to guard more against it.

I am not sure that that is the case. I think maybe what it further points us to is not just making distinctions about clinical versus nonclinical and whatnot but also the context of the education of the people involved and why they are interested in it.

DR. KAHN: That is actually very helpful and I think you are right. There are different cuts even within some of these categories and I certainly will do my best to tease that out.

PROFESSOR CHARO: Marjorie, I understand you wanted to say something.

DR. SPEERS: I want to go at the end to do a couple of comments.

PROFESSOR CHARO: Okay. Diane?

DR. SCOTT-JONES: Okay. I have a question for you about your identification of this paradigm shift from protecting to allowing access. Okay. You are saying that there has been a reversal of protection in favor of creating access. And I was wondering if you could say what particular line of research or series of studies excluded women in the past in order to protect them and now is including them in order to provide them benefits.

I am asking because it could be the case that women were excluded not out of protectionism but because it was believed that it was more important to study men, say heart disease in men or because the disease was more prevalent in men.

So I guess I am questioning your linking one to the other. Can you say what series of studies moved from excluding women in order to protect them and not for other reasons?

DR. KAHN: Actually I can defer to Alta, I think, on this unless you would like me to speak

because this is something that there is --

PROFESSOR CHARO: Yes. I can do it quickly because --

DR. KAHN: -- lots of evidence about --

PROFESSOR CHARO: Yes. I had -- a research assistant and I actually did do an empirical study going back a number of years in an IRB looking at all the studies and what they were studying and whether women were included so I can answer that for you.

And the short answer is they were excluded from pretty much everything and it was not based on prevalence of disease. It was based on the fact that in the absence of information that indicated a substance was actually safe for fetuses, it was presumed to be possibly dangerous and the presumption, therefore, was that they would be excluded.

They would occasionally be included when they suffered from an illness that was severe and the research presented one of the only possibilities for amelioration or cure.

So, interestingly enough, known fetal toxins in the chemotherapy area would not pose a barrier to enrollment whereas testing analgesics would routinely result in an exclusion.

We also checked to see whether the exclusions

were more frequent by for profit sponsors like pharmaceutical companies versus public sector sponsors like the government speculating that product liability fears would lead to higher frequencies of exclusions by for profit companies. And the result, surprisingly to us, was, no, not really.

The final thing we tried to do but were unsuccessful in doing, because our IRB would not let us study the phenomenon lest the identities be revealed, was to see if we could control for the sex of the investigator and to see whether there was a difference in the way men and women approached this but at that point our IRB said that it might be too revealing of the actual investigators and that they would now become the subject of our studies.

In a bit of performance art I found myself screaming and yelling about the difficulties of going through an IRB.

(Laughter.)

PROFESSOR CHARO: What has changed since then is that there has been movement from Washington, from NIH and from FDA both, that requIRBs researchers to explain why they are not including women if they are not.

Known fetal toxins are often an explanation

for why they are not including them. The fact that a disease does not occur in women, prostate cancer, is considered an explanation. And the justifications have to be presented to the IRBs.

Women are now routinely being included in most all studies.

What has not yet happened that was requested from the Federal Government was that they be included in numbers large enough and in studies large enough to allow disaggregation of data by gender in order to look for gender difference in responses, whether responses to substances or to the doses of substances.

DR. KAHN: There actually is a fairly strong line of evidence in the IOM report, women -- Women in Clinical Research, is that the right title? I am going to get it wrong. It is cited in here. If you like, I can sort of pull out some of that information.

So I think that there is a lot of evidence on the policy side that links in the way that you were asking about.

I mean, I will just say from my own experience working with IRBs that the regulations people read as saying do not research on pregnant women because of risk to fetuses but that has been expanded -- was expanded to include not just pregnant women but

potentially pregnant women, which meant sometimes, in IRBs that I worked with, women of child bearing capacity from 14 to 60 would be summarily rejected or not allowed to participate in research.

So if that is the case then I think it makes the kind of link that you are asking about.

PROFESSOR CHARO: Do you have anything further, Diane, that you wanted to comment on or ask?

DR. SCOTT-JONES: I will just pass and let other people have a chance.

PROFESSOR CHARO: Okay. Bernie?

DR. LO: I lost my train of thought. Let me sort of yield to the next person and get back in the queue.

PROFESSOR CHARO: You are back in -- you are in the queue.

Eric Cassell?

DR. CASSELL: Well, I just want to pick on something that Steve said before about what you called the "therapeutic misconception."

You have to be careful about that. If you want somebody to get a new cancer agent, they will not get that agent unless they are in a trial. But in that trial they will not be without therapy.

DR. KAHN: Sure.

DR. CASSELL: They will be getting what was standard therapy before, their chance of getting that therapy is 50/50. So it is not a therapeutic misconception in the sense we meant it before. I think if I am in this trial I am going to get -- being treated when, in fact, no treatment is intended.

So I think if you do that you get it wrong. People know what they are --

DR. KAHN: Sure.

DR. CASSELL: I mean the investigator knows but they also have come to believe that that is the best way to use any new drug. They do not want to use it outside of a trial, and that is a more complicated thing. It closes off its use elsewhere because nobody wants to -- they want to get enough patients for decent trials.

DR. KAHN: Sure.

DR. CASSELL: So it has another meaning, which you might pick up, but it is not a therapeutic misconception.

PROFESSOR CHARO: Let me go back a little bit. Bernie, did you remember what you wanted to say?

DR. LO: Yes.

PROFESSOR CHARO: Okay .

DR. LO: I keep having these senior moments

unfortunately.

(Laughter.)

DR. CASSELL: They will get worst, Bernie.

(Laughter.)

DR. LO: I know. That is what my kids keep saying. It has gotten worse and it is not getting better.

PROFESSOR CAPRON: When she calls your name and you don't respond, then we will know.

(Laughter.)

DR. LO: Actually I think I will respond when she calls somebody else's name.

(Laughter.)

DR. LO: When we talk about misconceptions, it seems to me that there is a tendency to lump research together as sort of a homogenous thing. And it strikes me that there are certain types of situations and certain types of research projects where there is a -- sort of a documented record that misconceptions are much more likely to occur.

So I think Phase I cancer trials, there is a lot of evidence that both patients and investigators think they are going to get therapeutic benefits when, in fact, it almost never happens. There are sort of dose toxicity studies.

I would sort of argue based on what we know in the public record about the "gene therapy" research that gene therapy research probably falls in that category.

And I think it might be helpful to try and highlight for us those types of studies and clinical situations -- research situations where there is a higher likelihood or at least there is some evidence that this is a real problem as opposed to it could happen anywhere because I think IRBs do not -- again I am sort of jumping to opinion here -- but it seems to me that IRBs need guidance as to sort of where particularly to sort of look for the possibility of therapeutic misconception in all the senses you used it and, therefore, to sort of require additional things to do in the process of obtaining informed consent that may or may not be standard for other types of research.

I am just afraid that if we do not try and make those distinctions people will sort of say, "Well, why don't we sort of have video tapes and consent monitors for all research" because potentially in any research -- I mean, the Radiation Committee study -- I do not know that you broke it down in different types of research but, you know, it is probably spread across the board.

DR. KAHN: Right.

DR. LO: I think we should, you know, sort of following Willy Sutton go where the money is and where we know there are problems we should at least get the IRB to sort of look at those projects with heightened scrutiny.

We went through some of this with the research on mental disorders that may impair decision making capacity where we said there are certain types of research projects in this field which require heightened scrutiny because of the following sort of history and track record.

I think if we could do it here that would be helpful. Not that that would be an exhaustive list but I think we would be a lot better off if we sort of did a better job -- have IRBs and investigators do a better job of where the known problems are than sort of trying to cast everywhere.

PROFESSOR CHARO: Arturo?

DR. BRITO: One aspect that I have not heard talked about here about this shift that you described, and I curious, is that the change since the Belmont Report in the availability of medical care for people in this country and how it may -- and this is anecdotal on my part, it is just my impression is that there is

an increase in discrepancy in health care availability in certain populations.

So how much of the shift in the perception of benefit, whether true or not, is out of the increasing number of people that are desperate, I guess, for medical care? That was one question.

The second question I had, I was also struck by the fact that in the proposals to NIH there were no requests, you said, for cultural differences or at least none that were granted. Is that correct?

DR. KAHN: Actually nothing outside of the United States. There actually were a fair number of studies -- and I do not know -- I think maybe two were funded that looked at cultural differences within communities in the United States.

DR. BRITO: Okay. So there are a couple.

DR. KAHN: Yes.

DR. BRITO: I misunderstood that.

And irrespective of that, how much of the -- in the United States is the new ways of looking at informed consent more due to educational differences because my experience is that a lot of the difficulty that people have with informed consent as a written document is when you get people that are involved in research to have less than, you know, a ninth grade

educational level. So things like that.

Is that something that is being looked at in these --

DR. KAHN: Yes. In fact, I think that has been broken out into things that are and are not research. I do not have this at my finger tips. It is out of my memory.

But reading level issues were among the most -- are among the most studied issues. How do we sort of overcome these problems of being able to read above say an eighth grade level when the information is extremely technical and detailed and complicated?

So presenting it in a way that is accessible to anybody, let alone people who are trained as physicians. You know, sometimes it is very hard even for people who do know what to look for to understand what is going on in informed consent.

DR. BRITO: And how much of that leads to the therapeutic misconception also? I mean, it makes me wonder about the topics we had this morning about the -- you know, sometimes we frame a lot of things under cultural differences but I wonder how much has to do with education level.

DR. KAHN: Well, there are some other issues which I outlined and I will spend some more time on in

the paper but I think if you ask people, and there have been surveys done on research subjects and potential subjects, why would you or why are you participating research. In almost every case there is this notion of I trust this person and they say it is a good thing for me to do. Or it is being done at the University of Minnesota and I trust that place. Fill in the blank. It does not much matter.

There is a real sense that there is a trust on the part of subjects in the people, in the place, in the system, and I do lay that out a little bit. I think we have to be very careful not to lose sight of that. That is a very important thing for us to know exists and to foster.

If you do not have that trust you do not do research and that is pretty much what it comes down to.

In answer to your very first question, I do not know that anybody has looked at whether it is driven by a lack of access to health care.

DR. BRITO: And it is not just lack of access. It is also dissatisfaction that has happened over the last two or three decades and it may actually probably -- I would guess it mirrors how people are going to alternative forms of medical care and clinical trials may just be another form of that than sort of the

traditional medical care because there is dissatisfaction with outcomes for themselves and family members.

I do not know if there is data on those things or not.

DR. KAHN: I do not know.

PROFESSOR CHARO: Okay. We have just under 15 minutes left if we stay on schedule and I have on the list Diane, Alex, Steve, possibly Trish, possibly myself, and Marjorie.

PROFESSOR BACKLAR: Yes, and Trish, right.

PROFESSOR CHARO: Trish, you are available to speak now?

PROFESSOR BACKLAR: Yes.

PROFESSOR CHARO: Why don't you go now just in case you get called away again?

PROFESSOR BACKLAR: Okay. This is in a sense sort of out of context with the discussion that is going on currently that you are having currently. I wanted to bring up the modest proposal about a way of documenting informed consent, the process of it, without having people write it down, and also a way in which one could discover how the discussion goes between the researcher and the participant, and that was to do it with audio taping, and I know that most of

you read what I suggested about it, and I do not know if you want me to go into details or if we could just start the discussion with looking at the advantages and disadvantages of audio taping the consent process.

I am giving you a question back.

PROFESSOR CAPRON: Is that a question for Alta or for Jeff?

PROFESSOR BACKLAR: Well, it is a question. If this is -- if you would like to -- if this would be a good idea to explore this for Alta and Jeff, how you would like to do it. Shall I just tell you what my ideas are or should we sort of discuss it?

PROFESSOR CHARO: This is the venue for discussing things so this would be the time to do it.

PROFESSOR BACKLAR: Well, I think that in my own experience in research we always have -- when we do research where we are getting information from participants, this has nothing to do with consent but the research itself, we always audio tape all the information processing that we get so that we know that the interviewers have a -- do not make up what they -- it is a way of checking what the interviewers, the information that the interviewers are getting.

And so I thought that it might work very well if the informed consent process, however long it takes,

would also be audio taped. This would be a way in which we would know that we would be able to find out that a participant actually understood because there would be a discussion, not just a reading aloud of a consent form, and it would allow for questions, and it does not mean that one would have to go back and listen to all these tapes but if there were some problem that came up about the study one could go back and find out if, in fact, the participants did understand what the research was about. They understood that they were in a research protocol and that their questions were adequately answered.

PROFESSOR CHARO: Jeff, do you have any observations, responses?

DR. KAHN: Well, I appreciate your comments, Trish. I think it is important that there be some sort of ongoing observation personally and maybe audio tape is sort of a stand in for that.

It is difficult. It costs money. It is people. It is resources to have somebody go and watch the informed consent process takes place.

PROFESSOR BACKLAR: Right.

DR. KAHN: But I think if you want to know whether it works that is the way to do it and whether that means just sort of spot audits, that people know

that it could happen, I think, is sometimes a strong motivator.

I guess my concern about audio tape is that what would then happen to them. It is sort of a record, I understand, but I think if you want to get out the nut that you want to just be there and watch the process and see how it works, which is more than just listening to what people have to say on an audio tape.

PROFESSOR BACKLAR: Of course, the issue is that often the -- if is the informed consent process is adequate, it is not a one time event, and so it is not simply somebody coming in for a spot check. If things change in some way, one is supposed to go back and explain and continue the discussion.

It seems to me that it is a protection not simply for the participants but also for the researcher and that it is a way -- a record for the researchers to be able to show that they continue to answer people's questions and continue to inform them of maybe the changes in the protocol.

PROFESSOR CHARO: Okay. Diane, you had --

DR. SCOTT-JONES: My question is on a different topic. I do not know if Trish had finished. It was something entirely different.

PROFESSOR CHARO: I am sorry. Trish, did you have anything further to add? I am kind of -- only because I am watching the clock at the same time that I am listening to you.

PROFESSOR BACKLAR: I am afraid I cannot hear you.

PROFESSOR CHARO: Did you have -- Trish, did you have anything further to add on this topic? I am watching the clock and the list of people who would like to speak.

PROFESSOR BACKLAR: No. Let everybody else speak. That is fine.

PROFESSOR CHARO: Okay. Thanks very much for that. That is very helpful and I know that Marjorie was taking notes here while you were speaking.

Diane?

DR. SCOTT-JONES: Okay. My question is aimed at trying to understand further the basic ideas that you have laid out so nicely for us and I want to ask you whether you see any inconsistency between this notion of the paradigm shift toward allowing access for the benefits of research? You used the phrase "hope and opportunity" that people seek when they go into research and you described the "therapeutic misconception" as an instance in which people wrongly

believe that the research gives them hope and opportunity.

So I am just wondering how you see those two elements, which are major elements of what you presented to us. How you see them fitting together? Do you see any inconsistencies there?

DR. KAHN: Yes. I would say that in the second case, in the definition concept of "therapeutic misconception" it is not about hope. It is about a belief that there will be therapeutic benefit from my participating in research, which is more than anybody can claim. I do not think anybody in their wildest dreams thinks that there is always going to be benefit from research participation.

As I said before, that is why we call it research because we do not know whether it will benefit people.

We do not want, on the other hand, to undermine people's hope. I mean, that is a lot of what motivates people in life, not just in research participation.

So I do not think we want to squelch that but we also do not want to exploit it. I guess that is the way I would answer it in a very short few words.

DR. SCOTT-JONES: Okay. Could I just follow-

up real briefly?

PROFESSOR CHARO: Sure.

DR. SCOTT-JONES: But in therapy isn't there also some probability that there will not be good that follows from the therapy?

DR. KAHN: Absolutely. And I think, though, that in the context of therapy in clinical care, we are less concerned about misunderstanding because the motivation on the part of physicians is the best interest of patients or it ought to be, certainly.

So if there is a misunderstanding and we say that maybe 10 percent of the people just never will get it, that is somewhat ameliorated by the fact that there is the best of interest of the patient that is driving the decision making or the recommendation at least.

In the context of research we always have to remember that attention because we are asking people to put themselves in harm's way and undertake risk so that other people -- we can learn something about what is going on with them to benefit others in the future.

And if they get some benefit, great, but it is not something that we can expect, although we might hope for it and individuals might hope for it.

Is that a distinction that is helpful to you?

DR. SCOTT-JONES: I will pass and let people

keep going.

DR. KAHN: Okay.

PROFESSOR CHARO: Are you sure? Do you want to just follow-up quickly?

DR. SCOTT-JONES: No, I will pass.

PROFESSOR CHARO: Alex?

PROFESSOR CAPRON: I wanted to suggest several things in looking at the role of informed consent as opposed to alternative means of making sure that the research process is acceptable. And the evolution in the post-Belmont era is one of them.

Certainly in the area of consent to treatment, I think today we have recognized more clearly and try to preach, as it were, to those who are in the position of getting consent the importance of talking about alternatives to whatever is being recommended in a clinical or therapeutic context. And I -- as opposed to the litany of risks. I mean, it would seem that very typically the risks themselves are always present and it does not tell a patient very much to just recite risk.

I was wondering about your thoughts on whether that is an equally important part in the research consent process and, if so, if we have any empirical evidence of what it means to give that.

A second question around informed consent is whether you see consent in the research context as legitimately allowing or demanding a formal assessment of the subject's understanding of what is at issue.

My own view of the history of informed consent in treatment is that the phrase "informed consent" is a misleading one if it suggests that what we demand is that before you can get treatment you have to be informed the way we would use the term in other contexts. Rather, what is at issue is a requirement of disclosure by the physician of certain information.

We could judge the information as being accurate but misleadingly disclosed or confusingly disclosed. There might be some point at which you would say, "Well, it is just so obvious that what is being done here is not going to convey the information," but we do not say that subjects have an obligation -- excuse me, patients have an obligation to have a certain level of knowledge or they are disqualified from making choices. We would rather say it is an obligation on the physician.

What about in the context of research? And, again, do we have any empirical studies that demonstrate whether it is possible and what the effects of demanding a certain level of knowledge?

And the third thing is the issue that you raised about the confusion that arises when one person is playing several roles and this issue of the doctor as -- the physician investigator as an agent here. Is he or she the agent of science or the sponsor of research on the one hand versus the agent of the patient?

And I hope that you will explore in your paper -- you may not need to respond to it now -- how practically one achieves that because situations in which a person is referred to a physician researcher precisely because his or her own physician says, "Well, this is something that needs a research examination, we do not have adequate ways of doing it here," does that mean that that research team needs to be made up both of a researcher and a new surrogate physician, maybe the physician?

So those are the three points: Alternatives, assessment of knowledge and agency.

DR. KAHN: I will take the last one first. I think you are right that it is very difficult to know how to proceed when there are the dual agency problems. And I do not have a quick answer for you.

People have very tongue in cheek said, "We ought to make researchers who are also physicians take

off their white coat when they are researchers and put on a different color coat," as a way of just making a visual cue this is not the same thing as it was before.

And obviously that is not meant seriously but it, I think, gets at what we want to try to do, make it clear that this is not the same thing. How to do that I will definitely explore. I do not know there is any great empirical work out there that answers that question in short.

I think in answer to your second question that we do need to have a higher standard of understanding to say that someone has satisfactorily gone through informed consent in the research context than we do in clinical care. Absolutely.

I do not know if I can I tell you where the line ought to be drawn but I think the standard must be higher because we are asking people to do something that is not necessarily good for them. In fact, it carries -- that is -- as I have said now three times, we call it research because we do not know whether it will work and what the risks might be.

So I think we do have to have a higher standard. I think we know that people are no better at understanding information in the context of research than they are in the clinical context.

You know, nothing magic happens when you become a research subject. In fact, it may go the other way. So does that mean people ought to be excluded from research if they do not measure up to a certain level of understanding?

You know, I do not know that we are so good at measuring what people's understanding actually is. We know how to measure recollection but that is not the same thing as understanding.

Now I will tell you at the last round of this NIH RFP, the last round of submissions, there was one study that will attempt to do that, to measure actual understanding, not recollection. Who knows whether it will be funded? You know, those study sections are interesting that way. You do your work, you think something looks really great, it gets the right number and then does not get funded, but that is another matter.

PROFESSOR CHARO: Excuse me, Jeff. Just because we have now actually kind of run out of our time, I am going to rush you along in your answers a little bit to catch up the last few people.

DR. KAHN: Okay. And I will finish by answering your first question very quickly. I think it is really hard in the context of research to talk about

alternatives because the alternative to not being in this research or not receiving the active agent arm in a clinical trial is not to be a research subject.

So I think it is a much more binary kind of choice unless I misunderstand the point you are trying to make.

PROFESSOR CHARO: If I can just say something.

Steve, you had asked to speak. You will pass. Okay.

I am going to pass under the circumstances as well.

I know that Marjorie and Eric had wanted to make some comments at the conclusion of the session.

DR. SPEERS: Just three quick comments to you, Jeff, of topics that I hope you will address in the paper.

We have discussed here as a group today clinical research and focused quite a bit on clinical research. I would like to ask you when you consider all types of research to include social science research, epidemiologic public health research as well because I think that some of the consent issues are probably different for those types of research.

Another issue that did not come up in the group that I hope you will also consider would be

consent issues in conducting research with children and the issues around child assent.

Of particular -- perhaps one topic that you would want to address would be research involving adolescents and whether the consent process might be different for adolescents.

And my last point quickly is there is focus in the regulations and a bench mark that is used in the regulations is to obtain "legally effective consent." Those are the words that are used. And I think because of those particular words in the regulations there is tremendous focus on paper and on the consent form and on obtaining a signature. That could be contrasted with something that I am going to call ethical consent or just consent -- you know, actually getting informed consent and making sure that people are properly informed and understand and agree to participate, and it would not necessarily actually -- necessarily translate into "legally effective consent," and inasmuch as you could address that issue in the paper, I think it would helpful to us.

DR. KAHN: How many volumes did you want?

(Laughter.)

PROFESSOR CHARO: Six or seven will do.

Eric,I think you have the last word.

DR. MESLIN: Very quickly, and this is just for Commissioners benefit rather than for Jeff's.

Everything that you are hearing obviously you will want to relate back to the International Report and vice versa, so among the comments that Harold shared with me late yesterday evening -- Trish, I hope you are still listening -- was that he felt that the issue of tape recording was an interesting thing to pursue for the foreign studies question when we were debating procedural requirements for documenting -- for assuring understanding and the like.

So it is staff's responsibility to remind Commissioners if there are recommendations being proposed for one report that affect the other, and the consent topic is obviously a clear opportunity for that overlap, and we will keep you apprised.

PROFESSOR CHARO: Okay.

PROFESSOR CAPRON: Alta, can I have just one -- Marjorie, I think you have raised an interesting point, which is not -- with all respect to the contract you have asked Jeff to do -- really a burden you should lay on him. If your understanding is the phrase "legally effective consent" means a consent form, I think it would be worthwhile having a member of staff, or if you have to get another quick consultation from a

lawyer to look at it, thinking back in the literature on informed consent for treatment, it is certainly true that there is often a consent document but the language that comes to mind that courts use in talking about consent does not talk about the document as such.

Sometimes the document is evidence that what was said was inaccurate and sometimes it is evidence that is thrown back at the patient to say, "You did -- it was right here in the form," and now the question is should you have understood it from that language.

But "legally effective consent" and "ethically effective" or "acceptable consent" do not on the face of it seem that far apart.

PROFESSOR CHARO: Right.

PROFESSOR CAPRON: So a researcher could look at the cases for you, though, and see if my impression is wrong. I mean --

PROFESSOR CHARO: We are going -- Marjorie, please do not reply. We are going to allow you to pursue that conversation privately during the break, if you wish, since it is about how to structure the contract work and does not really need to be on the record here.

We are going to break now and we are about five minutes behind schedule so we will return promptly

at 3:35 to hear from Dr. Schreck and Dr. Chin. Thank you very much.

DR. MESLIN: Thank you, Jeff.

(Whereupon, at 3:20 p.m., a break was taken.)

PANEL II: PRIVATE SECTOR ROUNDTABLE

PROFESSOR CHARO: Okay. If we could please get started with the private sector. If we could all get back to the table. I will invite everybody to please end their conversations and come back to the table.

Thank you very much.

I would like to welcome two people when have agreed to come and talk with us about human subjects research in settings that have not been extensively discussed until now where we seem to have primarily focused our attention on the biomedical sector and pharmaceutical sectors.

We have with us two people: Dr. Richard Schreck, who is the Secretary for the General Motors Human Research Committee, and also Dr. Henry Chin, who is the Vice-President for the Center for Technical Assistance at the National Food Processors Association.

Thank you both, gentlemen, for coming.

I understand that some questions were forwarded to you to give you an idea of the areas that

the Commission is particularly interested in so let me start by asking if you have any remarks that you would like to make in reaction to some of those questions and after that we will open it up to a more informal discussion back and forth between members of the Commission and both of you.

Dr. Schreck and Dr. Chin, if you have any preliminary comments.

RICHARD SCHRECK, PH.D., SECRETARY, GENERAL MOTORS HUMAN RESEARCH COMMITTEE

GENERAL MOTORS

DR. SCHRECK: I do not have my copy of the replies but they are probably all there. I think the general nature of what we said was that most of the work that we do -- the questions had to do with whether we would be conducting our business any differently if we were under the authority of the Common Rule and the national scrutiny of the NIH or one of the other agencies.

And I think the general nature of my replies was that we pretty much behave as if we were under the rules for federal research and we probably would not do much differently other than perhaps records keeping or reporting publicly that we do not do right now.

PROFESSOR CHARO: Okay.

DR. SCHRECK: But I think the make up of our committee, our procedures, our informed consent, paperwork and so forth, I believe, are pretty much consistent with what you use.

PROFESSOR CHARO: Thank you. And if you could just double check that your microphone is working. Okay.

Dr. Chin?

HENRY B. CHIN, Ph.D., VICE PRESIDENT
CENTER FOR TECHNICAL ASSISTANCE
NATIONAL FOOD PROCESSORS ASSOCIATION

DR. CHIN: I had not really prepared any remarks and I have not had a chance to actually prepare any written comments for your questions yet but generally the comments that we had for the questions dealt with the fact that in terms of the use of human subjects in research that is related to foods it really falls into two areas.

One is basically very similar to, I think, what you have been talking about already, the biomedical kinds of studies, which are under the control of medical facilities or health facilities.

And then obviously in the food industry we do a lot of consumer testing for the food products and there we do follow the principle of informed consent.

We do screening of consumers to make sure that, you know, allergies -- issues associated with allergies and intolerances are addressed.

But -- so that is kind of the general framework that we approach this -- the subject, human subjects in research. And, I guess, aside from that I think I will be glad to answer any questions.

PROFESSOR CHARO: Let me first offer Marjorie Speers and opportunity to ask anything that follows on to the questions that were delivered previously.

DR. SPEERS: Okay. I do not have any questions to specifically ask in response to Alta's question but what I thought it might be useful for both of you to do for the Commissioners would be from your respective fields if you could talk a bit about the amount of research that occurs just to give us a sense of how much research that you might conduct, the types of research. For example, Dr. Schreck and I had a conversation about research involving living subjects, research involving deceased subjects. You know, so the types of research that you do.

And then whatever you could say about your IRBs. Do your companies tend to have their own IRBs? Do they use independent IRBs?

Just give us a sense of the lay of the land,

if you will, before we ask some specific questions.

PROFESSOR CHARO: Sure, Dr. Schreck?

DR. SCHRECK: I will lead off since you want to know how we test nonliving subjects.

(Laughter.)

DR. SCHRECK: We have -- we have been in the business doing this for about 25 years. We have only done about 150 protocols over that time so we are really not a big IRB in terms of users. We probably have two, sometimes three meetings a year.

Our board consists of typically about a dozen people, about six from within the company and about six from outside the company. The only people who have a vote are the people who are extramural, no one from inside the company has a vote.

The intramural people are simply there for advice. They are scientists. They are physicians within the company. They are legal people within the company and they are there to see that things go together properly but it is entirely the vote of the extramural people that counts.

The extramural people consist of faculty from the medical schools in our area, the University of Michigan and Wayne State primarily. They consist of senior people at some of the large research hospitals

like Henry Ford hospital or Beaumont hospital in our area or some of the medium sized hospitals.

They consist of theologians, people like that. We have currently someone who is a Jesuit priest and teaches ethics at one of the local seminaries. And we have a unitarian minister who runs the Children's hospital at Michigan. She is the chief chaplain of the hospital system right now.

And those are the people whose vote counts in all matters.

Typically, we have our investigators write a protocol. If they are doing the procedure internally or if it is something jointly done with a medical school anywhere in the country, they will write a protocol. We mail that protocol to all members on the board at least two weeks in advance for them to review at their leisure.

Meetings typically take a half a day and we typically do two or three protocols in four hours. So we have probably at least an hour for discussion.

When there are researchers who are out of state, we will connect with them on a conference call and have them present during the time that their protocol is discussed as well.

It is an either up or down vote but they can

also say there are following reasons why they do not like a protocol and send it back again and have it revised but if they do not unanimously agree to the protocol it is simply not going to be done.

The general nature of our work consists of two broad areas. One has to do with trauma research and one has to do with toxicity and toxicology kinds of research.

Trauma, of course, is preventing trauma and trying to understand something about the biomechanics of the body and how it is injured and try to use that to design systems within the automobile to alleviate those kinds of problems in a crash.

Toxicology has to do with the effects of automobile pollutants. It has to do with the effects of air bag dust. It has to do with plastics and chemicals that are used to make the interior components of the car and how to deal with medical problems that may arise from those kinds of exposures.

Recently there has been a lot of interest in sort of information processing kinds of studies, and these are very interesting, and these are primarily how we have been drawn from strictly private research and doing the work with federal agencies. These involve things like not cell phone use itself but information

overload, shall we say.

There are all sorts of wonderful gadgets now that will tell you where in the world you are, what street you are driving on and where the nearest McDonald's is, and all sorts of things like that, and the question becomes, you know, how much information can you safely deal with.

For us, the question is when making a selection from many alternatives, what to incorporate in a car and how to do it in a responsible way so that we do not contribute to your driving task at the wrong time to make it an unsafe type of task.

There are also all sorts of wonderful space aged things coming up on the horizon now involving extremely precise radar systems that can shoot right down the highway and computer sized information processing systems that can reject dozens of false targets coming at you every minute, sign posts and trees and things that look like they are in your path but in another half a second they will not be in your path.

From that we can pick out real collision events coming up and the question becomes how do you understand the best way to communicate that information to the driver. Do you want to put the brakes on

automatically? Do you want to flash a light? Do you ring a buzzer? Do you want to have a voice appear? Do you want to use a haptic of some sort?

So these are the kinds of things we are beginning to do and these are the kind of things that we are working with the Federal Government on and primarily the Department of Transportation, and they review us again to make sure we have a bi-gender make up of our committee and so forth and are consistent with their thinking about what a proper committee is.

So that is currently -- that is basically what our committee is all about and how it functions.

There is an informed consent form in every case. Every informed consent form has a risks and a benefits subsection. I think every one that I have ever seen basically says that the benefit is you will get paid for your time and there is no benefit to you personally for participating. You are only contributing knowledge.

The risks are described as vividly as they can be and, if anything, I think the corporate lawyer insists that they be described more vividly than most investigators would be comfortable with because he is faced with defending these things should something go wrong.

The subject of cadavers came up about 15 years ago. Most early work in the area of biomechanics was done primarily with unclaimed bodies. I mean nationally this is where you first got material. This is where we first learned the compressional breaking strength of the femur and the cracking -- skull cracking and the fracture information that we currently know, et cetera. It was all done 30-40 years ago with this material.

Twenty years ago or so this became a sensitive issue, studies on cadavers, and we decided that cadavers should be treated like all other human beings and there should be some sort of consent for their use. And from that time on we have only used willed bodies so we do have a protocol. It is important -- again, as with living subjects -- that the investigator describe the reason why you have to do another experiment and cannot find this information in the literature. We would like to know that first of all and then again we only would use willed bodies for cadaver research.

PROFESSOR CHARO: Thank you very much.

Dr. Chin?

DR. CHIN: I guess I should give you a little bit of background first as to the organization that I represent. I am with the National Food Processors

Association.

PROFESSOR CHARO: I am sorry. Could you pull the microphone a little more close?

DR. CHIN: Sure.

DR. DUMAS: Yes, because I am -- Rhetaugh is having trouble hearing.

PROFESSOR CHARO: Thank you.

PROFESSOR BACKLAR: Yes, so am I.

DR. CHIN: Thank you.

(Laughter.)

DR. CHIN: Yes. I probably should start by giving you a little bit of background about who I am and the organization that I represent.

I am with the National Food Processors Association and NFPA is a trade association that represents the food processing industry. We operate three research laboratories: In Washington, D.C., out here in Dublin, California, which is in the East Bay, and a laboratory up in Seattle, Washington.

We, as a trade association, we do not -- we are not directly involved in any testing that involves human subjects but we do operate a commercial laboratory, a commercial testing laboratory that has a sensory testing group that does market research and consumer taste panels, and that kind of thing.

As I said in my opening remarks, the food industry basically uses human subjects in two areas, as I said. One is in the -- in those categories, which basically fall into clinical studies. These would involve the effects of trying to follow the effects of nutrients or anti-nutrients on health, looking at the health effects of either new or old food additives, color additives, that kind of thing.

And there are studies going on in terms of the assessment of food allergies and intolerances, and those are all -- those studies are all usually conducted or are conducted in clinical settings in a medical facility or under the control of medical research people.

The other area that Ed mentioned was consumer testing and, you know, that is -- obviously it is quite widely used in the food industry. It is used in two ways. I think most of you are familiar with the type of testing that we bring in consumers and ask them to evaluate food products, what their likes or dislikes of products.

We also have what are called trained test panels that are smaller groups of maybe half a dozen, a dozen people, who we train specifically to recognize certainly traits in a product, whether it be texture,

certain flavors, certain odors, and what they try to do -- what they do is to put -- to make those kinds of measurements more objective, put it on some type of scale.

In terms of the -- in terms of the consumer panels that are run in the food industry, we -- our company does that. We advertise for consumers to -- who are interested in doing this type of work. They respond to a number. They call the number that we provide. We have a telephone answer -- people who answer the phone who are then taken through a list of questions in terms of trying to figure out their likes, their dislikes, the -- whether or not there are any allergies or intolerances that have to be recognized.

And basically those people who have allergies or intolerances are screened out of that process so they are not brought in for taste panel work.

Then, in addition, the -- in the situation -- I noticed when I walked in at the end of the earlier discussion when you were -- the question about minors or adolescents. Obviously in the food business you have a lot of products that are targeted to a whole range of groups but obviously some are targeted to children and when products are -- when the taste panel is -- includes children, there is a special consent

form for the parents for their children in terms of, you know, making sure they understand what the products are that are to be tested and that kind of thing.

In most cases, since we are testing food products, there is a protocol that is going to be reviewed with the company that has requested the work. If there is any question at all about toxicity we have employed a toxicologist to review the materials that are in our study.

We have microbiologists on staff because we are dealing with food products, you know, in terms of looking at the microbiological issues in terms of whether or not there is any potential for food borne illness in terms of improper handling of the food because sometimes we send the food product home with the consumer. And, obviously, if that is the case, you need to make sure that they understand how to handle it if there are any issues associated with food borne illness.

The -- if there are situations that involve a food additive that is in the process of regulatory approval, that is to say it is not currently an approved food additive but this is part of the information that a company is trying to get in order to complete the petition process, then that protocol will

also -- we will also use an independent review -- internal review board in order to review the test protocol.

So that is kind of our history with human subjects.

PROFESSOR CHARO: Thank you.

Members of the Commission, do you have questions, comments?

Let me start then if other people are still contemplating.

One of the observations about the current system has focused on enforcement. Specifically the current system covers those people who receive federal funds or are working with products that are regulated in a way that requIRBs certain kinds of independent review and informed consent, et cetera, such as FDA regulated pharmaceuticals and biologicals, et cetera.

So that the enforcement that exists when protections are not observed tends to be the withdrawal of federal funding or the withholding of approval of a product.

When one contemplates extending these protections to the private sector where there is no federal financing and no approval process contemplated, the question arises what enforcement mechanisms would

be appropriate, if any, beyond those we are now familiar with. And they range in the proposals that have gone before Congress from criminal penalties to civil penalties.

And I wonder -- perhaps I will start with Dr. Schreck, to the extent that your committee reviews protocols on occasion that do not involve collaboration with an otherwise regulated person like an investigator at a medical school that has a federal assurance, what has your experience been in terms of enforcement of these kinds of rules?

I do not know if you have ever had the occasion of people not understanding them well enough to have followed the procedures or the procedures having run into a snag, inadvertent or intentional. But what has been your experience and what might you suggest would be an appropriate kind of enforcement mechanism if this were to go to the private sector as a general rule?

DR. SCHRECK: Well, I really do not know that much about enforcement so I leave that to you folks to decide what it is you need to do to get people's attention.

In our case, we are a very visible and collectible entity and we probably spent a lot more

time considering each one of these things than most academic institutions simply because we really have to be extremely sure we do not do anything that is going to hurt someone or is not justified.

We have never done a protocol outside the scrutiny of the federal system any differently than we have within the scrutiny. As a matter of fact, we have only really done things in the last three or four years that are collaborative with the Federal Government so of that 150 protocols, 147 of them have all been privately done and we would not have done it any other way.

I mean, this was done -- Bob Fraush was the head of NASA when he came to the research labs and was our Vice-President. When he saw that there was human work being done, he said, "You know, we have to set this up the same way we did at NASA." And the protocol was established in '74 and really has not changed at all since then.

I do not know what gets people's attention in enforcement. There are probably people in Washington that know a lot more about that than we do and what you can practically put into place.

PROFESSOR CHARO: Dr. Chin, do you have anything to add?

DR. CHIN: I guess, in general, most of the things that we are involved with do not involve federal enforcement. I mean, the activities that we are involved with are -- you know, they are with foods or approved -- most usually with approved food additives.

Those times which -- I guess when non -- not yet approved food additives are being studied, you know, those have to be reviewed by FDA in terms of, you know, testing on human subjects.

PROFESSOR CHARO: The second thing I wanted to ask actually is more pertinent, I think, Dr. Chin, to you. We have a situation now with regard to herbal remedies and that family of food supplements. A situation in which there is no longer FDA regulation in the form that would resemble that of a pharmaceutical.

So we are left with what is currently kind of FTC regulation of consumer advertising and claims, et cetera.

Now a lot of the kind of work you described struck me as being the kind of market research that might well wind up being exempted from the overall human subjects rules that are developed under one system or another but some might not.

And herbal remedies struck me as one area where they might not necessarily get the kind of

exemption that you might expect for a variety of kind of, you know, taste preferencing kinds of things.

And I am curious what difference it might make in the development of these products should there be imposed a general expectation that the development process would be accompanied by the independent review by a committee of experts for the risks and benefits of the use of the product, alternatives that people might have for using different products rather than the one that is being tested, and the whole process of giving informed consent under those circumstances.

DR. CHIN: I guess, the whole issue of herbal supplements and, also, dietary supplements is --

PROFESSOR CHARO: Sure, that is a good addition to the list, yes.

DR. CHIN: Yes. I think we would agree that that is an area that is certainly one of controversy. We -- you know, I think that -- well, I really cannot speak for herbal supplements and dietary supplements because we are not involved with that and they have -- they are not directly involved with what I would call the mainstream food industry for the most part.

So I do not know if I -- you know, if I should --

PROFESSOR CHARO: I am sorry. Would it be

fair to say then that your trade association does not incorporate within it the companies that are most directly involved in the development and manufacture and sale of those products?

DR. CHIN: That is correct. I mean, we are mainly the major food processing companies, the -- you know, the Campbell's Soups, the General Mills, the General Foods of the world as opposed to companies that manufacture herbal supplements.

PROFESSOR CHARO: Okay. Well, then in that case perhaps the question was poorly placed.

Bernie Lo?

DR. LO: I would like to ask a question of both of you. As we think about the federal regulations, we have heard a lot of suggestions that in some areas some of the regulations do not seem to be making much sense or are counter productive or whatever.

I was going to ask you in your experiences are there places where you find the federal regulations either to be problematic or not applicable to the type of research you do or in need of some improvements in any way?

DR. CHIN: Well, as I said, I think in -- most of the things that we do, we do not -- we do not fall

under the federal regulations and, you know, I think in terms of the types of consumer testing that we do, I do not quite know how we would implement -- first of all, I do not know what kind of shape -- what kind of form a regulation would take and then obviously how that could be transformed into a situation where potentially you do have, you know, thousands of people doing a test in many different locations. So, you know, in terms of that aspect of our research I really do not know where the federal regulations could work or how it could work.

PROFESSOR CHARO: Do you have any follow-up with that, Bernie?

Other questions, comments?

DR. MESLIN: Dr. Schreck has --

PROFESSOR CHARO: Oh, I am sorry.

DR. SCHRECK: I think, as I said, we really do not do that much and so I do not know that they would be much of a problem. We try to follow them anyway even when we are not required to because, I think, they give us good guidance as to what to do.

Once in a while you catch an overly enthusiastic researcher who wants to go do too much and has not done his literature well anyway and so I think the guidelines are protective for us even when are not

required to use them.

PROFESSOR CHARO: Alex?

PROFESSOR CAPRON: I think if there were IRB chairs from around the country who had heard your testimony most of them would be salivating, Dr. Schreck, at the resources which are apparently available in terms of time principally and obviously the very high quality of participants you have in your process.

You have spoken of roughly 150 research protocols over a 10 or 15 year period, is that correct?

DR. SCHRECK: About 26.

PROFESSOR CAPRON: A 26-year period. So half a dozen a year on average or something in that range.

Of that, do you have a sense of how many were ones which needed to be revised and, correlatively, are there any that involved such a low level of risk that you felt that there was a means of administrative approval that was acceptable?

DR. SCHRECK: That is a good question and I think it is one of the comments that was on your question sheet. Do we need guidance in any area? And I would say de minimis risk is one area.

Those typically -- those questions come to me and I decide whether there should be a protocol review

or not. Historically, we have had studies of the visual effects of air pollutants where people sit in a room and look at slides of Los Angeles' air quality on different days of the month and that is a de minimis as far as I am concerned. You know, I do not -- you know, eating in the cafeteria and looking at slides that are noncontroversial, those -- I pass those as de minimis. I send them a letter and say you do not need a review.

PROFESSOR CAPRON: And that is not included in the 150?

DR. SCHRECK: That is not in the 150 so they do have to ask because we have had faculty members from Michigan who say you cannot show slides at the University of Michigan because some faculty have slipped in some pretty off color things and have gotten all sorts of excitement going and parents' letters and what have you. And, you know, slide showing is not de minimis in an academic surrounding but it is if you are looking at pictures of Los Angeles' air.

So, if anything, it would help us to --

PROFESSOR CAPRON: That is what we think of our air in Los Angeles, it is de minimis.

(Laughter.)

DR. SCHRECK: It would help us to get some better definitions of what is de minimis risk. I mean,

I consider driving on the highway in a normal passenger car to be a known and accepted risk. We would not have a protocol if you were just driving a standard production automobile in a standard road course. You start fooling with the braking system and so forth, and now you are experimenting, you know, then it is no longer a standard acknowledged risk.

PROFESSOR CAPRON: And on the other half of my question, about what number out of the 150 went at least twice around? That is to say he had problems with the design sufficient that you had to ask for a second review.

DR. SCHRECK: Oh, I would say when you get new investigators sometimes -- I would say maybe 20 percent or so you basically said, you know, go back -- maybe not even that. Maybe 15 percent. You would send them back for, you know, do this, do this. Often times they do not understand how to draft informed consent well. We send them back for that.

We send them back -- the subject of women in research has troubled us for a long time and we did a lot of "men only" studies and now we are trying more and more to do women studies and so you send them back and say, "Why don't you want women in the study?" "Well, usually fetal protection." "Well, could you

take women of child bearing age if you knew they were not pregnant?" "Sure. How can I tell they are not pregnant?" "Ask them and you test them."

(Laughter.)

DR. SCHRECK: So we just recently did a wonderful study on the provocation effects of air bag dust on causing asthmatic attacks and we had women in that study because we went back and we made them do that, and they ended up testing a lot of women of child bearing age. In fact, they ended up telling one young lady who did not know it that she could not be in the study.

PROFESSOR CAPRON: She was pregnant.

(Laughter.)

DR. SCHRECK: Which caused a great deal stress for all the investigators that morning.

PROFESSOR CAPRON: Yes.

DR. SCHRECK: But that is the story of thing that does get reviewed.

PROFESSOR CAPRON: Thank you.

PROFESSOR CHARO: Dr. Schreck, I understand that you are not subject to the federal regulations in many cases, most cases, even though you choose to follow most of them anyway.

What is interesting to me in the reply you

just gave is that although there are some categories of research of de minimis risk that do not require fully committee review and instead only the sign off by the administrator of the committee is necessary, in other cases de minimis risk signals the ability to do research without all of the formal requirements of informed consent but committee review is nonetheless required.

So that if the existing federal rules as they are written were to be extended to the private sector, it might actually increase the number of protocols that would have to come to your committee rather than going through you or somebody in your position as a more administrative kind of matter.

How might that affect your ability to handle the scale of the work against the resources that you have as well as handle the question of people feeling like their time was well spent in the reviews that they were asked to do?

DR. SCHRECK: A good two part question, yes, because I think in terms of the extra work load on us, it would be no problem at all. I get a de minimis risk every other year or something like that. You know, maybe one.

I think the committee would feel their time

was wasted reviewing a protocol over someone who was sitting in a darkened room looking at slides of Los Angeles' air. They would say, you know, "Why are you taking our time? You know, we have all got real jobs and we are coming here and you are paying us less money than we make in our clinical practice. I am spending four hours with you today and I should be doing something else." I think that would be a problem.

PROFESSOR CHARO: David?

DR. COX: Yes. To follow-up on sort of your own suggestion because we have wrestled with this a lot on the Commission, which is how you define de minimis risk.

DR. SCHRECK: That is what I could use some help on.

DR. COX: So we do, too. And so how would you define it?

DR. SCHRECK: Well, I suppose the de minimis -- I guess the definition would be that the risk is so low that it is no different than what you are exposed to in your every day life, whether it is eating at the cafeteria, driving to work. The sorts of things that -- the kind of risks that you know and acknowledge and are willing to get out of bed and take every morning.

If a program -- a protocol involves deceit, we

would always run that and rehearse those people through what you need to do if you deceive the subjects for a purpose and the committee understood the purpose beforehand and then you went back and debriefed them afterwards, and recaptured their confidence. We would always review a protocol like that.

And anything with a possibility of a greater risk than that I think would have to be reviewed.

PROFESSOR CHARO: Just a clarification. When you say the risks of every day life, are you talking about kind of a national average, a local average, or of the particular subject you are recruiting?

DR. SCHRECK: I guess we are talking nationally about what it is like to live in America.

PROFESSOR CHARO: Okay. Marjorie?

DR. SPEERS: I have --

PROFESSOR CHARO: Oh, I am sorry.

DR. COX: Can I just say that is extremely helpful? Thanks. Because the -- these kind of practical issues from -- answers from the real world, I think, will serve this Commission in very good -- a forum for coming up with useful recommendations.

DR. SCHRECK: For our purposes, if we go out and modify the way a brake system works -- now there are all sorts of smart braking systems that can tell

you, you are about to hit the -- slow you down before you hit the car in front of you and what have you. That is no longer de minimis risk. It is not the way -- if you drive to San Francisco, take a rental car out of the lot and drive it, that is the way a car should drive. You understand that it behaves the way all 100 million of them do.

You start playing around with that, you are playing around with this person's interaction with that piece of machinery and he is going at high enough speeds. There is a lot of kinetic energy involved and you can get hurt so you are no longer working against that background at baseline.

DR. COX: Okay.

PROFESSOR CHARO: Okay. Marjorie?

DR. SPEERS: Yes. I have two questions. One is do you do studies that involve the use of medical records and, if you did, would that be the type of study that you would put through an IRB for review?

DR. SCHRECK: We have done some investigators at a university and they were doing a lot of work with alcohol and drug blood levels. So this did get involved in emergency room blood sampling and record keeping, and certainly that goes through because it has to do with privacy and it gets to be very sticky

because the police have access to that data or they can want to get that data. So that was a very difficult review.

DR. SPEERS: Okay. My second question is when you talk about following the federal regulations, could you clarify which federal regulations you follow? I ask that question because when we talk about the Common Rule, that is 45 CFR 46 Subpart A, there are -- the 45 CFR 46, which includes four subparts, A, B, C and D, and I just wanted to get a sense so that we are clear on when you talk about federal regulations what it is that you are following.

If it is, for example -- just to help you a bit -- if it is what the Department of Transportation requIRBs that you follow, that would be their Code of Federal Regulations or it would be the Common Rule.

DR. SCHRECK: That is really what we are following is the Common Rule as expressed by U.S. DOT.

DR. SPEERS: Okay.

DR. SCHRECK: Which is 45. I do not know. We set it up on 45 CFR whatever 20 some years ago because that was what was in existence at that time.

DR. SPEERS: Okay.

PROFESSOR CHARO: Other members of the Commission?

DR. CASSELL: Well, I just have a -- I mean, one nice thing about being on a panel is you learn things. Who contributes their body to automobile --

(Laughter.)

DR. CASSELL: -- crash research? Where do you get those bodies?

DR. SCHRECK: Those willed bodies?

DR. CASSELL: Yes. Who does that?

DR. SCHRECK: The State of Michigan logs on the back of your driver's license if you want to donate your body to medical research and --

PROFESSOR CHARO: Oh, it is considered medical research.

DR. CASSELL: And you get it, too? You get it or the medical school will get it.

DR. SCHRECK: If we are working with that medical school they may harvest other parts out for other purposes and you may end up taking --

DR. CASSELL: You mean I could end up driving an Oldsmobile even --

(Laughter.)

DR. SCHRECK: You may end up taking a short ride on a very fast sled.

(Laughter.)

DR. SCHRECK: Most of that work -- I think

most of that work is behind us. I do not believe there is much to be learned about what it takes to break a femur or crack a skull.

PROFESSOR CHARO: Eric, I have got to thank you because I was dying to ask that question.

DR. CASSELL: Yes.

(Laughter.)

PROFESSOR CHARO: It is not just me.

Other members of the Commission?

I did have one or two quick ones, I think, for Dr. Chin, if I may, and then if other members of the Commission do not have any further questions we may conclude this a little bit earlier than we anticipated and take a very short break while we get Don Chalmers on the phone in Malaysia.

Dr. Chin, as you may have noticed, there has been a bit of controversy worldwide about genetically modified foods.

DR. CHIN: What is that?

(Laughter.)

DR. SCHRECK: It is GM.

(Laughter.)

DR. CHIN: Oh, GM.

(Laughter.)

PROFESSOR CHARO: You understand this is why

you are here together, right, for GM and food.

I found myself wondering, again in a theoretical world in which your industry was now regulated in a way it currently is not with regard to certain kinds of research on food preferences and tolerances, et cetera, et cetera.

How you imagine your industry might structure its discussions of risks and benefits when there is a disconnect between risks that have been identified in the technical literature versus risks that are perceived or feared by the consumers?

It is a question and, in fact, Professor Capron actually wrote on this 20 years ago in the context of medical care about kind of point of view and whose point of view controls the information delivery.

DR. CHIN: I think given the current climate or debate in terms of GM foods, we would consider, you know, testing that involves GM foods in the same light as dietary preferences. That is to say if you are doing testing on -- in terms of doing the screening, when you are screening your consumers in terms of, you know, do they have allergies, do you have intolerances, do you have religious objections to any type of diets.

I think those would -- that kind of thing would go into the prescreening. You know, so obviously

if someone says that if they -- for whatever reason -- they have an objection to genetically modified foods, they would be screened out of that process, you know, if that type of product was going to be used, and if you are going to be testing a genetically modified tomato it would be, you know, ethical to let your consumers know that that is involved and go through a screening process, I think, to screen out those people who have those types of objections for whatever reason.

PROFESSOR CHARO: David?

DR. COX: Yes. Actually your discussions made me think of --

PROFESSOR CHARO: Microphone, David.

DR. COX: -- of a scenario that I do not know the answer to and actually it is sort of for both of you. It is do you ever use the same subjects more than once in more than one type of situation or is it almost always you go out and you get a different cohort of people, but are you -- do you have a reason or do you go back to the same people for whatever reason?

DR. CHIN: Well, I guess speaking for the laboratory that I am involved with, they have a pool of, I believe, something like 40,000 people in our geographic area and those are -- that pool is characterized according obviously to age, gender, types

of preferences but I think it is possible -- I mean, there is no process to eliminate people.

Say if we brought you in once to evaluate salsa and you like Mexican food, we are not -- there is no reason not to bring you in to evaluate another type of, let's say, Spanish rice. Okay. So there is no intent to exclude people on the basis of the amount of participation that they have had.

DR. COX: But to put that a different way, if somebody likes salsa do you actively recruit them to test Spanish rice?

DR. CHIN: Yes.

DR. COX: Okay.

DR. CHIN: As a matter of fact, yes.

DR. SCHRECK: We generally do not re-recruit people. However, if we have found a special category that is very, very hard to find subjects for and we have found a special subject -- I will give you an example.

While we were studying the effect of air bag dust that is generated when the bags inflate on asthmatics, we found that generally in the U.S. population about 40 percent of asthmatics are sensitive and have responses to air bag dust and about 60 percent do not. When we found these people we wanted to find

out why.

DR. COX: Exactly.

DR. SCHRECK: Was it the pH? Was it the dust level? Was it an ion that was in there?

DR. COX: Yes.

DR. SCHRECK: And we went back to the manufacturers of the inflaters and we said, "We want you to make a new inflater that has the same characteristics but has no sodium in it." And they made a dozen of those things.

We actively sought those people and said, "We know it was unpleasant. We will have the doctor there right outside the car the next time again. We want you to try a different bag that has no sodium in it and see if it was the sodium." So in that case we did go back a second time.

PROFESSOR CAPRON: Was it?

DR. SCHRECK: No, it is not the sodium. It is the -- well, of course, the pH is about 11.5 and it is a micron aresol and you can imagine a milligram of 11.51 micron aresol just penetrates right through all your respiratory defenses and goes right to the pulmonary area.

It was the dust level. If you get the dust level down below 200 micrograms per cubic meter and you

will not have an attack.

PROFESSOR CHARO: Bill Oldaker?

MR. OLDAKER: Dr. Chin, so that I might understand a little bit better, when your companies that belong to your association test a food ingredient that FDA has not listed as generally regarded as safe, a new additive, do you test those on human subjects, or how do you go about -- how do companies -- I realize the trade association does not do that -- how do the companies go about getting FDA to approve those for a food additive?

DR. CHIN: Well, I mean, that -- basically the food approval -- the food additive approval process is a multi-step. I mean, it includes the chemical characterization, the requisite toxicology tests, and then like obviously in the case of something like Olestra, you know, they then did some human studies.

So the human studies are, in essence, the last step of the process and it is probably also part of the process in terms of consumer acceptance. You know, after you have gone through the toxicology and determined that there is no risk to the consumer, it is at that point that you do a tastes panel and I think at that point is then when they start to do -- to determine what -- recognize what some side effects

might be. I do not know if that answers the question.

MR. OLDAKER: And those studies are regulated by the FDA --

DR. CHIN: Yes. I mean, those would be done in --

MR. OLDAKER: -- as far as human subjects.

DR. CHIN: Yes. Well, those types of studies would be done under a clinical situation setting.

MR. OLDAKER: Right.

PROFESSOR CHARO: Other -- well, I think as a potentially final question I would be remiss not to ask you to comment on these same issues in a transnational context.

To the extent that you have, in fact, overseen or have been involved with people who oversee human subjects research, what, if anything, has been done differently when there has been a collaboration across national borders and if you have no experience with that, feel free to just contemplate what it would be like if you were to work across national borders and speculate as to what might have been done differently.

This is like -- you know, it is like To Tell the Truth where the three contestants were always looking at one another and they would both begin to go up and down.

DR. SCHRECK: We have not done anything outside the country. However, we worked very hard at trying to set up air quality pulmonary studies about 10 years ago in a number of other countries where air quality was extremely bad and contained the same kinds of chemical problems that our air has and we were anticipating that as these countries came on line we would see an order of magnitude improvement in air quality and be able to use these people as their own controls.

Unfortunately, for various reasons and nobody's country wanted to cooperate with us, so the studies were never done.

But basically we looked around and these were Second World countries I would say who were coming on line. We looked for people who were graduates of U.S. medical schools who were practicing or at universities in those countries and tried to see if we could find that kind of collaboration.

PROFESSOR CHARO: But, for example, with your air bag studies concerning asthma attacks, since the cars that you manufacture are going to be sold widely around the world and not just in the U.S. and, indeed, you probably could list the five non-U.S. markets that are the largest for your cars or those kinds of air

bags, any interest, need, speculation about running similar sets of tests to see if the population of asthmatics there against the backdrop of pollutants and other environmental conditions there would yield different conclusions about what is a safe level of dust or an optimal level of dust?

DR. SCHRECK: No, differences internationally probably have a lot less to do with -- you know, given the concentrations of materials you are dealing with in a closed car, whatever your background air pollutants are in Brazil, are minimal compared to what you are being exposed to at that time.

I think generally the need for studies are different in different countries and what they require are different, and that is probably an overriding factor as to what you are going to use. You are going to have various other regulations. It is a funny thing but science does not seem to be the same in all the countries of the world that practice it. Have you noticed that? Otherwise, we would probably come to a common level of air quality control and certain crash performance standards for cars and yet they seem to be different in all sorts of places.

And so those might cause a need for study but then again laws are different in different countries.

In European countries you have a type of approval when the Federal Government decides that everything looks well done and what have you, they basically give it a stamp of approval and you do not need to do testing beyond that. So there is no motivation to go ahead and do any more than that.

PROFESSOR CHARO: Dr. Chin?

DR. CHIN: The only circumstance that comes to mind is a slight variation upon, I guess, maybe what you are asking. The circumstance that comes to mind most recently is that we were involved with a situation where a company wanted to bring a product into the United States. It was basically a product that was on the market in Europe or it would be similar to a product that is a product in Europe and what they wanted to do was to evaluate how American consumers would like this particular product.

And so they would have to have -- but it was going to be slightly different from what was actually on the European market so they were going to have to go through a special production run and so the kinds of issues that arose there was to make sure that in terms of the production it satisfied all of the requirements.

It happened to be a can product -- that it satisfied all of the FDA requirements in terms of

safety and that we would be comfortable with -- that they would not present any hazards in terms of food borne illness and that was what we were primarily looking at.

So it is not quite the same thing as you were asking.

PROFESSOR CHARO: Alex?

PROFESSOR CAPRON: Both of you described mechanisms for review of protocols and standards for that that are, as far as I can see, very close to, if not identical to that which would exist in a federally sponsored research.

Three years ago the President declared his view that all Americans should have the protection if they are research subjects of those kinds of standards and our Commission when looking at an area where there was a good deal of actual or potential private research, namely human cloning with the potential for fertility clinics if there had been a boom to go in this direction being likely sponsors since the Federal Government was not going to be a sponsor, went on record as saying that we thought there was value in all research, enjoying what are sometimes referred to as the triple protections of informed consent, risk/benefit assessment and prior review by a review

board.

And I wonder whether if you were speaking to others in your fields, other automobile manufacturers, other people involved in foods and the like, you would say that you think, indeed, all research that is privately conducted should adhere to the kind of standards that you have chosen to adhere to.

DR. CHIN: I think in terms of the kind of work that we do and interactions that we have had with companies that have been clients of the work, the issue has been a question of legal liability and so those kinds of issues -- the points that you have raised, whether it be -- in spite of the fact that a sponsor at this point -- I think people have undertaken to do that in order to protect themselves against the legal liability that would be associated with this type of testing.

And I guess that is the primary motivation for -- one of the primary motivations for doing the informed consent and doing the reviews and, you know, those kinds of a -- undertaking those kinds of actions.

PROFESSOR CAPRON: Right.

Dr. Schreck?

DR. SCHRECK: Yes, I agree. I think that getting outside the auto industry even, I think to any

Fortune 500 company would certainly not go in for these kinds of testing without following these kinds of rules either. I think that they understand that they have a certain liability. They would not want to do the wrong thing and these would give them some guidance as to what they ought to be doing.

PROFESSOR CAPRON: I guess the question that we face as a Commission is whether we ought to recommend that such requirements be made part of all such research. There are obvious questions about whether the Federal Government has the authority to command that outside those areas which are subject to regulatory approval like drugs or devices and the like. Perhaps food stuffs.

But whether -- to get to the ethical issue underlying it, whether these are standards that are so basic that it really -- we ought to live in a society in which anyone who is recruited into research has those protections and I understand the answer would be when you are looking at the kinds of companies you are talking about, they are going to do it because they would fear that if they do not do that they are going to harm people in ways for which they could end up being made liable.

I guess my question comes at it from the

ethical side rather than the legal side of whether these are the kinds of norms which would be reasonable to expect because they are the sorts of results and the sorts of protections that we would want everyone who is recruited into research to enjoy.

And I do not know if you can respond as to your evaluation as people who follow these rules and thinking about whether they really ought to be things which everyone follows.

DR. SCHRECK: Do we have any knowledge of how extensive this area of research is that is beyond the purview of the Common Rule?

PROFESSOR CAPRON: Well, you know, one of the problems is that we do not have that knowledge even about research which is covered by the Common Rule. It remains an issue and it is something that I have personally thought it is hard for the Federal Government to make this a commandment to others on the basis that you see we require it here and look at all the good it does when we do not know -- no one could give you either the numerator or the denominator on the number of people involved and the number who suffer bad consequences or the number who are in protocols that should not have been approved or the number -- I mean whatever fraction you want to do, we do not know

because we do not have those data.

There is a sense that if the agencies all got on the stick about this they might be able to say, "Well, at least as to research we fund, if not research that we regulate, we have some sense of how many protocols there are," and we could ask researchers to report back, "Well, how many people did you actually enroll in the last year," and so forth but it has not been done.

But as to the others, there is even a bigger shrug in saying, "Well, how would we know? I mean, how many people are in all these different studies that different people are conducting?" And maybe that is a reason for saying that we should not bother or try to regulate it because it would be so hard to get our arms around it or it might be a way of saying, "Gee, we would feel at least more comforted if we knew how many studies are going on." But I do not think there is an answer to your question as to the federal much less the nonfederal research.

DR. SCHRECK: I mean, to some extent America is an unusual place because we make up laws after something goes wrong and we assume that there is sort of a clear background space in which there are no laws and we just sort of fit them in as we need them as

opposed to other countries that set up general laws and try to fit circumstances within that legal code.

To some extent to make a rule before we knew there was a problem would go against that sort of philosophy of law making.

On the other hand, the companies that you talk about that are not the Fortune 500's, the start up companies that are doing genetic material and what have you, are probably the scariest practitioners of all.

So that is not an answer to your question either but I can see your concern.

PROFESSOR CAPRON: I think it is very --

PROFESSOR CHARO: And on that -- I am sorry.

PROFESSOR CAPRON: Yes. Well, I think -- just to finish the answer to your question. I think it is fair to say that the cases that have been enumerated to us where nonfederally funded research was done without the kinds of reviews that we are talking about, are to the best of my recollection -- others may recall other cases -- within the biomedical area and they were simply people -- practitioners or otherwise -- who stepped into doing something that seems to an outsider clearly to have been research without bothering to go through any of these steps.

So they are not so much the examples of things

from the entrepreneurial side, as it were, but we do not know whether those exist.

PROFESSOR CHARO: On that note, I am going to thank you both for having come and educating us about a sector that we had not really discussed very much before. It is very much appreciated.

And I am going to ask the Commissioners to please come back in eight minutes-and-47 seconds, which according to Eric's wristwatch would be at 4:45.

We will use the intervening time to get Don Chalmers on the telephone.

Thank you very much.

(Whereupon, at 4:36 p.m., a break was taken.)

PANEL III: ALTERNATIVE MODELS

DR. MESLIN: Donald, can you hear me? It is Eric Meslin.

PROFESSOR CHALMERS: Hello. You are a little bit faint.

DR. MESLIN: Okay. Donald, we are just about to reconvene. I just wanted to make sure that you could hear my voice. Can you?

PROFESSOR CHALMERS: Yes, I can hear you.

DR. MESLIN: Well, that is the only voice you have to hear right now since we are just coming back from a break.

PROFESSOR CHALMERS: Good.

PROFESSOR CHARO: Most people are not back. I wonder if we can -- could you please go out, thank you, and try to round people up?

For the Commissioners that are in the room, if I can encourage everybody to join us, we will let Professor Chalmers -- what time is it for you, Don? Donald?

PROFESSOR CHALMERS: Hello, Alta?

PROFESSOR CHARO: Hey. What time is it for you?

PROFESSOR CHALMERS: You are very faint.

PROFESSOR CHARO: Donald, what time is it for you?

PROFESSOR CHALMERS: Oh, it is only a beautiful quarter to 8:00.

PROFESSOR CHARO: Quarter to 8:00 in the morning?

PROFESSOR CHALMERS: Yes.

PROFESSOR CHARO: You are in a whole different place.

(Laughter.)

PROFESSOR CHARO: We are at the end of the day. Be merciful to us.

PROFESSOR CHALMERS: How have you worked on

today?

(Laughter.)

PROFESSOR CHARO: We had a few fireworks at certain points.

Okay. I think we have all gathered back in the room again. I am going to turn the microphone over to Eric for just a moment.

PROFESSOR CHALMERS: Thank you.

DR. MESLIN: Donald, greetings and welcome to the Commission meeting. This sounds a bit formal since I had spoken to you just briefly but I did want to extend the Commission's thanks to you for taking time out of your scheduled vacation and also for your extremely comprehensive paper that the Commissioners have been provided.

Harold Shapiro, the Chair of our Commission, extended his regrets that he was not able to be here to hear your presentation but he has read the paper and has a number of comments.

For the Commission's benefit and just as a matter of housekeeping, we have asked Professor Chalmers to just give a very brief, no more than ten minute, overview of the paper that he has provided summarizing what we believed were the key points about the Australian research ethics system.

It is a draft paper and there are opportunities for expansion and additional points that need addressing.

Let me just briefly introduce Professor Chalmers, who is the Dean of the Law School at the University of Tasmania, and he has just completed two three-year terms as the Chair of the Australian Health Ethics Committee about which you will hear more. I know that Professors Charo and Capron, who know Professor Chalmers quite well, will agree with me that it is quite a privilege to have him with us, both long-distance and in written form.

So, Donald, with that introduction, there are about 10 Commissioners in the room, a couple also on telephone, there are members of the public and our staff here in sunny San Francisco, and it is the end of the day on Monday, and that is the orientation that you need so with that I would like to invite you just to give your few brief opening remarks before we then turn it over to Commissioners for some questions.

DONALD CHALMERS, LL.B., CHAIRMAN
AUSTRALIAN HEALTH ETHICS COMMITTEE
FACULTY OF LAW, UNIVERSITY OF TASMANIA

PROFESSOR CHALMERS: Well, thank you very much.

Thank you for the invitation to speak with the National Bioethics Advisory Commission and, of course, a welcome to those members of the public who are present today.

I think it is a very healthy feature of the American system the way that you have these meetings of your Commission open.

You have asked me very briefly to address the overall Australian research ethics system. It is actually very close to the American system with, I think, some local differences. I have in the paper tried to explain that we have a three-tier system. I have tried to develop that because I think it is important that we realize that the researcher who carries a primary responsibility for ethical consideration and responsibility for protection of research subjects, I think in this country there have been at times feelings amongst the researchers that they are not trusted and that we have quite deliberately in our new national statement on ethical conduct in research involving humans reasserted at various places the responsibility that the researcher carries towards the design of the project and the ethical responsibilities to the research participant.

Secondly, we have human research ethics

committees. These used to be called Institutional Ethics Committees and are directly comparable with the U.S. Institutional Review Boards.

We introduced Ethics Review Committees about the same time that the United States introduced them following federal legislation. We were aware of the developments in the United States but it followed a slightly different path, which I will follow later, but there are direct comparisons.

The difference, I suspect, is that at a third level we have a national body called the Australian Health Ethics Committee, which has a number of specific responsibilities within the system. Notably, the Australian Health Ethics Committee has sole responsibility for the development of guidelines for the conduct of medical research. That is a power which is conferred by Commonwealth Statute. Commonwealth is our federal parliament, and it also has a number of other associated responsibilities towards developing health guidelines. But in specific terms it has sole responsibility for the development of guidelines for ethical conduct of medical research. So much so that it is the Australian Health Ethics Committee which actually carries out the consultation.

Those guidelines are then simply presented to

the National Health Medical Research Council, which is the governing body within which the Australian Health Ethics Committee is situated. The NHMRC cannot alter or change those guidelines.

And then finally the guidelines are laid -- they are formally presented to the Federal Commonwealth Parliament for 15 days, which is the usual procedure, and then those become binding within the system.

So that is our three layers, so to speak.

The other introductory remark I would like to make about the Australian research situation is one in realizing that we are not a nonregulated system. I believe there are occasions when I think the Australian system is described as entirely self-regulatory. That would have been absolutely correct about 1990 but over the last decade greater amounts of legislation have been promulgated which impact on our system so I think it is correct now to describe the Australian system as a hybrid or mixed regulatory, self-regulatory system.

Perhaps the most important change was the National Health and Medical Research Council Act in 1992. That is a Commonwealth piece of legislation, which brought the NHMRC from an entirely self-regulating organization into a formal regulatory institution which has reporting responsibilities to the

Commonwealth Parliament. It has accounting responsibilities and so on.

But the development of the Australian research system, of course, is related very much to the research culture, legislation, history and external influences. I think when we start looking at research ethics in different countries, we can see lots of parallels but I suspect that most of the individual stories are quite autochthonous. They are quite unique to individual countries because, as in your country, as I tried to say in the paper, you had some specific revelations about impropriety in research, particularly the revelations about Professor Beecher. We have had no such dramatic watershed event in our development so I have tried in the paper to spell out some of those nuances of the way in which the Australian system has developed.

Perhaps most significantly, we have actually tested the development of a national body from 1989 to 1991, a body called the National Bioethics Consultative Committee, which was briefed to give advice on matters of reproductive technology.

That was a very short-lived experiment but I think it later developed into a combination of the National Bioethics Committee with a research ethics

body within the National Health Medical Research Council, which was called the Medical Research Ethics Committee.

I apologize for the terrible number of acronyms and descriptions but these two bodies came together and eventually formed our National Australian Health Ethics Committee. And I think that particular flow suggests strongly that I think we can transplant the Australian Government to places such as California where I think it, in fact, has been actually transplanted but, of course, all transplants require considerable pruning to make them suitable for conditions. There are differences.

Well, that is, I hope, a useful summary of the roles of the Research Ethics Committee and Australian Health Ethics Committee.

I think the second major characteristic that may be of some interest to the NBAC is the recent development of a national statement on ethical conduct in research involving humans.

The Australian National Health Medical Research Council was one of the first government or first organizations to formally introduce a code of research practice within Australia following the lead of the Declaration of Helsinki in 1965. We have had a

statement operating right through since 1967.

For a variety of reasons, which are developed in the paper and I certainly shan't go into it now, there was a movement during the 1990's, which really culminated in a reference from the Commonwealth Minister because the Minister can brief the Australian Health Ethics Committee so there is a political connection there to say, "We would like you to review the old statement on research ethics." It was called "The Statement of Human Experimentation."

We conducted a public consultation and I think that is something which I am sure the members of the public present with you in your deliberations would be interested in and I hope that NBAC will be interested to know that we are required under the terms of the Act, that is the National Health Medical Research Council Act, to carry out two stages of public consultation.

At stage one we advertise our intention to review the guidelines on research ethics and we receive public submissions.

Once we have very carefully analyzed, assimilated, amended, discussed, incorporated those comments into a draft set of guidelines, we are then required as a second stage consultation to represent

those guidelines for public comment so that, as it were, there can be no suspicion that the Australian Health Ethics Committee has developed the guidelines themselves in the AHEC, excapitalitive (sic) statements are to be prevented.

So from that extensive two-year public consultation we produced the new national statement. It is a comprehensive statement covering all research on humans.

So the very first point in relation to this national statement is that we have a very comprehensive view of what is meant by research. It goes beyond experimentation in a medical setting. It is intended to cover all research involving humans, including health research, psychological research, or other forms of social science research involving humans.

We were not prepared to say that there should be some neat line of what might be called dangerous research and experimentation where the protections apply as opposed to other forms of research where there may be harm involved.

I think particularly in the case of harm, I think nowadays we think in terms of privacy as being an important component in our community. I think we also believe that there are obligations of researchers in

the way in which they conduct the research and the way that they interact with the community, which I think requIRBs high standards to be said.

So there is a number of comments which I have made within the paper, which again I will not reiterate here, explaining why we went for this wider definition of research.

Secondly, we have, as I mentioned earlier, tried to research the great responsibilities on researchers. I think we have become concerned with the -- with a view that all ethical review was conducted by ethics committees. Ethics committees are not police people. They are not the police. They have not got the resources to go around checking every single project.

Rather, we -- in an article which I wrote with a colleague we tried to compare them to the firefighters. When you want the community to take a responsibility, the research community to take a responsibility, and when there is an instance which occurs then the ethics committee should have the capacity to respond to address that difficulty. So we have got a very strong view that the researchers have to be reminded constantly that their professional associations, their professional standards matter very

much, indeed.

Thirdly, we have looked at the interaction between the public and private sector. I think as in the States, Australia in its public arena is very heavily regulated. It is not possible to conduct research with public funding without ethics committee approval. In simple terms, from 1967, the major funding body, the National Health Medical Research Council, made it a condition of receipt of public funds that the project was approved by an ethics committee.

Over the last decade, other public funding bodies have followed suit. So essentially the public area is entirely regulated by ethics review systems.

There has, however, been a feeling that the public -- the public protection -- sorry, the public coverage of publicly funded research does not compare favorably with the private sector.

What we have noticed is that we have not recommended any federal legislation at this stage to cover private institutions because we have actually found out through public consultation that for a variety of reasons many, if not most, of the private institutions are, in fact, complying voluntarily through self-regulation with the national statement.

The first reason, of course, is that many

private institutions receive public funding. They are not simply entirely privately funded.

Secondly, because there is no required standard nationally for the review of publicly funded research that is setting the benchmark and many of those private institutions are being legally advised that they opt sort of best practice standard so that if there was any untoward occurrence within the privately funded institution they could show that they were following best practice standards, which is of course in the public arena.

And then, thirdly, we are finding that some of our regulatory authorities such as the Therapeutic Goods Administration, that is a Commonwealth body which looks after clinical trials and the approval of drugs, they themselves are publishing internal directions which are saying you have to have ethical review.

So in the private area, the hybrid system, which I referred to, is drawing the private organizations in them.

Well, the fourth aspect, I think, of our national statement -- and I am conscious that I was to have ten minutes and I am way over time.

PROFESSOR CHARO: Not to worry. It is very interesting.

PROFESSOR CHALMERS: Okay. Let me just try and highlight just a couple of more. We have also got a much wider definition of vulnerable categories of patients. I think until 1992 we still pursued the idea of vulnerable within a medical research environment.

The focus was primarily on the subject or the participants themselves. Were they unconscious? Were they of a young age, et cetera? We have tried to extend the concept of vulnerability to situational vulnerability, that it is not simply that the subject is vulnerable per se because of particular limitations. There are some circumstances such as intensive care, terminal care patients, and so on that can because of the nature of the situation in which they find themselves be particularly vulnerable and we have tried to set up some additional consultations and requirements for consideration by these committees which might try to address that situation.

We have also within the document included for the first time some sections on human tissue, which I think is a particularly sensitive area nowadays. I think the blocks of human frozen material which are kept in hospitals and research centers, I think there is now a greater concern from the public about the samples which are retained because of the capacity of

those samples to divulge genetic information.

So we have tried to set up some new guidelines about the care, use and research on human tissue and we also have a new set of sections on human genetic research, which I think may be of some modest interest to your committee.

Overall, we tried to take a very significant step forward in the way in which I think research is looked at. I do not think it is something now within Australian which should be considered contained within hospitals and medical research centers. It is an activity which is carried out which involves and impacts humans and, as such, I think it is very important that very high standards are observed.

In the future, I noticed from the draft paper which you have circulated to me of your lightly chapter headings, that you are also, I think, considering very much the types of matters which we looked at over the last couple of years.

But I noticed with interest that you are looking to ask some questions about the overall system in the future. For example, you are asking questions about centralized or regional ethics review. Should we have every single research project carried out in an institution re-evaluated and reviewed again by another

IRB? Well, we again have tried to make some suggestion that the system of individual consideration of ethics review by an institution should give way to the possibility in some cases of multi-center research being able to be considered by one single institution.

And, finally, I noticed that you are thinking about accreditation. During our last review of the statement I think there were a number of comments from community organizations which said that essentially accreditation should be introduced. I will be very surprised if in the next peri-ennium the AHEC will not be required to really give very serious consideration to that because I think our system of licensing, I think, is one of those conditions which I think -- as part of the public accountability is probably quite necessary.

Look, I think I should stop there because I am sure that the Commissioners may have some particular questions and I am conscious that I have gone way over my time and I hope that is helpful.

PROFESSOR CHARO: That was very helpful. Thank you very much. And I would like to open it up to questions from members of the Commission.

Jim Childress first, and I am simply going to remind everybody that it may be necessary to speak very

close to the microphone to facilitate communication.

DR. CHILDRESS: Thanks very much for that most helpful presentation. You have indicated some changes that are being considered. I guess I would ask one question. Are there particular weaknesses in the system as you see it that you would like to identify and warn us about?

PROFESSOR CHALMERS: Oh, thank you. Well, I have tried to just very briefly hint at those and I made a start. I think one of the first criticisms which has made -- can you hear me clearly?

PROFESSOR CHARO: We can hear you clearly.

PROFESSOR CHALMERS: Good. I think one of the major criticisms which is made is the failure of the system to have adequate sanctions. If there was to be impropriety in research, what are the powers within the system to actually sanction noncompliance? That is a difficult question.

Formally, the only sanction which is available within the NHMRC structure is the withdrawal of funding. That has been threatened on a number of occasions. There have been full investigations and I assure you that major institutions take it very seriously, indeed, and respond very quickly.

But the question is what would happen if it

was a smaller organization that does not bother through its annual compliance report to actually let the AHEC know that there has, in fact, been some error or some noncompliance in the procedures.

I think at this stage that has not been seen within the system by the researchers or the institutions or the AHEC as a first order priority but I think it is something which we are very conscious that the public submissions, which we receive, often center on this. If something goes wrong, how do we know that there are going to be effective sanctions carried out?

Now we do know that in a hybrid system, like Australia, the individual research participant has the capacity to sue the institution and certainly there is references to some of the American writing on that point. We know that the NHMRC has the power to withdraw funding. Secondly, the NHMRC through its annual report could make critical comment to the Parliament.

Fourthly, we have -- because of our mixed -- and it is often called the "wash-minister system," we have a lower house in the Commonwealth, which is directly based on the Westminster House of Commons, but our Federal Senate was directly copied from your

American Senate with all the investigatory powers that institution possesses.

So there is also the possibility of investigations through the various standing committees of the Senate, and that has actually happened on a few occasions where the Senate Estimates Committee has rather rigorously questioned the AHEC about aspects of its work and aspects of the Institutional Ethics Committees.

But, overall, that is something which together, I believe, there is a reasonably effective sanctioning system and we would also say that the way in which research ethics operates it should not end loaded on sanctions. It really should be forcefully primarily based on a compliance, which is focusing on high research ethics by the researchers and by very rigorous consideration by the ethics committees.

I do not know if that is much of a help as an answer.

DR. CHILDRESS: Thank you.

PROFESSOR CHARO: Other Commissioner comments?

Alex?

PROFESSOR CAPRON: Don, this is Alex Capron.

PROFESSOR CHALMERS: Hello, Alex.

PROFESSOR CAPRON: I wanted just to get a little clearer on several of the points you make about the hybrid nature of your system. In your report you describe under the heading of accountability that the AECs are also required to report annually to the NHMRC.

PROFESSOR CHALMERS: Yes.

PROFESSOR CAPRON: And I gather that these reports contain information about the number of protocols that have been approved and can you tell us a little bit more about what is in that reporting system you have?

PROFESSOR CHALMERS: Well, I think it really leads on from the question which you have asked. That was always seen as one of the weaknesses of the AHEC that all we had was a very minimal annual reporting essentially about membership, number of protocols. It was facts and figures. Any difficulties with the operation of the privacy guidelines, specifically within Commonwealth legislation and so on, that has altered over the last two years.

We now have a far more detailed set of questions. I think there is now about 50 questions. Much more specific comments about the research. We also ask them now about the way in which the research

is being monitored. We also try to analyze the number of protocols which they are actually covering by multi-center research.

So we are trying to build up a far more comprehensive database about what the committees are actually doing as well as, of course, the secondary and legal requirement of having a proper report from them that they are actually compliant with membership procedures and so on.

I call it hybrid because there is no formal legal requirement on human research ethics committees to carry out that report. Rather the National Health and Medical Research Council Act through its provisions requIRBs the AHEC to look after and supervise, is the word which is used, the system.

So this reporting which was originally voluntary and self-regulatory has now come under the general umbrella of the statute and the second way in which it now operates, of course, is that the national statement in section principles number two has very detailed requirements much closer to your IRB regulations, might I say, about the kinds of procedures that have to be carried out by the committee.

And one of those principles is now within the national statement a requirement to report. Those

reports are then, in turn, amalgamated -- that is the 200 ethics committee reports -- are amalgamated into a section within the annual report which goes to the Parliament, and it is that report which has from time-to-time been the subject of examination and investigation by the Senate Standing Committee on Estimates.

If a Senator wants to find out what is happening within the Institutional Ethics Committees, the Human Research Ethics Committees as they are now called, that is the vehicle which is very effective that when the budget is being allocated they can ask all sorts of questions which are related to it.

So although we do not have a national research act, which formally sets up -- sorry, which specifically in its sections mentions the reporting and the types of reporting, rather what we have had is an umbrella act which establishes an institution which has prescribed in its national statement a requirement that you actually have to fill in these reports.

So it probably adds up to exactly the same thing but in a rather round about way and so I think it is better to describe it as a hybrid system because otherwise the intent to go around looking for the specific section in a specific act but this rather

tortuous and ill-defined way of finding out how the system operates.

PROFESSOR CAPRON: Well, I would say in some ways actually that your description of what you are calling a hybrid is very similar to our own, the National Research Act on this particular point is very brief. It is a few sentences vis-a-vis the Protection of Human Subjects and we have the Common Rule and all the other parts of the Federal Register from the different agencies that fill in.

But what strikes me as interesting is that while you make it sound like a very modest system, and in a way we are contrasting it, I think, with what you took to be a more regulatory system, we really do not have in our present requirements from the Federal Research Offices anything comparable to that annual reporting.

And I thought the other thing that was interesting was your analogy of that process in Australia and perhaps one could say also in the United States to the Fire Department as opposed to the Police Department where the Fire Department only responds when there is a problem that it becomes evident from a smoking situation, I guess, as opposed to a patrolman on the beat who is out looking for problems.

And in a certain way I am not sure where the analogy would fall but you made reference to an accreditation model which is certainly something that some of us have been pushing here. Would you say that falls somewhere outside the police and fire analogy or does it come --

PROFESSOR CHALMERS: Oh, no, I think accreditation is absolutely within the fire model and I should say that this is a personal view. I think it is very odd that we have not actually gone the full weight of all accreditation.

If I had to reflect again linking to the question before about weaknesses, I think we have tried to build in a number of ways in which the system ought to have public accountability. I do not think in public life we have any right to go around listening to professionals telling us that we ought to be trusted and so on.

I think in research we have to justify the research is in the public interest and I think when we set up systems of accountability we should be able to go openly to the public and say this is how you can actually navigate through it to see that the research is being conducted in your interest.

One of those which always strikes me as very

odd is that we have still institutions which can write to the AHEC and request that they set up a system of a Human Research Ethics Committee.

Over the last five years, and this is something which I have tried to say a little bit in the paper, the regulatory atmosphere has changed.

AHEC does not have the power to refuse registration. Now that is the word I have used. There is no reference to it but because you have got to send in a compliance report, we have, in fact, said, "Well, you have to register with us so that you can receive information, guidelines and so on."

So there has been, as it were, an assumption of authority by the AHEC, which, in fact, is not actually enjoyed, and I would have hoped that one day we could go further and actually go through a formal accreditation process, which would require presentation of the various terms and conditions, paperwork, systems of recording, the membership and so on.

We have various comments within the national statement about independence, about lack of conflict of interest, but how are we to actually prove that that is actually being seriously carried out?

We also have from time-to-time, and certainly over the last few years, a number of occasions where

small associations wishing to carry out what might be described as novel work, have written to us to say, "Why can't we just simply set up our own ethics committee?" You later find out that this is, in fact, not an institution at all. It is a group of professional doctors who want to try and carry out a procedure and fortunately we have always written back and say, "Well, no, the -- it is an institution which conducts the work and you should, in fact, now try and present your work to some other established ethics committee." But we do know that from time-to-time -- this is anecdotal about small clinical trials which have been conducted on a rather small scale.

So at the bottom level I think the good ethics committees in this country or in Australia are very fine indeed. They have been operating for many, many years. They are well-resourced. They are well advised. They have members who are not paid. They give up their time voluntarily. They read and work through it.

But as you work through the system, as I have tried to discretely state in the document, there are variations within the system.

By the way, Alex, just because an ethics committee is small -- for example, the National Red

Cross has a committee which only looks at a few protocols each year but because of the sensitivity of such thing as the quality of the blood and AIDS issues, it was decided that that specialist committee should really look and build up a professional knowledge in that area.

So it is not being small but it is the level of what I would describe as prove-able disinterestedness that I think I sometimes am concerned about and I think accreditation is -- I mean, I really do think as a public system it is -- inevitably it is going to happen, I think, in Australia.

PROFESSOR CHARO: Donald, Eric Cassell is going to ask you the next question but I would like, if I may, just to ask for one quick clarification on the accreditation discussion.

Specifically, you have talked so far about accreditation of the ethics review bodies as a successor to the current registration system. Has there ever been discussion in Australia about accreditation or licensing of individual investigators as a precondition to actually enrolling human subjects?

PROFESSOR CHALMERS: No, that has not come up as yet. I have tried to point out a little bit in the paper. We are a much smaller country with

concentrations of major research in three of the capital cities, that is mainly in Melbourne, then Sidney and Brisbane, in that order, although if I was in Australia I would never dare to say such a thing.

(Laughter.)

PROFESSOR CHALMERS: And because of that I think there really has always been institutional and research and knowledge of others, and I do not believe at this stage that we have really seriously talked about that.

There has been, for example -- let me give you a couple of examples. A few years ago we were being bullied. This -- I think I better be a little bit cautionary about my remarks. We were being -- no, we were being bullied by --

(Laughter.)

PROFESSOR CHALMERS: -- a couple of researchers that wanted to conduct some xenotransplantation procedures. As you know, in your country and in the interim xenotransplantation authority in the U.K., there are interim guidelines which are operating. We wished at the AHEC not to proceed to even interim guidelines until we were satisfied of the safety. There had been a whole series of really quite disturbing articles in Nature and

Science which really encouraged our committee to say we wanted the best possible scientific advice before going forward.

These particular researchers were, in fact, at one stage considering conducting the work themselves. It turned out, of course, that lawyers told them that they would not permit the institution to conduct the work unless it was according to guidelines.

We had not produced any so they were caught and that was an example where the researchers themselves -- we were being told informally by two or three other people in the field that they would not be considered as very experienced in those procedures.

So I think there are probably some cases in which I think the accreditation of researchers might be useful but I do not think that that has been really seriously considered as yet.

I think the second thing I would say is apart from researchers knowing each other, I think there have been a number of the professional associations who have been very helpful.

One of the things which I hope the national statement has done, apart from being comprehensive, it has also, as it were, become the focus where other organizations are now canceling their statements and

actually now referring to the national statement.

Let me give you an example. The Australia Psychological Society has decided not to proceed with their own guidelines as a review but simply to acknowledge and endorse the national statement which we have.

I think in setting standards I hope the national statement is becoming a benchmark for, as it were, bringing other organizations up to -- well, I think it is rather arrogant to say up to scratch but up to what we believe are prescribed high standards.

PROFESSOR CHARO: Thank you. Sorry.

PROFESSOR CHALMERS: So the answer is, no, we have not really had a serious discussion. There has only been a few examples of that.

PROFESSOR CHARO: Thank you.

Eric Cassell?

DR. CASSELL: Professor Chalmers, many people in our IRB system complain that they are so over loaded with bureaucratic details and paperwork on minor issues that they feel themselves short changing the more serious ethical review that come before them and does a similar complaint come from your ethics committees?

PROFESSOR CHALMERS: Well, I think in the paper I actually quoted your Office of Research for

saying that we are doing too much, too little -- with too little resources.

Yes, I believe that is exactly the complaint, I think, which has been heard internationally with ethics committees. By and large, they started off doing a few protocols. Then as institutions became more conscious of their legal and ethical responsibilities, I actually think it has been more legally pushed than ethically, more and more protocols are in place.

We have tried in our national statement to say that we would follow -- and we took the lead from the United States -- the system of expedited review. I think the ethics committees should not simply be given more resources and become a great bureaucratic tool.

Because rather if we believe that the majority of researchers are compliant and being responsible then I think what we would hope to do is through a number of strategies over the next years is try to improve and assist the ethics committees in their job. One, we are trying to produce a manual which will actually be a running commentary on the national statement, which should give hopefully sound advice about the way in which the statement should operate in practice.

Secondly, we are saying that the committees

should be looking at expedited review of particular low risk research which is being presented for approval primarily for the function of receiving the funding.

Thirdly, we are trying to say and we do say in various parts of the national statement that the committee should, in fact, try to -- and I believe you are doing it in your work -- try to focus on what we mean by risk, try to become smarter and more informative about what we think as a risk so the major amount of time should be spent on those particular projects.

Fourthly, we have tried to say that the committees should not be spending, as they often do, large amounts of their time worrying about the science. Institutions have really got to be more effective in giving sound scientific clearance to the project and then, hopefully, the ethics committee will not be spending quite so much time worrying about the science, although we did not accept in our national statement the principle that there is some neat divide between the science and the ethics. I think that is misconceived.

And, fifthly, we have tried to say that the discussions, which are frequently from many pieces of advice we receive through the public consultation,

devoted to editorializing and improving the grammar of consent forms really has again got to try to focus not on the wording of the documents but on the principles underlying it.

Realistically I think you will probably see that these are strategies, which if they are not fulfilled then if we have to revisit this in a few years, then I think that there will have to be further advice.

But one of the other -- sorry, the sixth thing. I have just forgotten. Multi-center research. We are fairly sure that there is a large amount of time spent by ethics committees reviewing again a project which has already been presented at another major institution.

By far the worst case scenario was a geriatric study at 96 institutions in Australia and New Zealand, which the researcher complained -- went through some 96 different processes and took two years to receive all the approvals.

Well, I mean, obviously an institution must be responsible for reviewing projects but if you have the clearance from a very well established, well-recognized and effective ethics committee, then that may be one which could be given ratification by expedited review.

I hope that helps. Does that answer your question?

PROFESSOR CHARO: I think that was very helpful. Thank you.

Diane Scott-Jones would be next. Thank you.

DR. SCOTT-JONES: I have a question about research on --

PROFESSOR CHALMERS: I am sorry. Could you just speak up slightly?

DR. SCOTT-JONES: Okay. I will --

PROFESSOR CHALMERS: Thank you. Thank you.

DR. SCOTT-JONES: I have a question about your statement on research on collectivities.

PROFESSOR CHALMERS: Yes.

DR. SCOTT-JONES: You tell us that your national statement requIRBs that there be a consent by the collectivities that are recognized legally in your country and I was wondering if you could say what the experience has been with this particular aspect of your national statement and then also could you say a little bit about -- a little bit more about the research with aboriginal people that is also mentioned in this same part of your document?

PROFESSOR CHALMERS: Good. Thank you.

You have actually raised what I think is one

of the failures of the document at this stage.

Very briefly, we had an interim series of guidelines passed in 1992, which are the Aboriginal Torre Strait Islanders Guidelines for Research. During the public consultation there was a view expressed that these guidelines required updating.

We looked and saw in the Canadian statement what we thought was a very good contribution to the concept of collectivity, which would in a multi-cultural country such as Autralia, with very diverse religious groups, particularly very many different nationalities who have come to settle in Australia, with very different cultural observances, that we are very conscious that when conducting research in -- I mean, questions of a sexual nature from one group may cause no concern but in another group could be deeply offensive and insulting.

But the idea of the collectivity that you would not simply be collecting individual consent. Consent, which also might be tainted with the fact that people are just politely saying yes but, in fact, they want to say no. All sorts of difficulties. We thought the collectivity was hopefully something which could be comprehensively applied.

Unfortunately, I have to confess that -- I can

provide a further bit of particulars if you require it -- when we came to the second stage consultation, and that is when we have actually produced the draft guidelines and circulated those, then a large number of the aboriginal organizations -- because although there is some peak (sic) bodies, each of the states may also have a body and then there are different land councils and so on. So there is no single point of entry to the aboriginal Torres Strait Islands advice and we really unfortunately received the full spread of advice about collectivity.

Some groups saying that this was a considerable advance in the way in which the Aboriginal Torres Strait Islander peoples were to be considered, not in isolation but as part of the community.

In the middle I think there were some which said, "Well, what was really wrong with the old guidelines. They seemed to have worked pretty well. There has never been any difficulties even although they were interim and never formally passed by the peak aboriginal bodies. They have operated --" To others, who I think found it absolutely unacceptable and one or two groups particularly were -- well, very critical, indeed, of that.

And because of that we were really left with

no option but to withdraw the -- sorry, we kept the collectivity generally but we had to reinsert Section 9, which kept in force the interim guidelines.

So I would actually say that we had -- I would not venture to give any advice to you about that. I would say rather that it is a cautionary tale about being even more assiduous in consultation.

I have often found that there seems to be one invariable rule about public consultation when you are asked the question how much public consultation should you do. The answer is always a bit more than you actually did and I am afraid we did not -- well, personally it was one of my disappointments during the process. But I am pleased to say that the discussions are going on and during the next perineum there will be revised guidelines but there will be specifically, I think, now for the Aboriginal Torre Strait Islanders communities.

PROFESSOR CHARO: We have got a little over ten minutes left for discussion if we kind of keep according to our revised schedule here. I have Alex and myself on the list of people who have questions. Are there other people who at this time have questions, let me ask first? All right.

Let me turn to Alex for the next question

then.

PROFESSOR CAPRON: Don, what you provided us was extremely comprehensive. In the printout of the electronic document that I received from NBAC, it runs well over 100 pages. And I would like, therefore, just to highlight a couple of points for the record and see if you have anything to underline on them.

And I do so because I was struck by the ways in which your experience seems so close to our own and I am sure this will give you insights then on what we should be doing.

On what is page 82 on the way it printed out for me, but I do not have any reason to think it will be 82 for anybody else, but you state the following in talking about the issue of voluntary compliance:

"On the other hand, private companies are essentially complying voluntarily." You are referring here to complying with the national statement on ethical conduct. "If they wish to access public funds they are required to comply. In addition, many private companies comply because they are conducting the research in public institutions. Finally, many private companies comply because approval by a registered AHEC is considered a prudent step in reducing risks."

Had you been here with us in the prior hour,

we -- I asked this question of the two representatives of private companies or private trade associations and got essentially that answer from them as to why they and other major companies, they believe, would comply.

You go on to note something else, which I think is important. You say, "For this and other reasons --" this is on page 83 again if it is your page 83 or not -- "For this and other reasons it was more appropriate to consider a single research code. Similarly a researcher has a number of common obligations and ethical duties to the research participant, which are common to research generally."

And this notion of universality, regardless of the sponsorship, is something which I believe is emerging in our own country.

And yet you note later on in your comments that "it is not clear whether the voluntary compliance will continue" and this is really the point that I wanted to ask you to elaborate on because you do not go into it.

Are there particular things that are forming a disincentive or driving a wedge between the national statement and the actions of private research sponsors that are not covered by public rules?

PROFESSOR CHALMERS: Well, I was trying to

stay very conscious of the time and what I am referring to there -- no, I am hoping that the national statement over the next three to five years actually becomes the benchmark that people move into, that it becomes, as it were, the beacon that people see that the moves which have taken place over recent years continue.

You will remember some of the early work which you did on the question is a human research ethics committee legally liable. Nobody has ever thought about it.

PROFESSOR CAPRON: Right.

PROFESSOR CHALMERS: The legal environment of research ethics has changed fundamentally. People realize they are involved in a process which is not amateurish. It is not entirely voluntary. It has legal consequences. So that, I think, is something which the private sector understands very clearly, indeed, which is if we are going to get ourselves sued, risk management.

What I was referring to rather was not that the national statement is not being complied with. I believe that if you want to do something which is ethically questionable in Australia, you just simply pack your bags and you go somewhere else.

For example, we know that the research which

has been conducted on embryonic stem cells, there are a couple of very competent research teams in Australia. They are doing that work in Singapore. It is just a short flight away. Because they could not because of research ethics clearance or legislation do that work in either South Australia or Victoria.

This is the thing which I believe is absolutely critical, I think, in the future that we do not create research havens. I think the comprehensive national statements should be consistent with comprehensive international statements because it is just very easy just to pack your bags and go somewhere else.

I believe, for example, some of the ART work, which was not being allowed in Melbourne, I think was originally being allowed to be done by the same company. I think it was either in -- I think it was in Los Angeles because of different regulations. That is what I was referring to.

No, I am hoping the national statement will, in fact, be advancing the standard setting.

PROFESSOR CAPRON: Well, thank you very much. I know that we have all benefitted since we are sitting here on Monday afternoon getting advice from someone on Tuesday.

(Laughter.)

PROFESSOR CAPRON: I also have to thank you for using the word "autochthonous" in a sentence.

(Laughter.)

PROFESSOR CHALMERS: Oh, sorry. It is rather early here. It must have been the tea.

(Laughter.)

PROFESSOR CHARO: Donald, it is Alta Charo again. In some ways following on from your comments just now about the research going on in Singapore, I wanted to ask you about two details in the Australian system. The first has to do with international or transnational research.

You mentioned in your paper that currently the ideas that researchers would follow domestic rules as well as the local rules in the host country should they be doing research abroad.

As you probably know, we are working on a report that has to do with U.S. researchers doing collaborative research aborad, and we have identified a number of situations where local rules or local customs in a host country might actually conflict with the norms of research that are operating domestically. It can have to do with individualized consent versus consent that is contingent upon or given by others,

husbands, village leaders, et cetera.

It can have to do with the notion of what constitutes a vulnerable population and the special rules that apply. It can have to do with notions of competence. Certainly there are lots of procedural variations on how one assures and documents these things.

To what extent has AHEC gone into some detail about how it will implement its goal of being sensitive to both Australian and host country norms?

PROFESSOR CHALMERS: Well, thank you. That is actually one of the sentences which was in its earlier draft much longer. It was one of those sentences, the principle of compliance both in the host as well as the funding country, where we were accused by certain researchers as being rather naive. In particular, you will remember -- and I have included in the paper the discussion of the AZT trials in Africa.

PROFESSOR CHARO: Yes.

PROFESSOR CHALMERS: Where there was the lower dosage being used to see whether there could be an avoidance of the HIV transmission to the fetus. Where some researchers were claiming that that scientific proposition had not been tested and simply because you had best practice of a proven treatment regimen in

France and the states did not preclude trying to accommodate a dosage that would have been affordable and effective in Africa. Well, I am not convinced about that but nevertheless I have covered that.

What we believe we should be doing, therefore, was to cut that down and at least put that compliance statement of recognizing that Australians do, do work in Indonesia, in Malaysia, in the Solomon Islands. They are not doing much in Fiji at the moment and New Guinea particularly. That being the case, it is there.

Secondly, we also believe that the compliance reports will now be amended to include requirements about the work -- you know, reporting of the work which has been done overseas and any difficulties which are encountered to start building up the knowledge base about those because we were quite familiar with the fact that your country, the NIH, as you know, funds something like nearly $20 billion worth of research and quite a number of projects are funded by your country in Australia. And those researchers, of course, have got to be compliant with your FDA rules.

So there seems to be nothing wrong with trying to move towards a high gold standard which should apply.

Unfortunately, Alta, we have not got the

capacity to answer what I think is an extraordinary difficult question which you are asking, which is once you set that gold standard and we can now all sit back in a bath of self-congratulation that we have actually done what we should do, which is bring up standards.

We have not answered what I think is the extraordinarily difficult question which you are asking, which of course some of the researchers in Australia accused us of doing, which was failing to recognize the fact that in some countries even a lower level of drug trials effectively at least is better than nothing.

I think that is -- as I have included in my paper under Section 6 -- I feel that is one of the great questions, which I think, you know, is going to be addressed over the next few years and I must say that I think NBAC has given great leadership through those summits and I think it is going to be back on the agenda later on this year.

It is a big -- a very, very important issue internationally and I think it is going to become more important.

PROFESSOR CHARO: Thank you.

Donald, my last question -- and then I am going to survey the Commissioners one last time if

anybody had any additional questions before we sign off -- had to do with the definition of research, which I --

PROFESSOR CHALMERS: Yes.

PROFESSOR CHARO: -- was looking for in -- my printout came to 106 glorious pages. We have been struggling with that in this report and struggling with something that captures only those people we would like to be protected by some special set of rules and not all others, especially as you look beyond the biomedical context and especially as you look beyond the federally funded context.

What is the definition you are currently using there to figure out what the scope of your jurisdiction is and that people out in the field are using to figure out whether or not they need to even go to one of your review bodies?

PROFESSOR CHALMERS: Well, let me say that we -- I go around the other way. We have actually tried to put a definition of research, which is wide and comprehensive in covering all research on humans, quite deliberately so, because if we can reflect on what I said at the beginning, the growth of research ethics in this country moved from experimentation to medical research generally, to health research, to research

which involved privacy and social science, and so on.

And because of that most of the institutions, particularly the universities, have tended to put research, which is not in the lab but when you are out there even administering surveys, they have usually had some kind of a system that we should be asking is this something which is properly respecting the privacy of individuals.

And I hope you may find a modest contribution in our report to try and separate identified from potentially identifiable from de-identified because I think internationally -- I think we are in a bit of mess the way we handle data and the consequences thereof.

And in that respect we have tried to reflect that I think there is a much more responsible review process going on.

Now that may, of course, raise the worries of the questioner earlier but does that mean you are heaping even more work on? No, you may, in fact, delegate the review to a department or somebody else but research should not be being conducted that is not complying with the national statement.

So we have not really gone by defining and then trying to fit research back in. Rather the

statement reflects what has been a growth of a fairly wide view of review.

PROFESSOR CHARO: Thank you very much.

Let me ask now if there are any other questions from members of the Commission?

Okay. First, Donald Chalmers, thank you very, very much for taking time out from your vacation to speak with us. It was very helpful and quite enjoyable.

PROFESSOR CHALMERS: Could I, in closing, thank you very much for the opportunity to speak with you and I would -- I am conscience that this is, in fact, being recorded. I would like to place something on the record, if I may, as my little sort of personal comment.

I have at one stage in the paper highlighted what I hope is a need in your country to have some national body. I think, as I have said from my personal knowledge, that the NBAC has been providing international leadership by the holding of summits and placing important issues on to the international agenda, particularly clinical trials.

In Australia, there has been a very fine comment by one of our distinguished lawyers and governor generals that said that the researchers should

be as active in their ethical imagination as their scientific imagination.

I believe that if America is giving great scientific leadership, I think it is essential that it equally undertake that responsibility for setting high ethical standards. I think you have a very distinguished history right from the Belmont Report through the present Commission to the work which you are doing in NBAC.

I think your work has been widely acknowledged and widely used in the Australian context. I do encourage you to, I think, bring forth that wisdom through some international -- sorry, some national body.

Thank you.

PROFESSOR CHARO: Well, thank you. Thank you very much for that, Professor Chalmers. It is flattering and since we are talking about things on the record I will note that we did not, in fact, pay you to say that for us.

(Laughter.)

PROFESSOR CAPRON: But our stenographer is now taking it down in stone and engraving it for us.

(Laughter.)

PROFESSOR CHARO: At this point I think we are

going to bid farewell to Professor Chalmers and I am going to turn the microphone over to Eric for any last housekeeping details about tonight's departure and tomorrow morning's beginnings.

DR. MESLIN: I know it has been a long and very productive day. Thank you to all those who have stayed.

Donald, thank you very much. Cheers.

PROFESSOR CHALMERS: All the best.

DR. MESLIN: He said, "All the best." That is kind of a Commonwealth thing that we say to each other.

There are a couple of things that have not been attended to, just so that you are aware. Bernie Lo handed out a document that he and Ruth and Alice have been working on. That will be picked up tomorrow, that is to say discussed tomorrow. We are going to make time during tomorrow afternoon's discussion. I know some Commissioners may be leaving early but just to let you know our plan is to continue the discussion of the oversight project tomorrow morning.

We are having a working lunch. That is why we sent around a note to staff and Commissioners. I am letting the public know that a working lunch means that the Commissioners are going to be eating while they are speaking and the Commission meeting is still going on.

That is when Chapter 3 is going to be discussed and then we will move into Chapter 4 and 5 tomorrow afternoon before people bid adieu.

The only thing I would encourage you to do if you have any time this evening is to read over Dr. Shapiro's memo that he faxed earlier today. Suffice it to say, he spent some time over the weekend working on that memo knowing that he would not be here and it would be, I think, inappropriate to not take up some of the points.

So I just simply encourage you to take some time either tonight or tomorrow morning because we will return to it.

Other than that, I think some dinner plans have been made. Staff can give you some of those -- some of that information.

PROFESSOR CHARO: All right. We are adjourned until tomorrow morning at 8:00 a.m. Thank you very much.

(Whereupon, at 6:02 p.m., the proceedings were adjourned.)

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