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I N D E X

Opening Remarks
R. Alta Charo, J.D. 1

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS RESEARCH

Panel IV: Independent IRBs

Erica Heath, President, Independent Review Consulting, San Anselmo, California 5

Panel V: Purpose of Regulation

Harold Y. Vanderpool, Ph.D., Professor in the History and Philosophy of Medicine, Institute for the Medical Humanities, University of Texas Medical Branch Galveston, Texas 53

Jonathan D. Moreno, Ph.D., Kornfield Professor and Director, Center for Biomedical Ethics, University of Virginia 72

Donald Magnus, Ph.D., Assistant Professor and Director of Graduate Studies, Center for Bioethics, University of Pennsylvania 89

Recommendations - Purpose and Structure 164

P R O C E E D I N G S

OPENING REMARKS

PROFESSOR CHARO: We are going to begin with a few words from Eric Meslin on some housekeeping matters and after that we will proceed albeit a little bit late, and I apologize to the first presentation of the morning.

So, first, good morning. I am Alta Charo. I will be chairing this morning. To my right is Professor Alex Capron, who will be chairing this afternoon.

I would like to begin the meeting with Dr. Meslin's Executive Director's comments.

DR. MESLIN: Just very quickly as a reminder to those who were here yesterday and to the people who have arrived for today's session, we are going to be splitting the day up in reverse order from what was discussed yesterday, beginning with a discussion of our oversight report, and then moving on in the afternoon to a discussion of the international report.

We will be having a working lunch, which is to say that the Commission will be functioning during the lunch hour and they will be discussing Chapter 3 of the International Report during the lunch hour.

Immediately following the lunch hour, just as

you are keeping note on the agenda, we will have a very, very short discussion of the revised recommendation that Dr. Macklin and Dr. Lo circulated late yesterday afternoon to you. It is a one page sheet of paper that says "alternatives." That will be a very short discussion.

If you are following along in the agenda, what we propose to do at 1:30 is stick with the schedule and discuss Chapter 4. There will be a break at 3:00.

It is Ruth Macklin's wish and my pleasure that Commissioners should be informed that the discussion of Chapter 4 will principally focus on the memo that Harold Shapiro faxed to you yesterday for discussion and comment. We thought that would be as useful an exercise as discussing the chapter itself since these are issues that in Harold's absence he wanted to have discussed.

And then from 3:15 until the end, we will be discussing Chapter 5. So if you are annotating your agenda, we have removed the 4:45 p.m. item that says, "Chapters 2, 3, 4 and 5, Revisited." We will not be revisiting those chapters. We will spend 1:30 to 3:00 talking about Chapter 4 and 3:00 until the end talking about Chapter 5.

Thanks.

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS RESEARCH

PROFESSOR CHARO: Thank you, Eric.

Okay. We are going to begin this morning with something that I think is quite welcome by way of information.

Ms. Erica Heath is the President of Independent Review Consulting here in California and has prepared a paper for us on the history and the future of independent Institutional Review Boards, something about which, I think, we all would like to learn more.

Thank you very much, Ms. Heath, and my apologies again for keeping you waiting.

PANEL IV: INDEPENDENT IRBs

ERICA HEATH, PRESIDENT

INDEPENDENT REVIEW CONSULTING

SAN ANSELMO, CALIFORNIA

MS. HEATH: Well, thank you very much. It is with some pride that I talk about Independent Institutional Review Boards. I have been working with IRBs for approximately 30 years, speaking at PRIM&R and ARENA, and writing about IRBs.

The development of Independent IRBs has been of interest because they have developed within a large

framework.

(Slide.)

What I want to do this morning is talk about four things: The place and the position of independent IRBs within the world of IRBs; the evolutionary changes that brought about the independence; some information on the structure and function; and then a little bit about the history.

(Slide.)

To take a very simplified view first, there are basically two systems. One is the assurance system and that is where the NIH through OPRR, the Office for Protection from Research Risks, reaching an agreement or an assurance with the institution. And for "NIH" you could substitute any federal funding agency that signed on to the Common Rule.

The FDA is a regulatory agency and regulates through a compliance mechanism through the sponsor.

Where are the investigators in all of this?

The investigators can be found almost anywhere.

(Slide.)

The investigators there in pink can be found in a lot of places. They can be found within institutions. That is very traditional. In hospitals

of any size, with or without assurances. We can also find investigators located within foundations, clinics, in their private practices, within sponsored companies.

I think you heard yesterday about General Motors.

The area of private practices is the area that I think is growing quite rapidly and is projected to grow even more rapidly.

(Slide.)

How do all of these investigators then relate to the FDA and the NIH? Well, obviously the one in the institution relates through the institutional channels to -- through the assurance and the guidance that they receive is through the institutional means.

All of the investigators that are working on studies of regulated products are in a compliance network with the FDA. FDA can come out and audit any of those investigators pretty much at any time.

(Slide.)

So in this big picture where are the IRBs? The red IRBs there are again located all over. There is one in every institution that has an assurance. FDA actually has one in-house. Some sponsors and companies have them. And then there is the independent IRB to the right. As the research world expanded, the

number of independent IRBs increased. How do those IRBs relate to the investigators?

(Slide.)

The IRB in the institute relates directly with the investigator in that institution. The independent IRB relates directly with the site and the investigator being reviewed.

I have dotted lines there to the investigators in the boxes. Those boxes are institutional organizations. We can review investigators from those places but only with the permission of the administration of that institution.

(Slide.)

How does the FDA relate to all of these IRBs? Again it is a direct compliance relationship. The FDA can and does go out and audit each of those IRBs. The independent IRBs get audited using the same general framework and investigation policies that are used for all IRBs.

(Slide.)

And finally how do each of these IRBs relate to the NIH? Again the ones in the institutions relate directly through a Multiple Project Assurance.

In smaller institutions that do not do as much research, there is a Single Project Assurance that can

be negotiated for each study. There are some very small institutions that are getting grants such as Small Business Innovation Research Grants, who have no IRB, and really have no interest in setting one up. They may be very small. They may not have the knowledge or experience to set one up and they are contracting with independent IRBs. The institution still holds the assurance and is responsible for the protection of subjects but they work directly with a more knowledgeable IRB.

That is pretty much where we exist in the larger world of IRBs. How did we come about?

(Slide.)

I think there were four major events or changes that were important in the evolution of independent IRBs and the first were changes in health care delivery.

When DRGs came in, the Diagnostic Related Coding Groups, and reimbursement for patient days went down, there were shorter hospital stays, fewer hospital stays, hospital census went down. Where did all those patients go? They were treated in an ambulatory setting.

One cannot keep on doing research on institutionalized patients, patients in hospitals, if

the care is being delivered outside that context. So more and more research was being done in new ambulatory centers.

Those centers became quite skilled. There are new ambulatories or new ambulatory centers, surgicenters, diagnostic centers. You could find MRIs in freestanding units. And the people who were staffing those units were graduates of the major medical colleges. Quite often they were people who had done research and they were quite skilled. They were interested in doing research.

There were expansions in multi-center trials. They happened about the same time. There were expanded expectations but also abilities to do large scale research. There were new technologies for handling the data. There were new communication modes. There was easier travel for monitoring and there was an expectation that more and more subjects, more populations would be included in trials.

An interesting one is the patient demand for access to clinical research and we can stress two words there. "Demand and access."

Patients were demanding that they be -- that it was their right to participate in research. And I think the best example is in the AIDS area where

instead of being afraid of being recruited, patients were demanding access.

The second part of that, the access, is that they were demanding access not in cities remote to them but in their own communities. They wanted the care given where they were in communities that were not necessarily blessed with having a local institutional IRB.

The fourth event was a regulatory change in 1981 with the FDA. I have mentioned that in the paper but in 1981 the FDA expanded the regulations, expanding the IRB coverage to all research, all human subjects in studies of regulated products. Previously they had only required IRB review if there was an IRB in the institution where the research was being done.

They recognized that when they expanded that coverage there might not be IRBs available and they suggested that new alternatives might arise.

(Slide.)

So what is an independent IRB? An independent IRB is an IRB which reviews research for the purpose of assuring adequate protection of human subjects, that is all standard, for entities that are generally not part of the same organizational structure as that IRB, and that is a critical part.

The organizational structure of the independent IRB is a different organizational structure from the site being reviewed; that is the site may be a private practice, remote from the IRB. It can be even a neighboring but the organizational structure is a different business unit. I think recognizing both the similarities and that difference is important.

(Slide.)

There is no typical IRB but thinking about what could be said to be typical, one of the baseline concepts is that an independent IRB is, in fact, part of a corporate institution. That institution, usually incorporated in one of the states, has at least two units. One is the administrative side and one is the IRB review side. The administrative side takes care of receipt of protocols, respondents, human resources, all the business aspects of running a business.

The IRB is more isolated. They are expected to convene, to review submissions, to make decisions, but are not part of the business side. That is done purposefully to address the potential for conflict of interest or interference, ideas about whether the business could affect the IRB decisions. I think in most cases, again typical, they are kept quite separate.

(Slide.)

Addressing for a moment the strengths and the weaknesses of independent IRBs, I think I hit the first weakness just now and that is it is a fee for service. Just like lawyers get paid for their services and doctors, IRBs are professional. The members are professional. They get paid for what they do and again we keep that separate.

We do remote review and I think all of the independent IRBs are set up to address the issues of remoteness.

And I know an issue in many people's minds is IRB shopping. Personally I do not see very much of it. We ask, I think, every independent IRB and, hopefully now, every IRB is asking the history of a protocol; that is whether it has ever been submitted to another IRB and what that determination was. I know that there is an internet discussion group where that comes up occasionally.

Our strengths we see as being a much longer list. First of all, we fulfill a need. There would be a void left in the research area that would be unfilled if there were no independent IRBs.

We offer efficient and prompt service. That is what we do. Just -- we are accused sometimes of

being too speedy but that is the role of an independent IRB. That is all they do. They concentrate on offering quality service but in a timely manner.

Independent IRBs can actually be more objective. The members are not part of the institutional structure that is receiving the grant. They are not tied into institutional politics and they can be more objective about what they are seeing.

They can offer uniform standards for multi-site studies. That is when you have a multi-site study done in a number of institutions, there are a number of consent forms. There are a number of changes by a number of IRBs. There are a number of adverse events going into any number of IRBs, all of which get a sampling.

With an independent IRB, it is one site that sees one consent form and sees what changes each site wants to make so it is a more uniform service.

We also offer review of research that is otherwise unregulated. This could fall into areas of behavioral research that is not now regulated but many investigators, particularly those trained in academic institutions, know that IRB review is a part of doing good research and they are happy to find a quality independent to submit their research to.

Finally, more recently, independent IRBs have offered support and "breathing room" to institutional IRBs that have found themselves in some sort of difficulty.

(Slide.)

What kinds of studies do we look at? I think basically we look at the same broad range of studies that any academic IRB sees. The major amount of our work is usually clinical studies of FDA regulated products. Those are all phases of products and the usual kinds of FDA regulated studies.

We occasionally see compassionate use or humanitarian device studies. Not all emergencies happen in the hospitals. Not all requests to use single use compassionate articles are in hospitals. And we occasionally see such requests.

We are seeing an increasing number of social and behavioral studies, as I mentioned, a huge rise in studies of biological specimens, some international studies, some records review studies, and I said other. I would imagine that anything that an academic IRB has seen some independent IRB has probably seen.

(Slide.)

The future, I think, is kind of wide open. There will be an expanding need for a variety of IRBs.

Not just independent IRBs but IRBs in a wide variety of research settings.

They are going to serve a rapidly expanding number of sites. Every prediction I have heard is that clinical research is going to expand. I heard one prediction that within five years we are going to have double the number of investigators than there are now. That calls for a rapid increase in the number -- in the infrastructure, the entire infrastructure for research.

We are going to need to serve new areas. Genetics is an obvious one. There is internet research that is going to be done. There are new populations to be served, not quite new, but there is more research on the elderly and on children and other special populations.

And then there is more technology available to perform that review. There is more and more ability for a reasonable cost to video conference, to evaluate sites, to look a web information, to share information, and more abilities to assess the information that we receive.

I think that is a very quick overview of independent IRBs and of where we are in the world, what we do, how we exist, and I welcome your questions.

PROFESSOR CHARO: Thank you very much. That was very informative.

We have approximately a half an hour for questions and discussion.

Diane, and then Steve.

DR. SCOTT-JONES: Hi. I have several questions to just get more information about what you have already laid out for us.

First, how much turnover is there typically in the IRB membership?

MS. HEATH: Typically there is a core group that is on for quite a while. That core group -- two years, ten years. There are, I think, on each IRB several members that have been on ten, twelve years. Those members are very well educated in IRB responsibilities, study design.

And then there is another group that is on for two years, three years. Often they offer specialty information when something new is developing.

DR. SCOTT-JONES: Can I keep --

PROFESSOR CHARO: Yes, please.

DR. DUMAS: Rhetaugh has her hand up.

PROFESSOR CHARO: Okay, Rhetaugh. I will put you on the list.

DR. DUMAS: Thank you.

DR. SCOTT-JONES: What is the outcome of the external audits of independent IRBs? You have mentioned on page 17 that there have been external audits --

MS. HEATH: Yes.

DR. SCOTT-JONES: -- of the independent IRBs. What has been the outcome of that?

MS. HEATH: Well, I think the outcome is very much similar to the outcome of all the audits. Many of the audits have found no identifiable problems. I do not think FDA will ever say you meet every criteria. They will say, "We could find no problems." And we have, I think, seen as many of those letters as any set of IRBs.

There have been untitled letters. Are you aware of the various levels of letters? There are untitled letters and then there are warning letters.

"Untitled letters" need a response but they are short of warning letters. And there have been warning -- excuse me. There have been "untitled letters" to independent IRBs as well.

I have heard it said that there were independent IRBs that were out of business after but I have heard that said of some academic or institutional IRBs as well and I cannot substantiate it.

So I think it is pretty much the same as the wider set of IRBs.

DR. SCOTT-JONES: And then how do you ensure some sort of community representation on the IRB?

PROFESSOR CHARO: Excuse me. Diane, if you can speak even more closely to the mike, it will help those on the phone.

DR. SCOTT-JONES: I am sorry.

PROFESSOR CHARO: Ms. Heath, we have two Commissioners on the phone, Trish Backlar and Rhetaugh Dumas.

DR. SCOTT-JONES: I am sorry.

MS. HEATH: Okay.

DR. MESLIN: Do it again.

DR. SCOTT-JONES: I will repeat the question. How do you ensure community participation in the independent IRB?

MS. HEATH: I think each of us look at community input slightly differently. First of all, we have a wide variety of members on the board meeting at our site. So there is a wide diversity of opinion just within the board.

We have probably a longer and more complete application form than most IRBs and a lot of questions on that form are about the community, the type of

community, demographics, literacy levels, languages spoken. That sort of thing so that we get a feel for the kind of population from whom the subjects -- from which the subjects are being recruited.

If we have a concern, if in reviewing the study we identify a concern, for instance, in recruitment or advertising or whatever, then we hone in on that area. At that point we have pretty good networks. I have been known to pick up the phone and call an IRB colleague in another city and ask about the investigator or about the community, about advertising media in that area.

I think there are a lot of various means and, of course, the web now is giving us a lot more options.

Does that --

PROFESSOR CHARO: Do you have any further, Diane?

DR. SCOTT-JONES: I have one last question.

You mentioned that you also review proposals from the social and behavioral sciences.

MS. HEATH: Correct.

DR. SCOTT-JONES: Could you say a little bit about how the review of that type of research is different from the other kinds of studies that you review?

MS. HEATH: Yes. Obviously it is different. Quite often it is qualitative instead of quantitative research. In many IRBs along the way they have found that they need a wider diversity of membership to evaluate the different designs that are presented by social and behavioral research.

We have had to add members again to account for the differences -- for the new fields being reviewed. So I think that is the number one change is that the membership was diversified again -- yet again to better understand the kinds of research we were seeing.

DR. SCOTT-JONES: Thank you.

PROFESSOR CHARO: Ms. Heath, you are very popular. I want to go through the list of people who would like to ask questions to make sure that I have been told about everybody's hand.

I have Steve, Rachel, Rhetaugh, Bernie, David, Arturo, Eric Cassell. Arturo is passing at this point. Something must have been -- and I put myself on the list, and Bill Oldaker as well, and Alex. All right. You are going to get the --

MS. HEATH: Are we serving dinner?

PROFESSOR CHARO: That is right.

(Laughter.)

PROFESSOR CHARO: Very good. Steve?

MR. HOLTZMAN: Madam Chair, is it Madam Chair? I have two questions. Is that okay? The first is a clarification question.

PROFESSOR CHARO: Please.

MR. HOLTZMAN: Okay. I am trying to understand a little bit more about the organization of your business because you have put up a slide which said over here we have what in my business we call the useless overhead. Us types. And then you have the people who do the work.

So that -- but am I to understand that you have a single IRB or that effectively that you constitute IRBs depending on what proposal you are going to be reviewing so that you can have the appropriate expertise? Number one.

And, number two: Are the members of the IRBs or IRB, depending on the answer to that first question, are they employees of your company or are they like a bull pen of outside experts who you bring in on a consulting basis?

MS. HEATH: The IRB is a standing committee as it, I think, is in most institutions and it is the same membership that meets regularly so it is one IRB.

MR. HOLTZMAN: Okay.

MS. HEATH: We do have a list of consultants to the IRB that we can count on for any particular area where we have questions but it is a standing board.

The members of the board are independent contractors. They have professional lives quite aside from their IRB membership.

MR. HOLTZMAN: Okay.

MS. HEATH: Many of them are fully employed. Otherwise, some are retired. None of them are dependent upon what they receive from the IRB as their means of living.

MR. HOLTZMAN: Okay. So my question is what do you say to the portrayal, which I have certainly heard of the last couple of years, that this is a blood for money kind of business, that these IRBs really should not exist, that it should only be in the pristine institutions that there should be these IRBs, and this is really about, you know, buying approval of protocols that, you know, if it were not for the money no one would be able to buy?

MS. HEATH: Well, we have put away our rubber stamp of approval. We try never to use it. No, I have heard that myself. The independent IRBs are professional. We exist based on our continuing reputation. If an independent IRB's opinion could be

bartered, I think it would lose any professional reputation it had very quickly. And certainly I would lose my integrity. It is a professional standing I have worked very hard for many years to keep.

PROFESSOR CHARO: Okay.

MR. HOLTZMAN: Thank you.

PROFESSOR CHARO: Rachel?

DR. LEVINSON: Thank you. In your remarks, you have mentioned that the independent IRBs are set up to deal with remoteness and Diane asked a question about community participation or representation that seemed to go to that, and then Steve asked about whether or not you had a pool of people with which you could draw upon that perhaps could be called upon to represent the locale of the research that you are reviewing.

But it does not look as if that is one of the ways you deal with remoteness, because you said you have a core standing body. Consultants that would come in, I would assume, are nonvoting.

So could you expand, I guess, on the point that you made in your talk about how you deal with remoteness as far as voting membership?

MS. HEATH: Yes. Well, first of all, remoteness, I think, was anticipated by the FDA and

there is an information sheet on remote reviews in the FDA information sheets. I noted it and attached it to my report. It recognized that there are times where review from any institution might be remote and, in fact, the first times I encountered remote review was when I was the IRB administrator at the University of California in San Francisco, and we were reviewing studies in Malaysia and Zaire so it was not unheard of.

As I said, on the application form we look for the kinds of communities. We look at the kinds of study and the kinds of issues that might be raised.

If there are any kinds of issues that are brought forward, any eyebrows raised, then we are -- it is very easy to pick up the phone to call a local consultant in that area. Those consultants are not voting members. If they were voting members on any IRB, we would have to be changing the roster with every meeting or every vote. They give information and input to the standing board, which that board can then use in making their decision.

DR. LEVINSON: I have one quick question. Thank you. Can you tell us how much research you look at as multi-site versus single site, the proportions?

MS. HEATH: The multi-site studies are quite big so if you have three or four multi-site studies

they can equal 20-25 small studies. I would -- it is different for every IRB. Our's are probably up 40 percent, I think.

DR. LEVINSON: Forty percent.

MS. HEATH: Multi-site.

PROFESSOR CHARO: We will not hold you to that number strictly.

MS. HEATH: Yes, please.

PROFESSOR CHARO: Rhetaugh Dumas on the telephone.

DR. DUMAS: Oh, okay. I cannot hear you too well.

PROFESSOR CHARO: My apologies.

DR. DUMAS: I wonder if the speaker would say something about what they perceive to be the potential for factors such as bias and conflict of interest and how they manage that.

MS. HEATH: The question as I heard it was about conflict of interest and bias.

PROFESSOR CHARO: How you manage it? Yes.

MS. HEATH: Okay. How we manage it? Well, first of all, by recognizing it. I think the recognition of conflict is the first step in recognizing any interests.

DR. DUMAS: What controls do you have that

would help you identify it?

MS. HEATH: Among members?

DR. DUMAS: Among the members of the IRB.

MS. HEATH: Well, first of all, we ask -- just as, I think, all IRBs do -- that any holdings in any company that we review be revealed. I think in academic institutions there is a disclosure form. We ask for annual disclosure of any holdings that somebody might have that could bias them in terms of review of any sponsored studies and then not only annually but if it comes up with any particular company.

We have sometimes less conflict of interest than an institutional board because the members are not involved with the institutional politics and biases.

And then I think members have personal biases as all members of all IRBs do.

PROFESSOR CHARO: Thank you.

Bernie Lo?

DR. LO: I want to thank you first for a very illuminating presentation. I want to follow-up Steve Holtzman's questions about sort of the actual nuts and bolts of how independent IRBs work.

As you know, there is a lot of discussion as to whether IRBs have sufficient resources and support to do their task. So, I was wondering, if I could ask

first what do you charge the sponsors of research to review their research? Do you charge more, for example, to a big, you know, 50-site clinical trial as opposed to a smaller study? Secondly -- just -- you can give us a range. And, secondly, what typically do independent IRBs pay their consultants? I take it these are not volunteers but are consultants. Do you pay them and how much do you pay them?

MS. HEATH: The fees that we get -- I think each of us publicly post our fee schedules somewhere. Our's is on our web site. I decided years ago that we would charge by the action. That is so much for review, initial review of a protocol and so much for initial review of each independent site. Therefore, a large multi-center study is that much more expensive than a one-site study. We charge for continuing review and each action.

I took that route because I think it is unfair to penalize those sponsors who have thought ahead. Their protocol is well thought out and they have no modifications by charging so much that I cover the costs of all those that modify every week so it is by the action.

A friend came up with a aphorism, I think, that is quite true and that is it is the simple

protocols that will get you. Somebody will call in and say, "Well, I just have a simple protocol. Can you charge less?" We charge by the action and over time I have discovered that that is a wise thing to do.

DR. LO: Could you tell us what the dollar numbers are?

MS. HEATH: The -- we charge $1,000 for an initial review of a protocol and $275 for initial review of a site, and I think every independent IRB is different and I am sure you can look up their web sites for their fee schedules.

The fees are based on the fact that we have costs. We have costs to go to meetings, costs for secretaries, for copies, for phones, for everything, rent, and all of those costs have to be covered.

The second part of your question was payment to reviewers and that is proprietary but we pay the reviewers for again the work load, not the decisions. I tend to pay for attendance at a meeting and the size of the agenda so, that if there are ten items, they are paid more than if there is one item. That is simply a work load question. They are expected to do more.

Does that answer sufficiently?

PROFESSOR CHARO: Yes.

DR. LO: Can you give us a range of what --

PROFESSOR CHARO: Bernie, you need to be near the microphone for those on the phone.

DR. LO: I am sort of a quantitative person. I was wondering if you could give us a range of what -- if not your own IRB -- other independent IRBs might charge? I mean, the sort of order of magnitude. Are we talking about $100 an hour for a full day, $1,000 an hour?

MS. HEATH: Pay for their members?

DR. LO: Yes.

MS. HEATH: No, I cannot. I do not know.

PROFESSOR CHARO: David Cox?

DR. COX: Yes. I, too, want to thank you very much for this because it has been extremely difficult for NBAC to collect even qualitative data, let alone quantitative data, on certain subjects and independent IRBs has been a difficult one.

So, I noticed that you stated, in the beginning of your paper that you are really speaking for yourself and your experience.

So my first question: "is how did you go about collecting this information about all of the different independent IRBs"? Like, for instance, how many are there?

MS. HEATH: Well, first of all, it is a very

small world. We all tend to run in the same circles. We see each other at IRB meetings, the PRIM&R meetings, the ARENA meetings so we run into each other a lot.

Just as there is no complete list of all IRBs, I do not think there is a complete list of independent IRBs. The best most complete list I have seen is the one on HemaNet, which I mentioned in the paper, but I must admit that on their list there are a couple of IRBs that I have never heard of.

DR. COX: So how many in total are there?

MS. HEATH: They must be very small.

DR. COX: About?

MS. HEATH: Between 20 and 50 but that is --

DR. COX: But that --

MS. HEATH: Twenty is those I could name.

DR. COX: And is there any sort of mechanism besides just people knowing each other and passing each other at meetings and stuff that sets a standard for the field? Is there a standard? I mean, your discussion was as though there was a standard because you make some statements that are sort of really important. For instance, that there would never be a person involved with the institution that was on the IRB. So how are those kinds of standards set

universally for all the independent IRBs?

MS. HEATH: I am not sure I said never. I try to shy away from never.

DR. COX: Okay.

MS. HEATH: But --

DR. COX: I may have misunderstood you.

MS. HEATH: Again, I was speaking for myself and those independent IRBs I know of and for the most part what I know is that there has been an evolution. When independent IRBs were first evolving in the early '80s after the FDA regulation and in some cases even before, I think there was a much closer interaction between board and administration.

Each of the independent IRBs was quite small. There were a limited number of people and there was not as much awareness. That has been changing over the last 20 years and I think definitely that the trend is towards complete separation. The leading IRBs, leading independent IRBs certainly have that separation.

PROFESSOR CHARO: Anything further?

DR. COX: Yes. So do you -- this issue of sort of standardization is a really vexing one in the context of non-independent IRBs.

MS. HEATH: Yes.

DR. COX: So do you think that it is an issue

for independent IRBs and, if so, then what should be the mechanism or how would you suggest -- I mean, you are clearly a very knowledgeable person about this -- -- about how to go -- about should there be a professional organization for this or how should this go about?

MS. HEATH: Well, first of all, bottom line, we all have to meet the same regulatory standards. At least anybody who -- or any independent IRB that is reviewing FDA regulated research. That is the bottom line. The minimum standard just as it is everywhere.

Knowing that we are about to have an audit keeps one having -- adhering to that line.

Beyond that there is professional reputation, competition. Not only are we competing in terms of speed, which clearly is an issue, but also in terms of quality. I know that there are a number of our clients who come back and say, "We appreciate the quality," and it is a selling point, if you will. We depend on that quality.

As to whether there is an organization, there is several IRB organizations. The leading one of which is ARENA. Most of us are members of ARENA. They have subgroups and there is a way for independent IRBs to meet within that subgroup, and there is a consortium of

independent IRBs that meets pretty regularly

PROFESSOR CHARO: Okay. I have on my list myself, Eric Cassell, Bill Oldaker, Alex Capron. Anybody else? And Steve has an additional question.

MS. KRAMER: Alta?

PROFESSOR CHARO: Bette, thank you.

DR. CASSELL: I am taking myself off the list.

PROFESSOR CHARO: You are taking yourself off the list. Okay.

The questions that I had actually follow directly on from David Cox's questions about the standardization of responses, etcetera. Certainly the regulatory requirements form a minimum but those of us that have served on IRBs know that each IRB tends to react idiosyncratically to things that go beyond the regulations. There are supererogatory duties, for example, those IRBs that have additional protections that they have chosen to implement for people whose capacity to make decisions has been impaired.

And then there is room for interpretation of the regulations. I remember seeing a protocol where a researcher wanted to replicate a study from another country that had been done only on people of one race. The question had to do with whether or not that was appropriate or inappropriate since this is clearly a

disease that touches people of all races in the United States, things like that.

The first question: "is whether in your experience your independent IRB or others tend to develop a set of interpretations or supererogatory duties that they then use as precedence so that there is internal consistency within the IRB across time as to how it approaches these problems"?

It does happen at institutions sometimes that way and I did not know in your case if it happens with your's.

MS. HEATH: I think the short answer is yes. I think independent IRBs can be as idiosyncratic as any IRB and I know that as a standing IRB they tend to look for what they have done before to set precedent and to build upon.

PROFESSOR CHARO: Then the question that arises from that is the following: In an institutional IRB there is a local culture of knowledge so that people know what that IRB's policies tend to be. In a sense it is published informally within the institution. Is there any formal publication of those interpretations so that those who are deciding to go to your IRB versus another could anticipate how your IRB might handle these questions that are subject to

interpretation?

MS. HEATH: Yes. Number one, it is a small world and I think people talk a lot. But, number two, we published guidances for our applicants. A guidance on what an independent IRB is, a guidance on how to write a protocol, a guidance on how to write a consent form. I just published an article that I know a lot of our clients have seen because I sent it to them on how to write consent forms.

PROFESSOR CHARO: Those are fairly general compared to the kinds of things I have been talking about.

MS. HEATH: Well, yes, but that is examples. It is examples.

Then we also -- most of us have web sites where we can publish recent information and opinions.

PROFESSOR CHARO: Opinions?

MS. HEATH: Not naming any client but we have been seeing a lot of studies on biological specimens. What do we require? What are the issues that are arising and how have they been decided?

PROFESSOR CHARO: That is very much the kind of thing I was wondering about. Very good. Thank you very much.

The next person on my list would be Alex.

Sorry, Bill. Okay. Bill?

MR. OLDAKER: Thank you.

Again I appreciate your testimony. It is very helpful.

Let me ask a question which you may not be prepared to answer but if you would try I would appreciate it. What do you think about certification or licensure of IRBs or alternatively the certification of licensing of the members of an IRB?

MS. HEATH: Thank you. I am on an accreditation committee for accrediting IRBs and I think that obviously if done correctly it could be a real asset to our whole field. I think it is probably something whose time has come. As a member of the accrediting -- the committee looking at accreditation, I am, of course, looking at how the opinions and policies being discussed, alternatives being discussed would apply to us. And what I am seeing now is that we would be able to meet the standards as well as an academic IRB albeit differently.

As to accreditation or certification of members, I do have some problem with it. I think members should be educated as to some parts. That is the Belmont Report should be required reading, that is that they should be knowledgeable about the regulations

and the source of regulations.

Beyond that, each of the members is asked to be on any IRB based on their backgrounds. Whether they bring ethics or religion or law or pediatrics to the board. I am not sure if certification of members would serve a good purpose if we have accreditation. So I am hesitant, although I am open to it.

MR. OLDAKER: If I might ask one more.

PROFESSOR CHARO: Sure.

MR. OLDAKER: In most professions when one looks to accreditation or certification, one looks to the training and the continuing education of those professionals. How would you propose to take care of that issue if the IRB was the sole certified or accredited organization?

MS. HEATH: One of the --

MR. OLDAKER: Thank you.

MS. HEATH: -- proposals is that the accreditation would take the form of looking at the entire program, not just the IRB. And, as you say, the program would include education, training, training of investigators, and again we have taken some pains in that area.

And I think that what you would look at is the overall functioning of the IRB rather than the

knowledge of the individual members because it operates as an entity. Each one contributing to that entity.

MR. OLDAKER: Thank you.

PROFESSOR CHARO: Thank you. We have got about, oh, seven or eight minutes unfortunately before we are going to have to move on.

I have Alex, Bette and Steve.

Alex?

PROFESSOR CAPRON: Thank you for your testimony and your paper, Erica. It is a -- the Commission is fortunate to be hearing from one of the pioneers in this entire field.

MS. HEATH: Thank you.

PROFESSOR CAPRON: And while there is always some risk with anecdotal information, I think there would be no one in the field who would be more familiar than you.

I have three questions. The first is just a question of clarification. You described 1981 and the FDA's recognition of the need for noninstitutional or nontraditional academic institutional IRBs as the origin of the process in some ways.

MS. HEATH: The turning point.

PROFESSOR CAPRON: The turning point. And yet the FDA directive that you cite here does not mention

independent IRBs. Can you clarify that for me, please?

MS. HEATH: The FDA requirement before was that any research done in an institution that had an IRB had to go through that IRB. That left a lot of studies that were done that were not required to go through an IRB. In 1981 they said that that regulation would apply, the same protections should apply to all subjects. It did not matter where they were but they should be given that same protection. And so they said, "You are going to have IRB review."

They did not establish where that IRB review would occur. They had a few ideas which they mentioned in the preamble. They mentioned perhaps medical societies would or regional societies or professional societies. They never did come up with large IRBs for those populations.

In fact, I was working at UCSF and I had the idea for starting this. I waited because I thought that was an obvious given. I actually went down to the Medical Society and asked if they had any interest in doing it because it would be terrible to try to compete against a group like that. There was no interest so independent IRBs grew up because there was a void.

PROFESSOR CAPRON: When you spoke of letters and untitled letters and warning letters, were you

referring to the FDA or the OPRR?

MS. HEATH: FDA.

PROFESSOR CAPRON: Throughout your discussion you have seem much more focused on the FDA. Do you, in fact, end up doing much research approval that involves OPRR as opposed to FDA?

MS. HEATH: We do some. It is a very minimal part of our work load. As I mentioned -- well, historically, OPRR would not consider an IRB that was external to the institution. The presumption was the very traditional presumption that the IRB was institutional, institutional review board.

More and more grants began going to entities that did not have a review board. They were forced to either go to a local board, an academic board, at a time when resources were becoming very, very tight and the academic boards were saying, "No, thank you. We do not need the extra work."

Their other alternative was to set up one in-house. They did not have the knowledge. They did not have the experience. With one or two protocols they did not want to go to the annual meetings. They could do an IRB. They could meet the regulation. It was optimal.

So, what? Three years ago? Four years ago?

There was the first Single Project Assurance issued to an institution that was contracting with an external IRB. Those continue now. I think we have six or seven. It might be up to ten but it is a very minor portion. We are pleased to be recognized by the funding agencies as professionals but it is not a major part.

PROFESSOR CAPRON: And the final question is you spoke of being involved with accreditation. I gather that is the PRIM&R activity in that, is that correct?

MS. HEATH: Correct.

PROFESSOR CAPRON: Would you think as part of that accreditation that the standards would reach the kinds of issues that have raised particular concern about independent IRBs such as the forum shopping issue? That is you describe your own practice and you suggest that it is common among independent IRBs to inquire whether something has been previously submitted and reviewed and what action was taken by another IRB or one assumes that an unfavorable action if that.

But you did not say that response an IRB should have when it learns that information. Does the thinking now around accreditation reach to questions of appropriate standards for a response in that situation

and the other kinds of issues, the financial conflicts and so forth, that do get raised?

MS. HEATH: Well, as I said, I do not know what will eventually result. I know the performance standards that were under discussion were quite broad. They set a standard that I hope is flexible enough that the issue would be looked at but with an open mind because there are a number of ways of handling money but many other issues as well. Shopping.

So I am not sure I could predict an outcome but I think it will.

As to shopping, again as I mentioned on the evolution of IRBs, with the administration and the IRB, this is something that is being recognized more and more and more. I do not know if all of you are aware of the IRB discussion group on the internet but there have been questions recently. "We are concerned about such and such protocol, is anybody else concerned, write to me."

There are times when it is acceptable. I have received protocols that the applicant said, "This has been reviewed by somebody else and we are moving it." The most recent case I can think of was they were very concerned because they did not think that IRB was adequate. They could not get records. There was not

an appropriate membership. And we accepted the protocol for review.

PROFESSOR CAPRON: Thank you.

PROFESSOR CHARO: Betty?

MS. KRAMER: Pass.

PROFESSOR CHARO: Betty passes.

We are down to only very quick questions. I apologize.

Steve?

MR. HOLTZMAN: It occurred to me as you were speaking that I used to think that there were two universes of IRBs, the institutional IRBs and the independents. But as you are speaking, there is a third universe, which is the sponsors having their own IRBs. So you have said your universe of independents is 20 to 50. Do you have any sense of how large the universe of nonindependent sponsored ones are?

MS. HEATH: I was actually surprised and I tried to get here yesterday to listen to the person from General Motors. I had never heard that they had one.

MR. HOLTZMAN: Do those folks show up at PRIM&R and ARENA and whatnot?

MS. HEATH: I have never met them but they might be. I mean, there were over 1,000 people last

year and I did not meet them all.

So --

MR. HOLTZMAN: You do not have a sense?

MS. HEATH: I do not have a sense of it, no.

MR. HOLTZMAN: Okay.

PROFESSOR CHARO: I have one last brief question if I may and that has to do with liability and insurance. Reputation is clearly the greatest spur to high quality work, avoiding liability and keeping insurance premiums low is another spur, and I was wondering how your corporate counsel had structured your arrangements in order to capture what was perceived to be a potential liability and how the insurance industry has responded?

MS. HEATH: Well, thank you for mentioning another way of keeping us towing the line. Certainly liability concerns are large. We do have a rather good insurance policy. We have negotiated -- renegotiated it several times and I am happy with it.

PROFESSOR CHARO: I guess --

MS. HEATH: We have indemnification agreements with the sponsors that we work with that we are obviously responsible for anything that we are negligent about but are not for issues raised due to actions by the sponsor or the investigators.

PROFESSOR CHARO: I guess to be --

MS. HEATH: Does that --

PROFESSOR CHARO: -- really clear, what I mean is this: In an area where there is not a long enough history or a large enough database for there to really be historically based ratings, how you have performed in the past, whether or not you have had claims, an insurance company might look to indirect markers to predict whether claims would arise in the future.

So that with drivers they look at age, sex, location, et cetera.

To your knowledge, has the insurance company reacted by creating its own -- in essence, its own criteria that they think indicate you have an IRB that is less likely than another one to generate some problem that would result in a claim?

MS. HEATH: You know, I do not know how they set the rates. I do not know what goes into it. I do know that the history and all the reports I have heard is that there are fewer problems among research subjects than patients, which should play well but I do know that our premiums are way higher than I should think necessary.

PROFESSOR CHARO: And don't we all?

MS. HEATH: But that is for my car insurance,

too.

PROFESSOR CHARO: Are there any other brief questions for this session?

In that case I would like to thank you very much. It was very informative and very, very helpful. We appreciate you coming.

MS. HEATH: Thank you.

PANEL V: PURPOSE OF REGULATION

PROFESSOR CHARO: We move now albeit just a little bit late to our second panel of the morning.

Dr. Harold Vanderpool from the University of Texas Medical Branch, Galveston, will be our first speaker on "The Unfulfilled Promise: How the Belmont Report can amend the Code of Federal Regulations."

Dr. Jonathan Moreno from the University of Virginia on "Protectionism in Research."

And Dr. David Magnus from the University of Pennsylvania on "The Justifications for Human Research."

Thank you, gentlemen, for coming and thank you for your patience this morning.

The way we would like to have this portion of the morning go is as follows: If you would each present your papers. I understand you were told more or less 15 minutes, is that correct?

DR. VANDERPOOL: How many minutes?

PROFESSOR CHARO: Say what?

DR. VANDERPOOL: Twenty minutes.

PROFESSOR CHARO: Twenty minutes.

DR. VANDERPOOL: Okay.

PROFESSOR CHARO: So --

DR. MORENO: Twenty-five?

PROFESSOR CHARO: Between 15 and 20 minutes.

And we will ask the Commissioners to restrict their questions after each paper solely to clarification of a point that was made because there is -- following a break after all three papers there is an hour for discussion of all three papers because they are obviously interrelated and we will certainly invite the authors back to collaborate with us in that discussion and questions can be directed at them or you can interject while we are speaking.

So with that, Dr. Vanderpool?

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DR. VANDERPOOL: Thank you, Dr. Charo.

Thank you all. I am truly pleased to be with you today.

So little time, so much to summarize and accent.

I have been charged by your committee and staff to provide an analysis of the relationship between the Belmont Report and the federal regulations, and include a discussion of the link between the Belmont and the federal regulations, and what those ought to be.

I have also been asked to make clear concise recommendations with respect to these linkages.

Through these highlight remarks about my paper, I will indicate how I have fulfilled these charges.

My paper's thesis -- and I will be walking through it with highlights, so join me please -- is at the top of page three.

The power of the Belmont Report to amend the Code of Federal Regulations has never been realized. This paper will indicate how and why an incorporation of the content and spirit of Belmont into the body of the Federal Regulations can rectify major problems in the regulations, strengthen the protection of human subjects, and accent the inescapable role of moral

judgments for assessing when research involving human participants is permissible.

I take the word "participants" back. I believe they should be called "subjects" but that is perhaps another separate discussion.

This thesis is defended in the topics listed on page two of the outline, which I will follow very carefully, and I have developed each of the topics by giving sustained and exceedingly careful attention to the actual text of the Belmont and the Federal Regulations in light of careful use of a host of commentaries, some from some of you present, and historical materials.

Topic I begins at the bottom of page 3 and notes that both Belmont and the Federal Regulations share the over arching purposes of promoting research as well as protecting human subjects.

The promotion of research is not explicitly stated in the document that it clearly evidenced by its content. If you read the history of the development of the PHS-DHEW guidelines for the protection of human subjects, it was fostered and fueled by the NIH's concern to protect its research integrity.

If you look at the bottom of page 3, and I invite you to read all the footnotes you wish, there

are many, you will note that the promotion of research is a de facto purpose in the Belmont Report, including being a moral obligation.

On pages 4 and 5 I just point to the most notable differences between Belmont and the regulations, which are really quite obvious. The regulations focus on rules that need to be followed as well as attention to organizational and enforcement mechanisms, laudable mechanisms even though you may wish to change some of them, while the Belmont Report, of course, focuses on principles -- ethical principles and guidelines.

Topic II beginning on page 5 and following gives an overview of Belmont's purposes and content. At the bottom of page 5 you will note that Belmont's objective is to provide an analytical framework for the resolution of ethical problems arising from research involving human subjects. This familiar framework is given on page 6 and includes, of course, its principles and its applications.

On page 7 I invite us all to look at the Federal Regulations through the lens of the Belmont Report starting near the top of page 7. From the vantage points of Belmont the present Federal Regulations contain a number of major problems, all of

which can be rectified by using the report to amend the regulations.

The problems include a negligible influence on ethics, a disorganized set of rules that easily confuse and confound researchers and IRB members as they seek to discover what the regulations want them to do; an irresponsible view of the sources that define and discuss research ethics; a seriously flawed understanding of the ethics of research; blind spots with respect to important protections accented in Belmont; a preoccupation with rule stating and rule following to convey the message that the Common Rule is a bureaucratic document without a soul; a distortion of the elements of informed consent found in the Belmont Report.

PROFESSOR CAPRON: What is it you do not like about the regulations?

DR. VANDERPOOL: I do, Professor Capron, appreciate the regulations a great deal but I think the Belmont gives the regulations a very tough time, indeed.

Now on page -- on Topic III -- this is a good question. We can discuss those and I will be very specific about these but on Topic III beginning on page 7, I talk about the meaning of Belmont's principles,

which I take to be widely misunderstood.

I do not consider them as -- in fact, I am working with the text -- it is not what I believe but I think it is what the text says. They are not abstract principles that serve as the ultimate foundations of ethical reflections. The Belmont principles are, as many bioethicists and pragmatists realize, are easily set -- a set of easily grasped moral standards rooted in cultural belief and tradition for persons of diverse background and training.

It is as if the Belmont framers and bioethicists and pragmatists and others are looking around at this host of rules and regulations and requirements and they are saying these are all connected with right making and wrong making characteristics of human actions.

How are we goign to make sense of these? You make sense of these by saying, "Oh, well, there is this division that deals with truth telling and there is this division that deals with justice, and there is this whole set that deals with non-maleficence, with protecting people from harm, and there are these that deal with beneficence and these that deal with gratitude." That is what the principles are.

They are summaries of those elements,

constitutive, comprehensive elements of human morality.

Now Belmont is rather unique about these. They do deal with beneficence and they do deal with justice but they are -- the Belmont's principle of respect for persons is a sort of an amalgamation. It has got some philosophy in there, a little bit of kant (sic) but it has got some more things. It has got some things from law, from constitutional law, and it has got some things from religion, and it has got some things for other things about culture.

So it is not clean philosophically but it is one of those principles that is supposed to draw in a whole set of things regarding how to regard people with respect.

Now you will notice at the bottom of page 10, beginning at the bottom of page 10, that we see Belmont applications and its principles are seen as ethical requirements. Both are seen as equally strong sets of ethical requirements. And then I want to make a position that I want to argue and I think it is correct -- I stand to be corrected on any of these positions if I take too strong a position then for you -- by all means, let me think -- let me know that you think it may be too strong.

But in the middle of page 11, what I say is

the equally strong moral requirements of principles and applications and the interplay between them directly relates to the protections provided by the Belmont Report.

The most noteworthy feature about the protections for human subjects promulgated by Belmont is that at critical points the protections are far greater in the applications section of the report than in its basic ethical principles section, which a lot of people have not really recognized.

The crucial place in which this occurs entails protections pertaining to respect for persons. According to Belmont the respect for person principle requires that persons should be treated as autonomous agents which involves giving weight to the opinions and choices of individuals who are capable of deliberating about and acting in accord with their personal goals.

Respect also requires refraining from heavy handed disrespect such as repudiating considered judgments of perspective judgments or denying their freedom to act in these judgments.

Now to give weight to a research subject's opinions and choices implies that the authority to weigh and judge resides with someone other than the subject. It is in the principle section of the report.

The phrase undercuts the ethical and legal understanding of autonomy, namely that individuals in the research arena are free and self-determining agents who have the final authority to decide what should happen to them.

But now what the principles of Belmont under respect for persons denies the applications supply. All persons, all subjects must be granted the opportunity to choose what shall or shall not happen to them, must be given all the information. Reasonable volunteers would need to know whether they wish to participate, must comprehend this information, which involves how it is organized, the time needed, the communicating that needs to be incurred, what level of communication with respective to subject's intelligence and so on.

Patients must be -- subjects -- prospective subjects must be situated in conditions free of coercion, free of undue influence, unjustifiable pressures -- these are carefully defined in Belmont -- over either the prospective subject or through controlling influence of a close relative.

All these are accents in the Belmont Report, which shows that the subject's choice should be free and final except in just a couple of places where

Belmont makes a couple of exceptions.

Now I think these are very powerful -- a powerful point where the applications secure with -- in a stronger way what it means to respect research subjects than do Belmont's principles.

Now you will note on page 13 that I set up this argument: I think one can look at Belmont and say that the principles of beneficence and its applications and the principles of justice and its applications are in a sense gatekeeper roles. They are the criteria IRBs must use to determine which research projects and protocols are acceptable enough to move to the stage of subject enrollment.

These serve, therefore, as essential but nevertheless initial moral screens prior to the ethical bedrock of Belmont's human subjects protections, the vital protections surrounding informed consent.

And I maintain that Belmont's great reliance upon informed consent accord with the fundamental dynamics of the values of free and democratic society.

You can -- and I think that in a sense we said, "Well, we have talked informed consent language a lot," but I think we need to strengthen informed consent. Either one goes with narrowing the distance between protections, make protections and enhancements

of research more of a zero sum gain or one can accent informed consent and do it right and allow for the greater possibility of risk and harms in research.

As specified on pages 14 and 15, the Belmont Report is a flawed and cracked earthen vessel. You can see the ways in which I identify that as true. But in spite of its manifest flaws, it can serve as a powerful basis for revision for the Federal Regulations.

Its power to do this is linked to its legal, historical and revered status as well as its intrinsic virtues, which are found on pages 15 and 16, and many of those are very powerful. Protection of vulnerable populations, insightful connections between ethics and research, and so on.

Now Topic IV, this is where Dr. Capron's question -- where the rubber hits the road. I deal here very specifically with the ways the Belmont Report could be used to revise our present Common Rule and here is where what I -- what seemed to be maybe overstated charges on page 7, I think are accurate charges, accurate concerns.

First of all, Belmont -- the Federal Regulations hardly mentions ethics at all. One time in the main body of the material.

Second, beginning on page 17, the Belmont has

-- the regulations contain irresponsible standards pertaining to sources that define an articulate research ethics. Now how does this occur?

In the one place where ethics is mentioned in the main body of the Federal Regulations, Section 46.103(b)(1) says, "The statement of principles for the protection of rights and welfare of human subjects is required in assurance of compliance agreement."

But if we notice about what this statement is, the actual content of such a statement is not taken seriously and its uses are not even addressed.

Here is the wording about the statement that is required: "This statement may include an appropriate existing code, declaration or statement of ethical principles or a statement formulated by the institution itself."

Now this is problematic. The Nuremburg Code by itself will not do. The Declaration of Helsinki will not do. Some statement drawn up by the institution often will not do. But this assumes, oh, well, any of these will do.

And let's say you chose the Nuremburg Code. If you did you would go against Belmont Report that argues that ethical principles are necessary to interpret the rules of Belmont, Helsinki, of the

Nuremburg code and Helsinki and otherwise. And so you simply have in the body of the regulations a sort of, oh, comme si, comme sa, develop the regulations you want.

And I propose very specific things. In the middle of page 18 I propose that instead of this open ended phrase with a variety of documetns can do, the phrase -- as you can see in the underlined parts of that midsection on page 18 -- the statement of ethical principles should include at minimum the tenets of the Belmont Report. This statement should serve as an ongoing basis for training programs and protocol evaluations by the institution's IRB members and investigators. That is not in the present regulations. Nothing is said about how the assurance compliance agreement should be applied.

Now, if anything, it is even more serious, Section, Part III, middle of page 18 is even more serious because the regulations contain a flawed understanding of research ethics. This is found in the regulations, 46.147(a) under the heading "IRB membership." And this is in the Federal Regulations.

In addition to possessing the professional competence necessary to review specific research activities, the IRB may be able to ascertain the

acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.

Now this is critical. How do you ascertain the acceptability of proposed research in the regulations by the vague unspecific category of institutional commitments and regulations? That might have been the Nuremburg Code. Who knows? It does not even mention ethics or sound ethical reasoning. It could be just sound deliberative reasons. And falsely assumes that the standards of professional conduct, presumably professional codes of ethics, directly relate to the ethics of research.

As we know in looking carefully at the final report of the Advisory Committee for Radiation Experiments, what the committee members argued was a historical record and their contemporary projects, which they did in the last part of this huge report, indicate that the distinction between the ethics of research and the ethics of clinical practice was and is unclear and that many of the problems of the past and the present may be due to a failure to distinguish between these two.

Now what I propose -- and again these are not

elaborate proposals but they give an entirely different cut the regulations -- is in the middle of page 19 that this wording should be the following: That proposed research in terms of -- should be -- you ascertain the acceptability of proposed research in terms of sound reasoning. It could be ethical reasoning. But distinguishing the ethics of research from the ethics of clinical care, applicable law and each institution statement of ethical principles and rules specified under 46.103(b)(1) and that is what we just reviewed in terms of specifying the Belmont Report.

PROFESSOR CHARO: Excuse me, Dr. Vanderpool.

DR. VANDERPOOL: Yes.

PROFESSOR CHARO: It is hard to believe it but the time has been flying and it has been about 20 minutes. Since we have been fortunate enough to have this to read for approximately five or six days, could I ask you just to commend to us for a second reading those items in the remaining part of the paper that you think are especially important to us?

DR. VANDERPOOL: Thank you. Thank you. Yes.

I think the other parts of the paper that are especially important would be Appendix B, which is in light of the criticisms of the sections of the regulations that deal with what IRB members and

researchers should do.

What I do in Appendix B is to indicate how -- is to answer this long standing question, which I have heard this committee ask, about how do you make research -- how do you make informed consent a process rather than a document. And it is a document in the present Federal Regulations because it says -- the Federal Regulations say that the basic elements of informed consent are as follows, and they are all informational, and they all belong on informed consent.

So informed consent forms.

So if you spend all your time really focusing on what the basic elements of informed consent are, you spend your time focusing on informed consent forms.

And what I offer in Section B is the process. The process is not -- to throw away the basic elements of consent in the present regs and talk about the three basic elements of consent, voluntary-ism, comprehension, understanding. So this makes consent into a process.

The other point would be that in the final section I have long been concerned about what is that regulations, and including regulations the Belmont Report is communicating pragmatically to IRB members and researchers, and I think it is probably that --

what it is communicating now is problematic. And I think the proposals I make here indicate that it should communicate a clearer set of things they should do to protect human subjects.

These are found on page 24. It should make thoughtful deliberations and so on and these -- I think every one of these elements on page 24 will serve to protect human subjects better and these directly relate to what the Belmont Report is about.

And on all of these grounds I offer two recommendations to you. On page 25, first, seize the opportunity to appoint an expert task force to finally utilize the Belmont Report to inform the Federal Regulations. And, second, consider -- to call for Belmont II for the sake of articulating a clearer and more comprehensive understanding of the ethics of research.

Thank you very much.

PROFESSOR CHARO: Thank you and I apologize that the shortness of time precluded a fuller presentation of what is obviously a detailed and careful paper that was provided to us.

DR. VANDERPOOL: And please understand I did not want to assume that you had not read the paper but I think when I read a paper it is helpful for an author

to say, "Okay, now this is the thing that has punch."

PROFESSOR CHARO: I think we all agree.

DR. VANDERPOOL: And I hope I was able to convey that.

PROFESSOR CHARO: I think we all agree completely. That is the purpose of having you come after you have given us the paper. Absolutely.

DR. VANDERPOOL: Thank you.

PROFESSOR CHARO: May I first just ask if there are any points of clarification rather than discussion or expansion?

If not, then we will turn to Jonathan Moreno for a presentation on protectionism.

JONATHAN D. MORENO, Ph.D.,
KORNFELD PROFESSOR AND DIRECTOR
CENTER FOR BIOMEDICAL ETHICS
UNIVERSITY OF VIRGINIA

DR. MORENO: Thank you, Alta.

I have some overheads that I am going to be referring to.

PROFESSOR CHARO: Can we get some help from staff? Thank you.

DR. MORENO: Good morning. It is always a pleasure to be back with NBAC.

My charge was to develop the idea of

protectionism as it appears in the Common Rule and I really tried very hard to do that. Although I have to say that I felt, as I will say this in San Francisco, it may be appropriate, the ground is somewhat shifting beneath my feet over the last several months because -- or perhaps my butt as I was writing this because, in fact, I think the moderate protectionism that is characterized as the Common Rule -- what I am calling moderate protectionism, we might be seeing the end to the era of moderate protectionism. And I want to elaborate on that as I go on.

In fact, what I have to say to you is in a certain sense more a study of protectionism as a case study in the history of ideas rather than a philosophical paper per se. Even though I am only a philosopher I often think the history of this area is more illuminating than the philosophy.

(Slide.)

Clearly there are two extremes that could set the boundaries of a philosophical discussion of protectionism in human subjects research. At one extreme we could prohibit human subjects research all together. That would be the most powerful form of protectionism. For various philosophical, economic and political reasons we have decided not to do that.

Harold mentioned the Belmont Report's position on that.

At the other extreme we could permit all human experiments, come what may, willy nilly, without any protections at all. Well, even the Nazi doctors' defense attorneys did not accept that proposition. They claimed that even their clients sought volunteers in the concentration camps.

So it turns out that nobody at least in public accepts either of the extremes. What we have instead is some several flavors of protectionism that stand in the middle. There is general agreement that persons who are subjects in human experiments -- and I am, by the way, going to use the term "human experiments" because it is historically the most generic term even though it has fallen in and out of favor over the decades.

People who are subjects in human experiments deserve protection from undue risks. This proposition is not controversial.

What is controversial is who bears responsibility for protecting them, how should we weigh or balance, and those terms have different significance, weigh or balance societal interests versus individual interests? And, by the way, the idea of medical practice is a way of merging, of meshing the

idea of societal interests to the advancement of medical knowledge and individual interest in being protected from undue risks.

And it seems to me that both of these questions can be merged through a certain theme that characterizes my historical account of protectionism. The theme is the idea of the discretion of the investigator. How much discretion in making judgments about who to bring into research, how to decide that they are truly volunteers, how much risk to expose them to and so forth, how long to keep them in the study, many questions. All these questions that we are familiar with can be brought under the heading of how much discretion should be allowed to the individual investigator.

And I think that it is the ebb and flow in the story -- in this story, the story of investigator discretion that is the story of protectionism in medical research.

Now in my first slide I have tried to characterize what I think again are the critical issues. The relationship between the interests of the subject and those of science and future patients.

Secondly, whether and in what manner the conduct of the investigator may be monitored or

controlled by third parties. This really goes to the issue of investigator discretion and a corollary to this is what special arrangements should be made for certain vulnerable populations.

By the way, the idea of a vulnerable population is very much historically based. For many years the only people who were thought to be really vulnerable were children. Antivivisectionist from the late 19th Century through the early -- through the 1930's anyway -- singled out children for special protection. Rarely were others such as mental patients singled out for special protection.

(Slide.)

I am going to dwell on this slide for just a moment. It seems to me, as I have indicated, that there are several levels, for want of a better term, of protectionism.

Under what I have called weak protectionism, the investigator has a great deal of discretion over all the issues that I have mentioned, recruitment, how to get consent or how to ensure voluntariness, when to decide that somebody should not be in a study, how to assess risks and benefits, and there are at best informal constraints. What we might call guidelines. What Henry Beecher, himself, as a matter of fact,

called guides. Guides.

I think that the era of weak protectionism really lasted up to about 1980 and 1981 and that the period 1947 to 1981 was an era in which gradually weak protectionism was being challenged and finally gave way to what we have today, which itself may be under attack, which I call moderate protectionism.

Under moderate protectionism there is limited investigator discretion but there is nevertheless still a lot of discretion. There is, for example, no necessary contemporaneous monitoring of study practices themselves under moderate protectionism and there are formal constraints or rules. What Henry Beecher called rigid rules, which he did not like. And he put the Nuremburg Code in the category of rigid rules that he did not like, which is why Beecher preferred Helsinki to the Nuremburg Code. Helsinki was more guidance oriented according to Beecher.

And then, of course, it follows as the night to day that if there is weak and moderate positions there must be a strong position and the strong position would be severely limited investigator discretion with formal interventions to ensure that the rigid rules, so to speak, are being followed.

This might go so far, for example, not only to

include independent review of capacity assessment. We might also tell investigators who they can have in their study. They might not -- we might require that they not even have a role in the recruitment process itself. So strong protectionism, as I conceptualize it, would be quite severe indeed.

(Slide.)

There are, of course, alternatives to protectionism other than the sort of horizontal ones that I have mentioned, which would be to allow anybody to be in research under any conditions and to prohibit research entirely.

There are also -- you might think of as vertical alternatives. For example, from the subject's standpoint you could have a position called -- we might called accessionism. That is to say you could take the position that there is a very strong interest, if not a right to be in research if you want to be.

And I think there are two versions of accessionism. That embodied in the position of AIDS activists in the late '80s and early '90s, which I call therapeutic accessionism, which is that -- essentially that research also is a treatment. This was the action cry of ACT-UP and that, therefore, people should have access to that medical treatment as well as any other.

There is also what might be called scientific accessionism, the position that women and children, and others who have traditionally been excluded from research should get in for good scientific reasons.

And then there is the philosophical view, not usually very clearly articulated, that underlies those defenders. The position of those defenders of investigator discretion. Which is that the virtue, the moral virtue, the moral uprightness, the integrity of the individual investigator is ultimately the last line and best line of defense against abuses of human subjects.

It seems to me that it is this view that is very central to the traditional notion of individual investigator discretion. One might call the position "virtue ethics."

Can I have the next slide, please?

(Slide.)

Now I am going to just run through these very briefly and I want to -- and this -- obviously everybody has their own highlights or their own landmarks in this history.

The point that I want to make is that every single item on this list, every single policy item, was preceded by a public scandal or a tragedy of some sort.

I was really impressed by Don Chalmers' remark yesterday afternoon that Australia did not have this pattern but nonetheless in the United States I think it is very clear that we have responded to a series of scandals or incidents.

(Slide.)

We do not have to perhaps go through -- some of you are familiar with these incidents and the scandals and tragedies that preceded them but I think you will see that in each case there was a specific incident or series of incidents that finally called forth a public response.

(Slide.)

And I have added only a few days ago the new DHHS initiatives and perhaps new legislation, and I want to return to that at the end of my remarks.

(Slide.)

The period that I have referred to as, I think, the critical era in which moderate protectionism with a lot of investigator discretion was being broken down was the period, as I said, from 1947 to 1981. A period that has as its beginning the results of the Nazi doctors' trial in 1947 and it is conclusion the DHHS rules in 1981.

And I think it is quite interesting that if

you take six major commentators in the 1960's through the 1970's on human research ethics you see the controversy within the community of distinguished commentators on the issue and you see the breakdown of traditional investigator discretion.

Take three distinguished physicians. For example, I have already mentioned Beecher. Beecher, as I have told you and as many of you know, was opposed to the Nuremburg Code. He considered them to be rigid rules. He opposed the Nuremburg Code as part of an Army contract for Harvard in 1961 and '62 but he embraced Helsinki as guides. He defended the virtue of the individual investigator as the last and best offense against the abuse of human subjects but Beecher was not alone.

Other distinguished medical commentators took the same position in the '60s and '70s. In retrospect, we can see that what they were doing was defending moderate protectionism against the critics, against the attacks that were on their way, and that were coming in waves as each new scandal appeared in the '60s and '70s.

Walsh McDermott, for example, said in 1967, "Medicine has given society the case for its rights in the continuation of clinical investigation." He uses

rights language perhaps not wholly self-consciously but interestingly, I think.

(Slide.)

Lou Lasagna said in roughly the same period, "How many of medicine's greatest advances might have been delayed or prevented by the rigid application..." Again the word rigid application "...of some currently proposed principles to research at large. For the ethical experienced investigator no laws are needed and for the unscrupulous incompetent no laws will help."

So that Lasagna took this position as a matter of fact during the early '70s when there was criticism of prison studies and Lasagna said of the national commission's recommendations with respect to prison research, which were by the way much more permissive than the rules that we finally came out with, he said, "This is a terrific example." He said this in an editorial. "A terrific example of some really smart people with some really stupid ideas."

So here we have Beecher, Lasagna and McDermott, the great eminences of commentators on human research ethics trying to hold the fort against the attacks on moderate protectionism in the '60s and '70s.

On the other hand --

(Slide.)

-- we have people like Hans Jonas, Paul Ramsey and Alan Donagan. Theologians and philosophers. Paul Ramsey in 1970 in the Patient as Person writes, "No man is good enough..." and now presumably woman either "...to experiment upon another without his or presumably her consent."

In the epigram to the paper that you have in front of you, I used this very powerful statement from Jonas around 1972, "We can never rest comfortably in the belief that the soil from which our satisfaction sprout is not watered with the blood of martyrs." Wonderfully Talmudic language here full of survivor guilt. "But a troubled conscience compels us, the undeserving beneficiaries to ask, 'Who is to be martyred, in the service of what cause, and by whose choice?'"

Or in a rather more hard hitting and even biting statement -- series of statements in a paper that he published in 1977, the analytical philosopher, Alan Donagan basically compared the position that Beecher and Lasagna and McDermott took by name to the defense of the Nazi doctors as crass utilitarianism.

Now I argue in the paper that that position that Donagan took -- Donagan was not a marginal figure by any means. The position that Donagan took was

intellectually respectable in the late '70s after the scandals and tragedies, and particularly after Tuskegee, and in the midst of the writing or just before the writing of the Belmont Report, and that was only from the standpoint of the history of ideas an acceptable position in the late '70s. It would not have been a respectable position in the early '70s and certainly not in the 1960's.

So what I am arguing in summary with respect to this historical tour is that the period '47 to '81 we see a critique and an attack mostly by nonphysician commentators, theologians and philosophers on the tradition of weak protectionism that predominated in the history of this and in 1981 we have the institutionalization of what I call moderate protectionism, our current system.

Now in the spirit of moderation, I did articulate some recommendations at the end of the paper. Frankly, to me they are the least interesting part of the paper. You can read them if you like. They are all moderate but I think there are more interesting questions that face us right now and it is one that I foreshadowed earlier and I am going to end with these sort of rhetorical questions.

Is it possible that perhaps beginning with the

UCLA schizophrenia study scandal in '94, continuing with the TD case in New York, continuing with the Gelsinger case a few months ago, embodied in the Secretary of DHSS initiatives and the Kennedy bill and the Getty bill that are both being introduced soon, and the report that this Commission is developing, and the transition in OPRR, and so forth. Is it possible that we are witnessing the end of a very awkward, roughly 20 year, compromise called "moderate protectionism?"

And that we are entering an era suggested perhaps by some of NBAC's own recommendations in the Mental Disorders Report of a more interventionism in investigator-subject relations. An era of stronger, if not strong, protectionism. An era in which every IRB might be expected to have, for example, a liaison who will actually go unannounced to the research site and observe the way consents are being done, observe the way subjects are being recruited, observe capacity assessments.

This would be, at least in a matter of degree, if not of kind, a strengthening of what I would call moderate protectionism leading us perhaps to a -- ultimately to a very interventionist position with respect to investigator-subject relationships.

Now there are some dangers in strong

protectionism, at least as an idea, and it is an -- there actually is a particular danger that was illuminated by the writers of what we have come to call the Nuremburg Code itself. Namely that the -- if more responsibility is perceived by investigators as having been taken from their shoulders and instead that more responsibility transformed into legal and regulatory responsibility for other parties, the IRB, the risk manager, the Vice President or Provost for Research at the university and so forth, the nursing liaison from the IRB, if the responsibility for the welfare and interests and rights of the subject is perceived by the investigator not to rest finely on his or her shoulders because a system has been created that is supposed to ensure that those rights and interests and welfare are respected, then will investigators begin to divorce themselves from the traditional sense of moral responsibility that at least in principles -- in principle from the Hippocratic era to the present -- physician investigators are supposed to have with respect to those in their care.

So there is a temptation, I think, to see -- and I think to some extent it is happening -- to see the history I have described moving us inexorably in the direction of strong protectionism.

I think that 20-30 years from now people like us may find themselves sitting around a table like this in a hotel like this reflecting on the consequences of that trend and bemoaning the loss of a sense of moral responsibility among physician investigators and other scientists who are responsible for the well-being of their subjects.

Thanks.

PROFESSOR CHARO: Thank you very much. I can only say in 30 years I suspect we will be doing it by video conferencing and we will not have the pleasure of one another's company over breakfast and lunch.

Questions of clarifications?

Okay. Our third presentation, Dr. Magnus from the University of Pennsylvania on "Ethical Underpinnings." In some ways I suppose this is rather backwards. Your's was the most general of all papers.

DAVID MAGNUS, Ph.D.
ASSISTANT PROFESSOR AND DIRECTOR OF GRADUATE STUDIES, CENTER FOR BIOETHICS
UNIVERSITY OF PENNSYLVANIA

DR. MAGNUS: Right. This is, I think, the most general paper.

Thank you very much for giving me the opportunity to speak to you about this subject.

Over the past several years, public response to gene therapy and other innovative therapies have been very interesting, especially in light of the recent death of Jesse Gelsinger at Penn.

The public for several years has demanded that new and better therapies, including gene therapies, be developed as quickly as possible. Many articles have been written bemoaning the obstacles to getting patients enrolled in clinical trials and the barriers to getting research out to develop products.

At the same time the response to the Gelsinger death suggests that the public also believes that no persons should be harmed in the process of research, and I might add it would be nice if no animals were hurt either.

On the surface, to those with knowledge about research, these would be seem to be contradictory desires and evidence of a schizophrenic attitude on the part of the public. This is not necessarily the case.

The two statements only conflict provided an adequate understanding of the necessity of human subjects research even without possibility of benefit and substantial risks that must be undertaken to make medical advances. This has simply not been conveyed to the public.

If computer models, animal models, research at the cellular level and theorizing were together sufficient for a full understanding of the impact of new therapies on humans for good and ill, there would be no contradiction between the two public demands.

The biomedical research community, including the bioethics community, has failed to convey the need for human subjects research to the public. The number of variables in research on humans is far too great, the human body far too complex a system for us to be able to predict what the impact of a given therapy will be on most humans.

Treatments that work well on animals and even on human cells often fail to benefit when applied to a human subject. This not only happens, it is the norm.

Similarly, it is difficult to understand all the risks that a human will be exposed to until a trial has actually been performed. Even then long-term effects and dynamic interactions may not reveal problems until much later.

In the comments that I will be making I will be considering the case for -- the fundamental case for and against the value of research in human subjects at all, and try and derive a few conclusions, particular conclusions about protections from them. But I think

it is important to remember that in the end the best safeguard to protect subjects is ensuring that they have a better understanding of the nature of the benefits, risks and burdens of research and that a well-informed public that engages in subjects as subjects in research, and to an increasingly large degree, is in the end much better than any form of protection that we could really offer.

First, what is the value of research on human subjects? Fundamentally there have been two sorts of justifications about why we should allow research on human subjects. First, there is scientific or intrinsic value to the research. We are interested, in general, in knowing things about the universe. It is the reason why we -- one of the major reasons for justifying science at all. And, of course, research on human subjects deals with issues that are of particular concern to us and, therefore, there is a great deal of intrinsic value in research on human subjects.

Secondly, there is also instrumental value attached to research on human subjects and this often goes without saying but it is important to remember that this is an important moral good to society as we develop better therapies, better preventative agents, better palliative agents that all come about as a

result of research.

In addition, we also as we develop more knowledge -- I mean, it also goes without saying, we learn more about some of the problems associated with other kinds of treatments that we already offer. Think about the research that gave rise to the discovery that Phen-Fen had some deleterious effects in terms of heart valves.

Clearly, these are important and in some sense it means that scientific research, including research on human subjects represents a kind of social good. It is important to note that it is only a contingent good, that it is a good that society as a whole has deemed of value and something that it is willing to make a commitment in as a social good but not necessarily something that is necessary. Society does not require medical research in order to continue to survive as long as the death rate and the birth rates remain more or less in balance. There is no way in which this research is absolutely necessary.

Given that this is a social good, there are nonetheless problems that arise for research that really call into question whether or not the extreme view that Jonathan presented a little bit, the extreme form of protectionism, namely we should not allow it

all, does not, in fact, have some philosophical justification.

This particularly is a problem when you consider research that has no -- is not designed to provide any therapeutic benefit but conveys risks to subjects engaged in research.

For research without any -- with any substantial risk of harm to the subjects or even a highly uncertain risk, researchers and would be regulators face an acute moral dilemma.

Phase I research can be done, whenever possible, on healthy volunteers. This involves exposing people to risk for no possible direct benefit. Allowing medical practitioners to knowingly harm or risk harm to healthy subjects without any prospect of their personal benefit runs counter to some of the most central ethical tenets of the practice of good medicine. Do no harm is a moral norm that is firmly entrenched in the ethos of health care.

The ethical picture concerning the justification of research becomes even darker when we realize the motivations for many of the subjects of this kind of research.

Financial gain: Paying research subjects either monetarily or in services has become an

increasingly important part of Phase I research. Payment may produce several problems, including subjects who do not attend closely to the nature of the risks involved in participation, bias sampling in the selection of research subjects, and injustice as those with financial need are asked to risk their health for the benefits of others. Without payment, however, there may simply not be enough volunteers for research to be feasible.

The second harm in the dilemma of whether research can be ethically justified at all can be seen if the pool of subjects for Phase I protocols is restricted, when possible, to those who are already afflicted with a condition or disease whose treatment is being sought.

For therapies with substantial risk of serious harm, it is common to restrict research to subjects who are terminally afflicted with a disease.

There are serious problems with using the dying as a way to avoid the conundrum posed by undertaking research that is not intended to benefit the subjects. First, these are the most vulnerable subjects possible. They are sick and often desperate patients who have become reliant on the medical community for any kind of hope and for the alleviation

of suffering. They may be too ill to refuse suggestions put to them by clinicians regardless of their values in decision making when in a more empowered position.

Moreover, the desperation of many of these patients means that they are looking for benefit even when it really is not there. This often arises and occurs due to two complimentary factors.

First, the desperation of the patients may mean that they cling to a desperate hope that a trial with no real possibility of therapeutic value will make them well and represent their best last hope for a cure.

Second, clinicians who want to offer something to the dying are tempted to play to this desperation and often obfuscate the line between research subject and medical patient. I think this is, in fact, a real fundamental problem with the ethics of research for Phase I research on human subjects. This has already been alluded to but the line between subject and patient is something that is typically obscured in much Phase I research.

Researchers usually believe in the trials they pursue. This is often conveyed to the subjects. Indeed, many researchers defend the need to convey hope

to patients. Even careful researchers who have well-designed informed consent forms and say the right things to patients may also convey a sense of hope and cautious optimism that reinforces the things that the patients are looking for.

This seems to reinforce the desperate hope of the patient. Using vague and misleading language this may or may not help you. We cannot put a numerical value on any chance that it will help you. It can certainly help to reinforce the impression that the subject is a patient receiving therapy, not a subject in an experiment designed primarily to test the safety of a treatment, and with virtually little -- no or little chance that it will benefit the subject and a much greater chance that it will cause some form of harm.

Empirical studies have shown that as many as 85 percent of patients, cancer patients enrolled in Phase I trials are under the impression that they are receiving therapy. And in some qualitative research being done by some of my colleagues, they have found that patients enrolled in -- cancer patients enrolled in Phase I trials not only typically believe that they are receiving therapy but you can actually identify very clearly things that the clinician said that helped

to reinforce those beliefs.

If the primary reason for using terminally ill persons in research that lacks any real prospect of benefit is that they cannot be harmed. That is these are patients who are beyond harm or subjects that are beyond harm. And that reason could be used to justify experimenting on the same subjects for treatments that are unrelated to the condition that afflicts them.

In short, terminally ill patients would be utilized as human guinea pigs for any and all dangerous research projects on the grounds that they are beyond harm. This grisly prospect would seem to cast some doubt on the strength of this justification for using the population.

Moreover, the assumption that this population is beyond harm is also false. There are important differences in the way people die. For some patients they may well be better off preparing for the end at home rather than desperately clinging to a false hope while suffering indignities in a medical setting. For others, dying will be far less burdensome outside an invasive safety study than in such a study.

One other problem with using the terminally ill in safety studies is that in the end the Phase I studies may not really scientifically be of much value.

Depending on how ill a patient is, death may be a foregone conclusion so that little about safety is gleaned and it makes it easy to blame the underlying condition rather than the therapy for at least some trials.

The recent revelations of a number of undisclosed gene therapy deaths nationwide shows the problem with this approach. In fact, the first reported death from gene therapy, Jesse Gelsinger, who died at the trial at the University of Pennsylvania, revealed new safety concerns about the type of vector being used in that trial.

Had the patient been an infant with a devastating liver disease, OTC deficiency -- these infants are typically born with a life expectancy of often a few days, it is doubtful that any serious safety problems of the sort that came out as a result of the Gelsinger death would have been detectable.

In spite of all these objections, clinicians often behave as if it were irrational not to enroll in a trial, even a Phase I trial, if there are no other plausible treatment options.

This is especially problematic for conditions which are rare. Researchers need to enroll subjects from a very small pool and they may convey a

therapeutic goal and a false promise of hope when none really exists. In fact, even the name "gene therapy" is misleading for what are really gene transfer experiments with no real hope of therapeutic benefit at the present time.

Now are there solutions to this dilemma? There are several possibilities. One, we could allow people to engage in -- sorry. We allow people to engage in risky behaviors all the time. We let people ski. We let people become test pilots. We let people smoke. There is no reason why we could not, in principle, allow genuine volunteers, healthy volunteers, to be the test pilots of medical research as long as you really truly have informed consent and no coercion, and this might possibly require little or no monetary considerations. It may be that this will serve as a larger pool of research subjects than is commonly believed.

Second, we could consider changing the way we do Phase I research when we are dealing with situations with terminally ill patients and possibly combining Phase I and II research at the same time so at the same time we are starting to do safety studies on individuals. We can also be going quickly for particular individuals to higher dosages so that we

might at least have a potential that there might be some therapeutic benefit to them.

Above all, we need better informed subjects. Informed consent must be a part of any system of regulation but it must move beyond the current understanding of the concept. It is not enough for a clinician to state that a trial is a safety study and that there may be no benefit. That is done now.

All the right sorts of things typically are said and all the tapes we review of Phase I informed consent processes, the right things are said, the right things are in the informed consent form, but the underlying assumption of the research and the subtle cues involved in the interaction often nonetheless manage to convey to patients that this is their best bet and that this, in fact, is therapeutic and not -- then they are not simply subjects in experiment that has very, very little chance of having any benefit to them.

Better communication of benefits and risks and burdens of different kinds of research must be conveyed to patients and it must be done so through conveying information to the public as a whole. This helps introduce the conditions necessary to create an obligation on the part of the public to serve as

research subjects.

People who benefit from cooperative social schemes are obligated to bear the risks and burdens of participating in the activities that the cooperative endeavors require. There is something problematic about free riders who allow others to take on the risks and burdens when they fully intend to take advantage of these sacrifices.

For example, the decision to use a tertiary care teaching hospital can serve as quite a cooperative social endeavor and that means anybody who chooses to go to that kind of an institution agrees in principle to serve as a subject for demonstration and teaching purposes.

In terms of biomedical research, if someone benefits from care in a research institution, that would seem to suggest at least a prima facia obligation to participate as a research subject, and again this applies to patients who freely and voluntarily choose to receive care in a research setting.

But this means that patients need to have a much better understanding of the benefits and burdens of being a patient in certain kinds of settings and that any expectations need to be made clear at the outset. Moreover, curtailed power to choose the kind

of institutions patients want to utilize underscores again the importance of the willingness of patients to participate voluntarily in research.

The upshot of these arguments is the importance of informed consent of subjects is still an important aspect of protection from abuse although it may need a revamping and I think the sort of pernicious influence of language like autonomy has actually been problematic in seeing that simply conveying the right sorts of risks is sufficient when it clearly is enough, and it may mean that we need a successor notion to the concept of informed consent to do the work that informed consent currently does.

Second, patients need a better understanding of research prior to participation. Engaging in the medical system is a cooperative activity.

Third, current protections of relatively healthy volunteers from engaging in risky research needs to be reexamined. This is the one area where I think extreme protectionism could be problematic and run counter to the sort of libertarian argument that is really essential to being able to justify research on human subjects.

Fourth, it may well be that Phase I research on very ill terminal patients is problematic, and in

extreme cases, an argument could be made for combining Phase I and Phase II research and really changing fundamentally the way we do research on terminally ill patients.

PROFESSOR CHARO: Thank you. Thank you very much.

Questions by way of clarification?

No matter how fast you talked it is still clear.

Okay. It is 10:25. I would like us --

DR. MESLIN: Arturo?

PROFESSOR CHARO: Excuse me. Yes, Arturo?

DR. BRITO: Dr. Vanderpool's paper makes reference to Appendix A and B but only -- only A is out there and B is nowhere to be found.

PROFESSOR CHARO: It was -- the electronic version had it and --

DR. BRITO: Yes. I was not able to --

PROFESSOR CHARO: I am happy to provide my copy to you during the break. Okay. And we will make photocopies for you of Appendix B.

Okay. I would like to propose that we be back here and start promptly at 10:40 and then we will shave five minutes from discussion with the presenters and five minutes from our own discussion to get back on

track for the international report at 12:30.

(Whereupon, at 10:26 a.m., a break was taken.)

PROFESSOR CHARO: We are on the record again and I do know that some people are still grabbing the last cup of coffee or taking their seat.

As they do, I would like to just clarify what we will be doing at this point is a kind of combination of discussion as well as question and answer. People on the Commission should feel free to simply make observations without specifically directing questions to the speakers or to direct questions. And to the extent that a real dialogue develops among Commissioners, I would like the speakers to feel free to ask to be recognized so that they can intervene as well.

First, let me ask if there is anybody who would like to start the discussion from the Commission?

Bernie Lo?

DR. LO: First, I wanted to thank our panelists for their thoughtful papers and presentations.

DR. MESLIN: Bernie, could you go right into the mike for the people listening?

DR. LO: Yes.

DR. MESLIN: Sorry about that.

DR. LO: I wanted to ask a question which is actually a little different than what you have talked about. It is almost the flip side.

It strikes me as I read your papers, particularly Dr. Magnus' paper, that we do not have a very clear explanation of the rationale for doing research. What is the moral justification? Obligation is something I guess you would not want to agree with.

But it seems to me one of the things that is striking, for instance, when Jonathan talks of protectionism, what we hear from some segments of society is that they want more research and they think being in a clinical trial is the fastest way to get therapy for a condition for which effective therapy does not now exist.

And at least among some people, some clinicians, there is tremendous pressure to do more research, and it is not viewed as something optional that we can sort of forego if you have ethical scruples about it.

So I would like you all -- each of you to comment on that. Maybe particularly David and Jonathan since it was more in your papers. And could you also tie specifically to the issue of HIV research in developing countries? I think if there is a situation

that rises to moral urgency, it seems to me there you have an epidemic which is really causing a lot more than just quality of life.

But in Dr. Magnus' paper I was struck with, you the discussion you had of -- I guess going back to Hans Jonas saying that, you know, as long as you have got more people being born than dying, you do not really need research, the cycle can go on.

I mean, I am not sure that view would be accepted today where quality of life as well as just mere survival is at stake.

Also, does that hold for Sub-Sahara in Africa and the AIDS epidemic where, at least in some countries, the projections are the population is going to take a tumble?

So, I think what is -- the other part of this is what is, -- where can we find a coherent persuasive articulation of the morality of not doing research when -- and foregoing the goods that might occur?

DR. MAGNUS: Okay. Well, clearly I definitely agree that research has -- is an important value in our society. I think the fact that it is not necessary to survival underscores the fact that it is a contingent value, that is it is something that is not necessary to survival. It is not something that, therefore, there

is sort of a very -- that in some ways it limits the claim of an obligation on people to enroll as research subjects. But nonetheless it is of societal value and so society has decided that this is something that is important.

Now HIV research is interesting in lots of ways. The demand for more research is clearly there. That speaks to it as a -- perceived as a social good and perceived that the research is important and that it is a social good. But at the same time I think we have to be concerned when people want the research for its therapeutic benefit. That is for its immediate therapeutic benefit and see a therapeutic benefit to enrolling as a research subject.

And that speaks, I think, to the failure that the biomedical community has to communicate the nature of Phase I research to the public. Phase I, Phase II, Phase III research. These should be part of the common understanding of anybody who walks into a doctor's office.

This should be common language that everybody understands and it is not. So I think that the -- and so the trade off is between wanting to get to the final value, and wanting to get the end therapies that research requires, and the -- and making sure that, on

the other hand, that patients understand what they are doing and what the value is of engaging in the research.

DR. LO: Alta, if I could ask a follow-up.

One of the other reports we are working on is an International Report, and a lot of the impetus for that concerns the ethics of HIV research in developing countries where these are not by and large Phase I trials. These are trials sort of -- trials of interventions that are well tested and shown effective in the developed countries, and are modifications of dosage and administration and the like.

We are also considering proposals, recommendations that would require researchers to give -- help me with the phrase here -- effective and established therapies to the control group so that, in fact, in those countries, people would get a considerable clinical benefit from enrolling in trials. So these are not the Phase I studies you so nicely wrote about, but we are trying to develop guidelines that would cover both reports, in a lot of situations, and if you could help us there it would be --

DR. MAGNUS: Yes. Actually I want to say two things about that.

For HIV research, obviously one of the

exceptions, even Jonas in his original article, made an exception for plagues. Obviously, if you have got something that is really a scourge, that is sufficiently dangerous and lethal. In those times, you can actually make a case for a much, much stronger obligation because it is necessary for survival and you might be able to make a case that HIV represents such a scourge in developing nations. Clearly that is something that is of clear value.

But I want to say, when you are thinking about research in developing nations, I certainly would not want to overstate the value of that for those societies since, in developing nations, 80 percent of deaths are a result of waterborne pathogens and pollutants.

If you are thinking about bang for your buck, there is a lot better ways to spend resources than on research for improving the health of the populations overall.

PROFESSOR CHARO: Drs. Moreno and Vanderpool, did you want to add any comments?

DR. VANDERPOOL: I would like to add a comment.

It seems -- Dr. Lo has asked an excellent question. What is the real rationale? I think it is a

very complex and interesting cultural rationale.

Part of it is seen in the rhetoric we use. Alot of the rhetoric is war related rhetoric. Let's exterminate hook worm disease. Let's declare war on cancer. And once that rationale gets interred into culture, then it has its own power.

And I want to relate that rationale -- that rhetoric, to one concern I have for protection. As I hear Dr. Moreno's paper, I hear that part of what he would mean by greater protection would be greater surveillance.

But I think there are other avenues to greater protection. And one avenue to greater protection is to have a more careful scrutiny of the research initiatives that go forward. I mean, when -- after Richard Nixon declared war on cancer in 1971, we have had a war on cancer and we have had the SWOG group meet every few months in the Southwest part of the United States, and they approve hundreds of research protocols on cancer patients.

The thing about it is these research protocols are incremental, at best, incremental changes. Let's change a little cisplatinum there, a little bit of something else here, and let's hope to get a slightly better percentage. And so you have to recruit

thousands and thousands of cancer patients into these protocols for, at best, incremental changes, that over time have not made a heck of a lot of difference.

So I think protectionism needs to consider what research initiatives will really be effective and not keep enrolling and enrolling patients into initiatives that are surrounded with war time rhetoric that are not going very far. So that is a cultural analysis.

I could have some other points to add to that but I think I have made one important point.

DR. MORENO: I think that is well taken. Although I am not sure -- I think Harold and I would have to talk about the boundary between scrutiny and surveillance. It seems to me that deciding on national initiatives for research programs would count as a form of surveillance of what physician-investigators were actually intending to do but that is a semantic question and it does not need to concern us.

But back to Bernie's really interesting question. It is very hard to find, I think, a religious or philosophical tradition that does not encourage medical experimentation for the greater good. With the exception perhaps of a faith tradition, like Christian Science, that takes itself out of the secular

medical tradition entirely, it is really hard for me to think of one. And, therefore, I am -- at least from the point of view of wisdom traditions -- kind of at a loss to know where to look for a compelling argument in favor of the morality of fully foregoing research.

Even Jonas and Ramsey were not in favor of completely foregoing research. They wanted to do it with consent. And Ramsey, himself, took what, at the time, was a radical position and now would be considered a very moderate position on kids in research.

So I think it is very hard to find a rationale.

Can I say something, though, about -- if I may, Alta, about the liberty argument? I think David raised a very interesting point that you could argue that protectionism -- stronger protectionism-should not apply to healthy volunteers for the reason that people ought to be able to express their altruism or get involved in science, whatever it is.

But it is interesting, that liberty argument historically has applied to patient subjects, not to normal subjects. And the argument can go both ways, that patients -- and this goes back to the access issue as well -- that patients ought to have the right to

decide whether they want to take the chance and get into research.

As a matter of fact, the earliest arguments in favor of strong protectionism in the 19th century came with respect to normal subjects in vaccine studies. And by the way, vaccine studies are a context in which normal volunteers can potentially benefit. And so there are significant questions of compensation in those studies. Historically, there have been.

PROFESSOR CHARO: Thank you.

Steve Holtzman?

MR. HOLTZMAN: Thanks to all of you.

This was going to be a question directed to Dr. Magnus and Dr. Vanderpool's last remarks about the cancer trials that may play into it, and it has to do again coming to this notion of a therapeutic misconception.

And what I am having trouble squaring is the descriptions I hear from philosophers talking about this, which is the phenomenology of my experience when we are doing Phase I trials.

And what I mean by that is, when we are going into a Phase I with healthy normal volunteers with a 5LO inhibitor for potential use in asthma, and all we really care about is looking at PK and PD, it is very

clear to the subjects what is going on there.

On the other hand, when we are doing a Phase I, with deathly ill cancer patients with a proteosome inhibitor; yes, we are looking for, the dose limiting toxicities but those people are there, also quite rationally, hoping against all odds that maybe their metastases will shrink and a couple of times it does.

All right. So why is that a therapeutic misconception? Why are we being dishonest? All right. We are not and I just -- the phenomenology that you guys sometimes describe here, you are talking about these "trials," thousands of trials to just adjust the cisplatinum, and it is not. These people are dying. All right. You have got to go in and you are making modifications.

It is not a lot different than the practice of medicine where you are trying to make the adjustments so I am just having trouble because I live this stuff.

DR. MAGNUS: That seems to me to be exactly what the problem is, though. If you think about Phase I trials, especially the early -- I mean, it is a continuum. If you think about the beginning of a Phase I trial where you are starting off at 1/1,000th of the dose necessary to have any effect according to your animal studies, there is -- I mean, there is no chance

that this is going to help these patients and it also depends on the therapy.

Think about all the gene therapy trials on cancer. By now it is pretty clear, that if you are doing a Phase I trial on HSTKGCV system, there is not going to be any therapeutic value to that. I can tell you that right now.

Somebody might get better. You might get a little too much shrinkage. They might get that if they take some laetrile, right. We do not apply -- I think we do not apply the same standards of evidence when we think about the potential value of Phase I research that we have applied to, say, unproven, complimentary medical systems.

If we had the same attitude and the same critical scrutiny of value -- of therapeutic value of Phase I research that we do to those other things, we would see that, really, it is not therapeutic and we need to draw a sharp line there.

If the patients are there because the --

MR. HOLTZMAN: But my objection is, you keep saying it is a Phase I research. Phase I research covers an enormous gambit.

DR. MAGNUS: That is true.

MR. HOLTZMAN: All right.

DR. MAGNUS: Okay.

MR. HOLTZMAN: Sure, you are absolutely right. I mean, we walk into that knowing, right, that most drugs fail. All right. And when you are starting with a lower than expected dose, it is not working. You are building up to your maximum tolerated dose. That is one species of the genus (sic), is Phase I research.

DR. MAGNUS: That is right.

MR. HOLTZMAN: It is another when I am going in at full bore, okay, to someone who is going to die in two weeks. All right. And, in fact, we revert their metastases. That person can very rationally, and we can be with appropriate disclosure, not misleading them in saying, "Look, most drugs fail." Okay.

DR. MAGNUS: Okay. Our experience -- again, I think it is a continuum, but I also think looking at the tapes and the conversations of the Phase I trials, at the qualitative research that has been done, the right sorts of things have been said. You are right. But the way it is presented, and other sorts of things that are said convey, you know, I think a far greater sense of optimism and of therapeutic value than really exists.

The probability even for late Phase I research on cancer -- for, you know, late -- depending on how

far the metastases is -- is extremely, extremely low that this is really going to help them.

And so if they really think this is their best chance, and that they are in it primarily for a therapeutic value, it seems to me that they are in it for the wrong reasons, and that is misleading them. These are very vulnerable subjects, who have been taken advantage of, and especially when you add all the incentives on the part of the researchers to do the research, both economic incentives, publishing, promotion, all those sorts of things, it seems to me that has created a system where we feel very comfortable allowing patients to feel that there is a therapeutic value when there really is very, very little or none.

PROFESSOR CHARO: Eric Cassell?

MR. HOLTZMAN: Can I just --

PROFESSOR CHARO: Very, very briefly. Only because with three people on the panel, it is tough.

MR. HOLTZMAN: Yes. Go ahead. Never mind. It is okay.

PROFESSOR CHARO: Are you sure?

DR. VANDERPOOL: I tend to agree with Mr. Holtzman, though, and that is that I think for some patients in Phase I cancer trials, this is their hope.

It may be thin. And then the challenge is to give fully informed consent about the hope, and for the physician to recognize that at this point, you are a researcher and you would be very wary about recommending that, yes, if I were in your situation, I would go on it because that is when the consent form may as well be tossed out, because that physician trust is communicated as researcher trust, and that is difficult to do. But for some patients it is the chance they have and they still want to go for it rather than go fishing.

DR. MORENO: Can I just add I think that the question of therapeutic misconception needs to be treated as a psychological question and I do not know, Diane, if any psychologists have taken up this question but you could, in theory, if it were ethical, and you could get it passed by the IRB, manipulate the variables in such a way that you could find out what it was about the situation that led to people, if they do, led to people being misled or allowing themselves to be misled.

For example, what if you had brought somebody into an office building, being met by somebody who did not have the M.D. diploma on the wall and was not wearing a lab coat, rather than a hospital and the lab

coat and all the paraphernalia and so forth. Would that make a difference in the way people feel about the situation, and would they be able to filter the information, without the impress of the great medical institution into which they have just been taken up on the elevator and passed all the offices with all the impressive looking scientists and laboratories?

So it seems to me that there is -- this is partly an empirical question and that we can identify whether the elements of -- if there is already such a thing as therapeutic misconception, which I take there to be, if those elements can be modified or managed.

PROFESSOR CHARO: Eric Cassell?

DR. CASSELL: It is tempting to jump into that but I do not want to do that.

Jonathan, you make a point about the changing intensity of -- I will call it -- investigator virtue, over the period of time and how, as we go to strong protectionism, we may act to diminish further that virtue. But don't you really understand that this virtue has, in fact, diminished -- appears to have diminished? Also, it is an empirical question, you know. So we are driven to increase the protection and so forth and so on, on up the -- but nobody has, so far, suggested that if we decrease the protection that

it is going to increase the virtue, have they?

DR. MORENO: Well, we might this morning. Look, I do not think that there is a direct -- an inverse proportion between the virtue of people who in a certain era happen to be in the medical profession or in medical science, medical research, and the amount of regulation that society imposes.

In other words -- and I certainly do not have any reason to think that my colleagues today in Charlottesville or anywhere else in the country, at least, are any less virtuous than their predecessors 100 years ago or 2,000 years ago.

So I do not think that any alleged --

(Phone tone.)

DR. MORENO: I am sorry. I am busy now. I am talking about the --

DR. CASSELL: It is the wrong answer. That is what that is.

(Laughter.)

DR. MORENO: It is Henry Beecher calling to support me.

(Laughter.)

DR. MORENO: From the great beyond.

DR. CASSELL: You did not know him very well.

DR. MORENO: So I do not think that the

decrement -- any alleged decrement, or speculative decrement of virtue among physicians, is the reason we find ourselves where we are in our regulatory system. I think it is because of alot of social, economic and political developments, and to some extent philosophical evolution. Not because doctors or physician-investigators are necessarily less virtuous than they were 50 or 2,000 years ago.

DR. CASSELL: Just one quick follow-up. You said you did not know of any faith tradition where -- which did not support research. Well, actually during this scholastic era when all knowledge was really knowledge of the evidence of God, investigation into the natural world just was not part of it and did not come along until Roger Bakken and that is already by the 13th century.

But since that time, it is not about research. It is about knowledge. It is a position about knowledge and secular knowledge versus purely theological knowledge.

DR. MORENO: Well, they still supported observational research à la Aristotle. I mean, they still supported classification.

DR. CASSELL: Oh, no.

DR. MORENO: They preserved. They preserved

the science classification.

DR. CASSELL: They preserved that but they did not do their own.

DR. MORENO: Well, they did some.

DR. VANDERPOOL: Could I add --

PROFESSOR CHARO: Yes, Dr. Vanderpool?

DR. VANDERPOOL: -- a footnote to this?

The Jewish tradition in the wisdom of Bensark, (sic) 200 years before the rise of Christianity, blessed the physician as an instrument of God. Christianity comes in as a healing cult and beats the Clupeine (phonetic) cult, and Muslims developed institutions and so on.

So I think Dr. Moreno's point is secure that religious traditions really are pro-healing for a whole host of different reasons, but part of it is the sake of special -- specialty needy people and one is giving a particular kind of blessed concern when one cares for the sick.

So I very, very much agree with his point on that score.

PROFESSOR CHARO: Alex Capron?

DR. CASSELL: Except the Christian tradition was anti-medicine until quite late into the era and religion -- and priests were conjoined not to

participate in medicine.

DR. VANDERPOOL: Right.

DR. CASSELL: Healing, yes. But medicine, no.

DR. VANDERPOOL: Christian happens just to capture it by superstition about the Fourth and Fifth Century and beyond. But I think you raise a really important question about physician's virtues, and I do not think we just should let that go. I mean, I think our training programs -- another way to protect is to protect at a national level, in terms of what research initiatives can go on.

Another way to protect is to protect through training programs, and there -- in my own university, we have had very good responses to physicians and fellows, as they explore research ethics and see who they are and what they can do in this arena.

So I think we -- too long we have just kind of let it slide instead of seeing this as a special calling for physicians to exercise their minds and their hearts at the same time.

PROFESSOR CHARO: Thank you.

Alex Capron?

PROFESSOR CAPON: I am going to forebear from engaging in this theological discussion. I want to take you back to your basic framework, Jonathan, first

as a question.

Yesterday we heard from Jeff Kahn, reminding us that his view of the post-Belmont era is one of the movement from the protection to inclusion, and a view of -- emphasis of the benefits of research, and you have in your own paper that quote from even research is treatment or some such phrase from ACT-UP.

And it seems to me that what we see in all of this, is a question of whether we favor type one or type two errors. If a type one error is the inclusion of an unwilling or unwitting person as a subject in research, without full information and voluntary consent, and a type two error is the prevention of a research project in which there are willing volunteers but it is judged to be unacceptable.

In the early days of the space program serious thought, as you know, was given to sending up a manned vehicle, that would not be capable of returning, and that would create, in effect, glorious heroes of those who undertook that trip to the moon and there would be no lack of volunteers among the astronaut corps for that.

And yet NASA concluded that it could not do that. Partly it was public relations that they thought that, in the end, the public would not be fully

supporting. But they also concluded, I believe, that it was -- that was a type two error that they did not want to commit.

And it seems to me that you are -- you are suggesting that we are in an era of moving more towards trying to prevent type one errors if I understand you correctly. Is that right? I mean, that is the way you -- if you are looking at a historical sweep of things, that is the direction?

DR. MORENO: I think that is right, yes, in the long run, and I would say that the emergence of inclusionary efforts -- what I call sessionism --

PROFESSOR CAPON: Yes.

DR. MORENO: -- not in the therapeutic sense but in the scientific sense, is to say justified, by the need to know more about how drugs and devices affect populations who have not historically been included in systematic research. That is completely compatible with protectionism as I understand it.

PROFESSOR CAPON: I guess this is simply a question of -- for which no one has any answer but it is, in a way, exploring what you raised with one of the earlier questions. And that is why we would expect that if we move in that direction we would 30 years from now bemoan, as you put it, the lack of virtue.

The late Grant Gilmore famously remarked about in heaven there would be no laws and the lion would lie down with the lamb and in hell all activities would be regulated.

(Laugher.)

PROFESSOR CAPON: But what he -- it is not clear from that kind of a remark whether it is -- that heaven is achieved by the absence of laws, or rather in a situation in which you have only virtuous persons, who are fully angelic, that you would have no need for that, that the lion in heaven would not eat the lamb.

I do not see the connection running the other way. I mean it does not seem to me that the fact that we have laws against certain activities, in fact, makes people less virtuous because they decide to be law abiding, that they -- I mean, it is sort of a view that all they are doing is obeying the law and they have no virtue, and they become unregulated were it not for the fear of the law.

I guess that is your -- but I want to understand is, that your suggestion that that is the direction in which things inevitably move, as we try to be more protective?

DR. MORENO: Well, not to be outdone in reference to the great sages, that great protectionist

philosopher whose work also emerged in the 1960's, Woody Allen, observed that the lion shall lie down with the lamb but the lamb will not get much sleep.

(Laughter.)

DR. MORENO: Which is absolutely irrelevant to your interesting question.

(Laughter.)

DR. MORENO: Look, I think the question which Harold indirectly related also in his remark about education, can virtue be taught, or are some simply born with it, or do they acquire it in some mysterious way, perhaps by inspiration from God. It is not one that I am prepared to answer this morning, nor do I know, therefore, under what circumstances there would be a decrement of virtue in an individual or group.

It is entirely possible that, what you say is correct, and that it would not make any difference if say, people on hard money at an academic medical center who were not involved with the research, had the job of recruiting the subjects and doing the consents and doing the reviews and observing all the research maneuvers and procedures and functioning like a DSMV and deciding when they should be in or out and basically stay on the back of the investigator literally continuously.

That may make absolutely no difference with respect to the way that the investigator sees his or her moral relationship to the patients or subjects. It is entirely possible. It is an empirical question again.

But I will bet you that if we move to a system like that, 30 years from now, somebody like Eric Cassell will be sitting at a table or perhaps simply communicating through the ozone through our brain top -- brain inserted computers to each other at the next Commission that something bad happened recently. And the reason is that we moved to this system where these guys are constantly being tailed by people, who have taken the moral responsibility for their relationship with their patients or subjects from their shoulders.

Now will that person be right or not? I do not know and we are playing what Isaac Asimov called "The Future History," a kind of parlor game.

Again, I think it is a psychological question. I am not really prepared to do anything but speculate about it.

DR. CASSELL: But you were not arguing against the education of investigators like Harold suggests? You are not suggesting that that might diminish their knowledge of ethics and so forth, are you?

DR. MORENO: Well, I think it certainly enhances and contributes to their knowledge of the history of research ethics, of philosophical issues, of the rules and so forth.

How it actually influences their conduct, I do not think anybody knows. It is very hard to measure the outcomes of ethics training in the professions.

PROFESSOR CAPON: It has not been done much, right?

DR. MORENO: It has not been done and I am not sure we are very good at knowing how to do it.

PROFESSOR CHARO: Arturo?

DR. MESLIN: Harold?

PROFESSOR CHARO: Oh, I am sorry, Harold. You wanted to make a comment?

DR. VANDERPOOL: Yes. Just one comment. I think that I am very wary, though a historian, of ever predicting what the future will be. I think it is basically a set of surprises.

But I think one can construct just the opposite argument historically built on Eric Cassell's interesting survey of the degree to which clinicians have been regimented through managed care.

We could face a backlash against, that in the coming years, and the orientation could be, please get

off of our backs. We will do what is necessary to deserve your getting off of our backs but get off of our backs.

And so I would hate for researchers to be, -- first of all, you regimate medicine through managed care and then you regiment research medicine through a whole set of surveillance mechanisms. I mean, I would tread carefully on that if there are other ways to do it.

PROFESSOR CHARO: Arturo?

DR. BRITO: This has to do with -- actually it kind of comes full circle here because this has to do with Steven's concerns earlier in a conversation, and something you mentioned, Jonathan -- I think it was you -- during your talk about the therapeutic misconception from the investigator side. And Jeffrey Kahn made mention of that yesterday.

As far as I am aware, there is -- there are no psychological studies of physicians, who are also investigators at some point in time, of how they contribute to that therapeutic misconception, and I think it is an interesting point and something that needs to be looked at. Not necessarily regulated but just something that needs to be looked at and some education for the physicians themselves in that area.

I, myself, have found myself in that position at times.

I wanted to go back to the process, Dr. Vanderpool, about the -- that you have talked about and written about the process of informed consent, and that is something that I have -- I have thought about for quite a bit and read a bit that Appelbaum and others have written about that, and more from a longitudinal point of view.

How does one go about assuring, in a regulatory fashion, that that process is adhered to when we know that, at the onset people get a document, a written document, and it is very hard to absorb all that information and understand it regardless of your educational level or your point of vulnerability?

How does one regulate, or not regulate, but how does one make suggestions for regulations that do that? I just got the appendix now but I do not think it is in there. Any suggestions of over a longer period of time, you know? Do you have any suggestions in that?

DR. VANDERPOOL: Well, my belief is that, if one revises the Federal Regulations where the basic requirements of consent are no longer informational items on a consent form, that you already have gotten

somewhere.

If what you look at, day after day, is the three items -- basic elements of informed consent, are voluntarism, comprehension and information -- the IRB is going to spend some time on voluntarism, comprehension and information. And that to me is the process of consent.

Now whether that will ever get back to the research subjects, it is still there, day after day. It is what they are supposed to be doing as they review protocols and as they structure protocols.

So what I am saying is, try to insert institutionally the kind of conceptual apparatus and the language that goes with it that make it a process.

See right now we preach about Belmont, and we preach about process, but when you look at the Federal Regulations, the Federal Regulations have a primarily rule orientation towards consent forms. And, by golly, most IRBs, the ones I have concern about, have gotten the message. Let's refine the consent forms, let's make sure they say the right things, and you spend a lot of your time just making sure that consent form is right.

And so it seems to me that just very basic things can restructure the way you look at consent and

if the three elements, as I say, are voluntarism, comprehension and understanding, and you are pretty clear about what this is, then you are going to be asking in your committee meetings, do we think these people are really in a situation to volunteer.

Do we think they comprehend what is going on? Do you think there is a test we need to have the researcher do, in order to see if comprehension is occurring?

And then what is on the consent form in terms of comprehension, and do we give them time and what all to do that comprehension?

That is my point. I am not for preaching anymore. I am for plowing something into the regulations that make it into a process ipso facto as it is being analyzed.

PROFESSOR CHARO: Eric Meslin?

DR. MESLIN: First, just a point of commentary on something Jonathan had said. I want to give him a chance to either confirm that this is what he meant, because he was referring to NBAC, and then maybe ask a question of the panel.

Jonathan, in one of your overheads you included NBAC's Capacity Report as part of the historical legacy of some of these issues. Because

there has been much discussion about the impact of that report, as being one that is proposing a significant increase in the types of protections for a particular population, I would be interested to know whether you were implying that that is the exclusive legacy of NBAC's four reports, or you are only including the Capacity Report as an example of that version of protectionism. Because clearly some have argued, even in the literature to which letters have been written in response, that NBAC's HBM report goes the other way and offers too little protection in the way of consent and such.

So I am just giving you an opportunity to either clarify that point because then it will allow me to ask David another question.

DR. MORENO: It was only with respect to that report and, indeed, only with respect, as I say in the paper, to the recommendation concerning independent capacity assessment for nonbeneficial higher risk studies.

DR. MESLIN: So the good news is for Commissioners, as we are watching how our reports are being interpreted out there, I do not -- I would not want the public or Commissioners to assume that there is a linear progression that NBAC simply is writing

reports about protection.

DR. MORENO: Not yet anyway.

DR. MESLIN: Not yet.

PROFESSOR CAPON: We are all over the map.

DR. MESLIN: Yes.

(Laughter.)

DR. MESLIN: So here is -- my question really is focused to David but could go to all three. And it is if you could imagine -- although it is not in your paper, but could you imagine what the strongest possible case would be, philosophically strongest case would be, for inclusion of individuals in research?

What might that look like? I mean, it follows up on something Bernie asked really at the outset, and you touch on it in various places, and I am not asking for a dissertation. I mean, it is 20 minutes after 11:00 and we have other questions to go but --

DR. MAGNUS: Well, I think it is a combination of the perceived good of the research combined with the libertarian argument. I mean, we allow people to engage in risky behaviors for bad reasons, given that this is a socially desirable end, allowing people to genuinely, in an informed voluntary manner, engage in research. That seems to me to be difficult to see why -- what there could be to stand in the way of accepting

that.

PROFESSOR CHARO: Others? Marjorie?

DR. SPEERS: I have a question that I would like the three of you to address.

When we undertook this project, this oversight project, we began by asking some very basic questions. One of those questions was, what is the purpose of a federal oversight system, and the purpose of federal regulation.

As a result of asking that question among ourselves, we asked the three of you to write your papers on the various positions.

Having heard your papers today and thinking about this topic, and knowing now that the Commission needs to move forward and make recommendations, it makes -- it causes me to raise the question of what is the purpose, what ought the purpose of a federal oversight system should be. And can it be a multiple purpose? Can it have multiple purposes? That is, to enhance research, or promote research to protect individuals who participate in research, and to promulgate ethical principles, or try to make us more ethical perhaps than in our research endeavors.

My question is, can we -- could we have a system, an oversight system and regulation that can

meet those three purposes?

DR. MORENO: Yes.

(Laughter.)

DR. VANDERPOOL: Yes. I think we can and I think Belmont does a pretty good job of it. It is not a perfect job but a pretty good job of it. Belmont does not promulgate ethical principles just to be promulgating ethical principles. Belmont is doing the ethics of research in order to protect subjects and protect research. I think that is what it is there for. It just uses ethics as a tool. For those two purposes, and it seems to me those two purposes say that we need to both promote research, protect research and we need to protect human subjects.

So it is not an easy challenge that you all have to find that balance, an effective balance. I would like to see the protections increased but the research enterprise preserved. But I do think there is a lot of research that probably is superfluous, in terms of dangers, and perhaps these people have a loss of confidentiality and so on.

So I think the research purpose -- the research enterprise will need to be modified at a certain point and expanded at other points but the research enterprise itself will continue but I think we

need them both. I think we need them both and I do not think we should see ethics in the spirit of Chalmers' last comments. We should see ethics as something superfluous to both these purposes, the promotion of research and the protection of human subjects.

PROFESSOR CHARO: Jonathan Moreno?

DR. MORENO: I will expand on that at the risk of sounding facetious. I think it is in the underlying theme that you identify, that unites those elements as the public's trust in the research enterprise, and since the New Deal anyway, federal regulation has been regarded by the general public as a way of ensuring that, more or less, public institutions are operating according to some standards of integrity.

Those regulations were not often -- in fact, were not usually the result of some incident that was directly relevant to them. Thalidomide gave rise to new authority for the FDA that it had before thalidomide. Prison research scandals were not the reason that prison research has been so contained. But there were political and sociological factors that seemed to impel the need for regulation.

So it seems to me that that is the underlying motivation, and now the question is, in 2000, what kind of system will insure the public's trust. That is what

is really going to drive, I think, what comes out of this era more than any specific incident. It is the way that that incident is processed in the public mind, and the response that government regards as necessary to allay public anxiety. That is what is going to drive this.

PROFESSOR CHARO: We have approximately between 10 and 15 minutes left for discussion, and the people I have left on my list are myself, David Cox, Bill Oldaker, Alex Capron. Are there other people who would like to get on the list, the infamous list?

DR. VANDERPOOL: Could I make one quick footnote to Jonathan's comment about the public trust?

PROFESSOR CHARO: Sure.

DR. VANDERPOOL: To me the looming problem will be the degree to which industry becomes involved, and co-opts many things in the research enterprise, including the privacy of research data. And that is just a huge problem and I think we are looking at new anti-industry -- and we may end up returning to the '60s when people said, you know, "Power to the people."

But, I mean, we see already against the Organization of American States and the World Trade Organizations, we see the anti-industry approach. Well, industry is getting the reins of research in an

unprecedented way, and one of your real challenges is to say, how do you keep the public's trust in research when industry is doing more and more of it and keeping the results to themselves?

PROFESSOR CHARO: So it would be fair to say that there is another goal here, which is to make sure that the lamb can sleep regardless of whether it would get eaten?

DR. MAGNUS: Can I --

PROFESSOR CHARO: Yes, Dr. Magnus?

DR. VANDERPOOL: It is your metaphor and I love it.

DR. MAGNUS: Two things. One, again I just want to reiterate the point that one of the problems that could erode public trust, is the fact that the public does not understand the nature of research. And if they do not understand the nature of the research, they do not understand why people are hurt or die.

I mean, if the public thinks that most -- initial research where most of the most important facts are able to be done for safety before you ever get to human subjects, that is going to be a real problem in terms of public relations, if you will, when you have -- when people are hurt during the course of Phase I research.

The second thing I want to say, though, is about the general issue about regulation and a sort of caveat about the ability to be able to construct regulations that are going to be able to achieve all of the goals that you laid out.

It seems to me it is sort of history and some of the history that Jonathan was talking about earlier. The regulations that we have got now are a legacy of a historical context that was developed in response to certain kinds of scandals and they do a pretty good job of stopping those sorts of things from happening again.

We have got a system really that does a great job of making sure Tuskegee does not happen again. But it is not clear that the concepts of that, and the basic framework that we utilize, it seems to me, is going to be adequate for moving forward. But it is really hard, once you have got a framework in place, to do more than just tinker with what you have already got.

A sort of analogy would be the typewriter. The QWERTY system, the standard typewriter, was designed to be not an optimal keyboard, but a keyboard that was optimal in the early 20th Century when, if you typed too fast, the keys got stuck. So they designed something that would go fairly fast but not too fast.

Well, we have been stuck with it ever since, even though we now could -- now we do not have to have that problem and we could have much, much more optimal keyboards.

So I worry that we are just going to be tinkering with something that is really designed with problems that are outdated.

PROFESSOR CHARO: David Cox?

DR. COX: First of all, I found this panel incredibly instructive and to the point, so I would like to thank all three of you. It has really helped focus me.

Specifically on this point that, ironically, ethics are not part of the regs. I will just reflect in my experience as a biomedical researcher that, when I speak with most of my colleagues that is, the fundamental problem, is that they do not actually see that the regs have anything to do with ethics. And that they do not understand how ethics is involved with research.

So all three of you have said that and I would just like to put on the record that that is a fundamental thing that we have to deal with or else that we are not going to either advance research or protect human subjects.

Now my question, though, is to David because it was the most troubling thing to me, and it squares with the reality that I have experienced.

You can say the right things and you have all the things in the informed consent, but it is the wink and the nod that basically causes the problem.

If we simply focus on saying the right things, and even if we focus on the process, it will not deal with the wink and the nod issue.

So how can we even begin to deal with that at a practical level? Not on a philosophical level but at an implementation level, because this is the part that worries me the most.

DR. MAGNUS: Well, there are obviously several different things that can be done ranging from not doing certain kinds of research, and the way that we do on those subjects who are vulnerable to also guaranteeing more quality assurance for those patients ranging from making sure that it is not the investigators doing the informed consent process.

Some institutions, when they are doing research on HIV patients, to avoid these kinds of problems, they have people who are not the clinicians themselves doing the informed consent process to make sure that they do not have those kinds of problems.

You could also tape the informed consent process. I mean, it was really illuminating when my colleagues at Penn were taping informed consent processes, and doing analysis, and doing coding schemes of them, which were not very hard to do, to see the sorts of things that were said both -- and you could detect the wink and the nod in the course of taping those things.

I mean, if we did something like that where it was commonly -- where these were commonly taped and maybe randomly just examined -- not necessarily for an oversight or policing purposes but just from an informational point of view, where somebody could say, look, here is where you might have misconveyed therapeutic value of this to the patient right here, that might be helpful.

DR. COX: So just to reflect back, because I think Steve Holtzman has really, you know, said in a very nice way numerous times, he reminds us of the richness and the texture -- textural complexity of what we are doing.

So what you are saying is that we have to also keep that in mind, and so have a textured level of regulation. But your primary basis for the texturing is the vulnerability of the population.

DR. MAGNUS: Right.

DR. MORENO: Can I also jump into this, David, just to respond to your observation, which I think is right, as Harold points out that our physician -- our investigator colleagues do not perceive the ethics in the regs.

It is worth asking ourselves how human subjects research, and the activities of researchers, acquire moral integrity in the eyes of the public and in the eyes of the profession before the regulations. And it is striking but I think that the most important way that happened was that in very novel, cutting edge, controversial -- potentially controversial research, people self-experimented, and that was widely publicized by the profession.

DR. COX: Indeed.

DR. MORENO: And I mean we have Walter Reed that inspired -- an example that inspired several generations of later researchers to do the same thing. Even, as for example, in the first polio vaccine trials in the early '30s when it made no difference because it would not affect them at all, the two investigators publicized the fact that they inoculated themselves.

DR. COX: Right.

DR. MORENO: And this gave people confidence that this was okay prior to an era of regulation.

Now, of course, auto-experimentation is frowned on today. Often it is simply irrelevant. Even more irrelevant perhaps than vaccine research. But it is something that I have sometimes thought about. What if we encouraged colleagues to engage in self-experimentation again rather than frowning on it the way IRBs do? What would that say to the public about the deep commitment that investigators had to their work?

DR. VANDERPOOL: I think Dr. Cox is exactly right about the wink and the nod part of it.

A real challenge we have, and I think this is primarily due to the final report of the Advisory Committee on Human Radiation Experiments, that floored me at first, and that is, how trust between researcher and subject is a problem, is a real problem.

And I think the question would be, if you really do have some good training about the distinctions between clinic practice and research, the doctor-patient relationship and the researcher-subject relationship, you are probably going to need to really -- you will have to spend some time on that trust and what all you can do to undermine informed consent, both

facially, both by body language and by words.

And unless that is done, unless you really do -- unless we think much more seriously about those distinctions, there are going to be some connections, too, but some distinctions. Physicians and physicians-in-training have to think. You know, well, wait, I have made a mistake if I do this with my subject.

Until you get to that level of sensitivity, it is going to continue. The wink and the nods are going to continue and then the consent form -- it will not matter whether it is five pages long, two pages long or what is on it, it is going to get signed.

PROFESSOR CHARO: Bill Oldaker?

MR. OLDAKER: Let me ask a question, if I might, that deals with -- emanates out of what David said about Phase I clinical trials having almost no hope of having any productive outcomes but some risk.

But looking -- and I guess that is something that is necessary. Is that right? Would you say that is a necessary part of research?

DR. MAGNUS: Yes, under normal circumstances.

MR. OLDAKER: Let me ask a broader question. To deal with that and make sure that people are informed, how do you create a regulatory framework that will inform people of that, because I guess that is

what informed consent is supposed to do, without causing the ability of research to go forward or without negating the ability of research to go forward?

DR. MAGNUS: Well, I mean, some of the things that we have already talked about are ways of guaranteeing that we have a better process. I think making sure that researchers do a better job of keeping in mind that they are conveying, in very clear terms, that their patients are subjects, not that -- sorry, that those are subjects enrolled in trials, they are not patients, and that that needs to be conveyed very clearly.

I think there are framing issues that are important and that we need to do a better job of educating researchers of those sorts of things. IRBs might be able to play a role in that.

There also might be ways, as I suggested, that for, at least some trials, that you could combine Phase I and Phase II so that you could have a more plausible claim to at least some therapeutic value in at least some cases for the individual. You might be starting off at very low dosages, but for that individual, raise the dosages so that you can make a more plausible claim that there is going to be some therapeutic value.

Again the biggest problem is for the first

patients. I mean, you cannot do research at all if you do not have those first few patients, and it is for the first patients that the problem is most acute because for them especially there is really no therapeutic value.

DR. MORENO: You could also prohibit the therapist from -- that is to say the primary care doctor from doing research on his or her own patients, and as in some European countries, I gather, separate those roles so you would have a continuing advocate for the therapeutic side for the patient and a very much more expensive system that I do not think we are going to see tomorrow but that is another option.

MR. OLDAKER: Thank you.

DR. VANDERPOOL: The other comment I need to add to this is that I hope this helps you rethink what the vulnerable populations should be. We tend to think of ethnic minorities and the poor. The most vulnerable, in many research settings, are those who are desperately sick and this is a major population, vulnerable population, for your committee to think about.

PROFESSOR CHARO: I would like to take advantage of an opportunity to ask a question of my own if I may, and it is something that is pertinent to the

International Report as well as the Domestic Report.

The Belmont Report and the International Codes consistently treat medical -- participation in medical research as fundamentally different than participation in other physically risky or psychologically risky activities, so that there is a demand that there be a scientific justification and risk minimization, and often a concrete benefit anticipated in the future to society as a whole, before one can even offer to individuals the opportunity to agree to participate, often in exchange for filthy lucre as it was called yesterday.

In the International Report, this has actually come to be quite relevant in our discussions about the point at which it is appropriate to say that people can, in fact, be invited to enroll, regardless of whether there will be any medical benefit by virtue of participation in the study, or any realistic expectation that interventions are products that are successfully developed would eventually appear in that population or for those research subjects.

I understand the history here and the political history here, but at this moment in time, do you think that a case can be made and, if so, how would it be made that participation in human subjects

research is different than volunteering for pay to be a stunt man in Hollywood, or a stunt woman, I suppose -- I have to be consistent with yesterday, right -- stunt person, there we go -- or any other kind of activity that we recognize as being dangerous, and often with very little significant public benefit, although great public entertainment in that case.

DR. VANDERPOOL: Alta, that is a tough question. I mean, there are offers you cannot refuse. You and I can refuse -- I think you can, I am not sure about me -- a $10 bill. But you give a $10 bill to someone in Guatemala and they are going to take the stunt option. And I think those can be very coercive, those kinds of things so that is my biggest concern about research in other settings.

Often times the patients do not end up getting the pay anyway. It is going to be the village chief and so on.

So the OPRR, as you know, has the standard that you have to do -- use equivalent standards in the field that you use in the United States. Now there is some discussion about what those equivalent standards are.

PROFESSOR CHARO: But, Harold, I am sorry but if I can be -- if I can clarify my point.

DR. VANDERPOOL: Okay.

PROFESSOR CHARO: I want to focus on a point that is prior to the moment at which we begin to feel like it is a Godfather offer, where somebody could, in fact, refuse and choose to earn money another way, but they are being offered this opportunity to earn money.

The current approach in this area is to say, that that offer cannot be made for one dollar or fifty cents until there has been a prior review that has minimized the risks, and that has determined that there is some gross societal benefit or scientific benefit that justifies making the offer at all.

So we do not treat it like an ordinary offer of employment, and my question really is in a noncoercive setting, is there a reason why we should continue to treat this in a singular manner?

DR. MORENO: I think the question, Alta, goes to the question why do we sequester medical activities from the usual moral hazards of other forms of human commerce? And I think the answer is that -- whether it is realistic or not -- we like to put medical -- the profession and medical activities in a different moral category. We like to think of it as having an integrity that is -- needs to be preserved against the day that you and I will need to rely on our -- in our

last days and moments on a representative of that fraternity.

I think that is why we do things that way and I think otherwise we cannot justify it.

We conclude that there is a difference in quality between the values of the medical profession, and the values of other human pursuits, and in spite of the short-term consequences, which can be baleful for many people, of holding medicine to a different standard, we think that in the long run, it is better for everyone that it be so.

PROFESSOR CHARO: Other -- David?

DR. MAGNUS: I would just like to agree with that completely. I might just also add that in addition to the sort of professional community of medicine, which gives rise to a sort of special ethic that is at stake here, it is also important to remember that medicine is dealing with the care of the body, and there is also a tradition of thinking of the specialness of the body in a certain way. And even outside the realm of the medical, it is one of the reasons why, you know, the things that I make I can own and I can sell and I can do certain things to, but I cannot for my body. That is true both within the medical realm but also legally, you know, I do not have

any property interest in my body parts.

So -- I cannot own -- I do not own my body. That is --

PROFESSOR CHARO: Just on the record as -- on the record from a lawyering point, let's just say that the law is horrendously unclear on this point, and quite varying from state-to-state.

Harold, did you want to add anything before I turn to the last question?

Alex, you will have the last word before we move on.

PROFESSOR CAPRON: I have a question for David Magnus but I wanted to note that, while I agree with this last exchange that medicine makes research -- even nonmedical research seem special, I think if we were sitting here with people with deep experience in securities transactions and labor law and employment practices, they would tell us that there are endless restrictions on free exchange of activities and money for all sorts of things.

And the picture that you painted, Alta, of this being so different, I think they would simply take strong exception to.

The question I had for David was in response to a question from Eric Meslin, who asked you to

summarize your reasons why research is justified. You did not repeat something which you had -- I understood you to have said when you were presenting your paper, which was this notion of a social obligation that people have, if they avail themselves of modern medicine, which is built on the prior efforts not only of scientists, but of prior subjects.

DR. MAGNUS: Right.

PROFESSOR CAPRON: And I wanted to know if you included that and, if you did, given other points in your paper where you turn to Hans Jonas' work and his writings on the subject, I recall Jonas as arguing against that view.

DR. MAGNUS: That is correct.

PROFESSOR CAPRON: And very strongly.

DR. MAGNUS: That is correct.

PROFESSOR CAPRON: You do not entail that. There was a vigorous debate between Dick McCormick and Paul Ramsey around the use of children in research, and part of the argument entailed there, too, was whether parents might reasonably consent on the basis that a child looking at what his life was, including his life as a subject, would say, "You did the right thing because I was fulfilling my obligation to society." And again, too, that was very controversial.

DR. MAGNUS: Right. Given the time limitations, I did not take time to go through the different versions of the social contract argument, but that is right. There is, at least, one version of the social contract argument that I think Jonas very persuasively argues against and that is laid out in my paper.

The sort of fair play argument, I think, is another justification for doing research. It is not just -- that -- I did not mention that because that is not -- that is even more than just a justification for research. That is in some sense, I think, a pretty good argument for suggesting that, under certain circumstances, there is at least a prima facia obligation to engage in research under certain circumstances.

PROFESSOR CAPRON: And you accept that?

DR. MAGNUS: I do accept that.

PROFESSOR CAPRON: Thank you.

<u>RECOMMENDATIONS - PURPOSE AND STRUCTURE</u>

PROFESSOR CHARO: We are going to move on to the next session but I would like to invite those panelists that can to please remain and participate, as seems appropriate, as we try to segue from the purposes of research to the structures that might accomplish

those purposes.

So the conversation is certainly going to be one that integrates those two sets of concerns.

I would also like to mention that, as you can see, I am a squirmer up here, and I have already gotten one request for stretch time.

Since we must end promptly at 12:30, I am going to suggest we continue the conversation but we be quite tolerant of one another getting up and stretching and walking, and listening while they are walking so that we can make sure that our limbs do not become frozen permanently in place.

Marjorie, would you like to say a couple of words to start us off on the structures, their alternatives, and maybe get people thinking of how they tie into the purposes they most want to accomplish?

DR. SPEERS: Yes. Okay.

We are going to switch gears somewhat here, from our previous discussion where what we have been hearing about and discussing has been the purpose of regulations, and based on that purpose then one would write a set of regulations and concentrate on the substance of those regulations.

What we want to discuss now is the structure, the federal regulatory structure, and this takes us

back to several meetings ago, where we have been discussing the current regulatory structure in terms of the Common Rule, some of the issues in trying to implement the Common Rule, and -- the roles of the various federal agencies in our current regulatory structure.

At least one meeting ago if not two meetings ago, we shared with you a wheel, a red and blue and black wheel, that graphically displayed the current regulatory structure. You should have in your packets of material that chart. So I think it will be helpful if you can refer to that chart.

We have blown up that chart as well as others for our discussion today and they are posted in the back of the room so that others can follow along.

Let me walk you through these charts. What I am not doing is going over the background material and I am not doing that in the interest of time.

In your packet, what we have done is we have -- as I said -- provided you with the same chart, the same wheel that we looked at a meeting or two ago, that describes our current regulatory system.

The second chart in your packet is the same current federal regulatory system minus the additional rules and regulations that the various federal agencies

have. And for those in the audience that chart is not in the back of the room for you. It was not posted.

We just gave you this one to take out the superfluous information and to leave you with the current regulatory structure under the Common Rule.

The next three charts that are in the back of the room describe the types of changes that could be made to the current system, and those changes are based on three key decisions that you need to discuss and decide where you want to go.

One of those decisions is -- one basic decision is whether the administration of the oversight system -- whether that should be a centralized function or a decentralized function.

Another basic decision is, whether the system should be extended beyond its current scope, and we can talk about scope in terms of extending federal regulation to other federal agencies that conduct research, who are now not part of the Common Rule, or even extending it beyond to include the private sector.

And the third basic decision is whether the regulatory structure should be uniform across all agencies and departments that are part of the Common Rule. This specifically addresses the issue of whether the protections, additional protections for vulnerable

populations should be common across all agencies as it is currently not.

So the possible changes that we have given in change number one in this model -- the current subparts would become uniform across all agencies. And what that would entail would be altering the Common Rule so that the Common Rule now becomes subparts A, B, C and D, and then each of the federal agencies who are signatories to the Common Rule would have to codify regulations of the federal policy.

The second change is one that would occur only within the Department of Health and Human Services, and that is simply to bring the FDA regulations and the HHS regulations together under one uniform set of regulations.

And then the third possible change is expanding authority to all human research and doing that through a single set of regulations coordinated from a central office.

There are many possible changes. We have only given you three of them to try to make the points and to begin discussion.

Various permutations of these are certainly possible but they certainly -- what they do lay out for you, is moving from perhaps what I will call modest

change, in terms of simply putting FDA regulations and HHS regulations together which could be done, for example, by a directive from the Secretary of HHS, to a more extensive change that would require an executive order by the President to request, or require, all of the current signatories of the Common Rule to adopt the subparts, to a major change that would require congressional authority to create a new regulatory structure involving one set of regulations that expands perhaps all of the Federal Government and could potentially include the private sector.

PROFESSOR CHARO: Thank you very much.

Would anybody like to get us started contemplating which of these seems to accomplish which purposes and best?

Bill Oldaker and Bernie Lo, first of all?

MR. OLDAKER: Go ahead, Bernie.

DR. LO: Well, Marjorie, I want to thank you. I always love seeing color charts. It really sort of wakes me up and makes me focus, and this is really helpful.

It seems to me you are posing a couple of questions which are interrelated but separable.

One is who should fall under federal regulations concerning human research, and do we extend

-- the issue we face is, do we extend it to projects that are not now under the Common Rule?

A second question which I think we have not really dealt with is, what should those regulations be? I mean, the way we have it here, we are sort of starting with the current Common Rule and the other subparts to 45 CFR 46, but there is also the possibility that, maybe, that is the wrong approach to take. Although it has served us well for these many years, maybe we need a fresh approach.

A third question which you posed was, who should sort of oversee, coordinate, enforce, whatever the verb is?

And it strikes me that there is a big overriding question here, which is do we become very practical and say let's be realistic and figure out what is most likely to happen and go for that?

Or do we say that this is an opportunity to really take two giant steps back and say, what would a more ideal system be and leave it to others to sort out the pragmatics of whether any of this feasible?

I mean, I am really torn personally between not wanting to recommend something people would just look at and say, "Oh, that is nice. These guys are a bunch of dreamers. They are in San Francisco on the

two sunny days in June." You know, obviously this is just --

PROFESSOR CHARO: It is sunny?

DR. LO: It is sunny outside.

(Laughter.)

DR. COX: It is foggy.

DR. LO: It is foggy.

DR. COX: It is not nice outside.

DR. LO: Or are we going to say, you know, what is really needed here -- it is kind of a reorientation, a wake up call, sort of a fresh way of looking at it, that just tinkering with regulations in an incremental way, is not going to address some of the issues that the panel posed, namely there is no ethics in the regulations or the -- you know, it is just -- it is misguided in some way.

I feel that we need to think about where we are headed, what our big goal is before we can really start addressing the three very substantive issues you are proposing.

DR. SPEERS: Do you want me to respond or --

PROFESSOR CHARO: If you feel the need to respond, sure. Of course. Marjorie, do you want to?

DR. SPEERS: Yes. Two responses. One is that one can proceed by looking, perhaps at structural

issues as we are doing now, and then deal with some of the substantive issues. That does not necessarily feel as comfortable as if we had started with some of the substantive issues and then come back and looked at structure.

However, one of the reasons for deciding to move in this fashion, in addition to logistical issues of when papers were available and when we could discuss certain things, is that even playing out various scenarios of what substance might be, the various options for structure seem to be the same under various scenarios for substance.

I think we end up at the same place so that is point number one.

Second, I think that the Commission can do two things and needs to do both in a sense. This is an opportunity for this group -- for this body to think very broadly and strategically and to make recommendations of what the system ought to be, what an ideal system would be, to address some of the issues that we are hearing from the researchers and IRB community that sweeping change is needed, that tweaking is not going to be enough. This is an opportunity to make those kinds of statements.

At the same time I think that there could be

recommendations that would say this is the ideal. If you cannot do the ideal, here are some other things that could be done. So that, for example, even with the options that have been given here, it does not have to be pick only one, but it could be, here is the first tier and here is the second tier.

PROFESSOR CHARO: Bill?

MR. OLDAKER: At the risk of, seeming to, I guess, speak at speed or decibel, at least in theory, more than we are at this time, it seems to me we want to be somewhat radical. We want to do something that will have an impact for change and actually have some lasting events.

Now my problem -- Bernie laid it out at the end -- my problem is, I do not think we have stated basically what we view that we are trying to cure at the current time. And I think we have to set that out. There is a -- in my mind, and I sit more distantly than the rest of you from these issues, but I think there is an issue now with public perception, and with credibility, with a type of research that if it is not taken care of, could have a caustic effect on biomedical research. And I think it -- but we should try and state that -- what the problem is we are trying to deal with first and then attempt to rectify that

problem with -- at least my initial feeling is with some fairly dramatic recommendations. Not alternative recommendations because I know the body politic generally disregards alternative recommendations. But recommendations that would stand out and set a mark that we would hope people would try to meet, and that would also gain the appreciation of the general public as a way to actually build their confidence in the system.

So, you know, I guess it is a two step process in my mind. We cannot solve all problems, but we should identify what we think the problem is currently, and then we should try and -- that is not an easy process necessarily. And then we should aim our solution at that problem, realizing that we may be doing some other things, instead of looking at kind of a scattershot governmental issue and maybe that is part of the problem, too. I do not know but -- and trying to solve all of the problems that the government may have in this area.

PROFESSOR CHARO: But if we understand you correctly, Bill, one of the problems that you would agree we have, is the problem of maintaining public trust in the research enterprise? Did I understand you correctly?

MR. OLDAKER: Correct.

PROFESSOR CHARO: Okay. Alex, and then David Cox? Anybody else?

DR. CASSELL: I want to underline what Bill just said. I have been sitting here listening to testimony the last couple of days, and I am still trying to say what is the problem that we are going after. The fact that there is an uneven set of regulations, that is a problem. We could bring people under one set of regulations that are poor, and I do not think that would be very helpful.

So I would like, also, to hear much more clearly what do we think is the problem.

PROFESSOR CHARO: Okay. Alex?

PROFESSOR CAPRON: Well, this is very much in line with what Bill and Eric just said. My sense is, that the kinds of issues we have seen, Marjorie, cut across both structure and the activities that are carried out within that structure. And the criticism from the Office of the Inspector General of the IRB system is, in part, a criticism of IRBs not having the resources they need, being over worked, not necessarily all being as well informed about the regulations. But it is, in part, of course, a criticism of the assurance model, which is the predominant model from the Federal

Government.

And I do not think it takes fully into account, how that model does or does not achieve goals that are different than the compliance model, much less what we have been talking about of an accreditation model.

It would seem to me that responding there might have some implications for the structure as well because an accreditation system makes a lot more sense if you are thinking of a single central office that has the responsibility, than trying to design an accreditation system that involves a lot of different -- 20 or so different agencies, each with their own responsibilities.

What are some of the other concerns we have seen? Well, the fact that the regulations do not embody a very clear set of ethical precepts. Again, as Eric just said, you could centralize with bad regulations, or you could have good regulations without centralization. Those do not necessarily go hand in hand.

But I have the sense that one of the reasons we have the problems with the regulations that we do is this divided structure. Every time, in our first two major reports, that we thought about ways in which

changes really ought to be made to take into account the mentally disabled or human biological materials, we kept coming up against the Common Rule problem.

That is to say, try to suggest how these can be reinterpreted but do not -- please do not suggest any changes in the regulations themselves. Or if you do, think of it as a new subpart, that is totally optional, and is not part of the central -- because you will never be able to get these baronies to agree.

There are times when you need a monarch and this may be one of them.

Now, obviously -- and you have that nice list in the little handout that we have -- the results to avoid include rigidity, bureaucracy and disproportionate burden. There is some risk, I suppose, that a central office might tend in that direction, but it is also part of the experience of people that, having different departments and agencies, including the differences between the FDA and the rest of HHS, amounts to some excessive burdens because you have to adjust what you are doing depending upon which regulatory structure you are having to deal with.

The fourth thing that you said we should avoid is redundancy. Well, certainly having all these departments taking up different places in the Federal

Register, with their little curly Q's built into them, leads to a good deal of redundancy.

So, I mean, I think that some of the weaknesses we have seen in the present system, some of the problems with the quality of the regulations, and particularly, the ability of the regulatory system to respond to new findings from empirical research about what works and does not work in informed consent, to new ethical thinking about what is important and how it should be balanced. The paradigm shift that we have heard about over the last 15 years -- it is not the last time we are going to have a paradigm shift. This is a pendulum, and it will always be swinging, and in response to those swings people will perceive new problems.

I mean, I was trying to say the difference between the type one errors and the type two errors. Well, you can substitute different errors in there and it is always a matter of saying, how do we not get too many of one but while we are trying to avoid the other.

A system that has central authority on its face is more able to adapt to those changes and adopt change in language as that becomes necessary.

The final thing is, it does seem to me that a centralized office would be in a better position to

marshal the overall resources necessary for education and outreach.

To the extent again that responsibility is spread around, there is always the issue of, well, why do I, Secretary of X, Y, Z, want my budget to have to be, you know, boosted up by this and I have to defend why I want money for this. Why isn't that other office doing it? They do more research than we do anyway. Let them take care of it.

And so I think that it is possible for us to identify weaknesses with the present system and most of those weaknesses, it seems to me, would be better addressed by the model that we have talked about over the last three years as a possibility, which I do favor, of having a government-wide office.

DR. MESLIN: David?

DR. COX: Yes. I agree. I really agree with --

DR. CASSELL: I do, too.

DR. COX: -- what all the different speakers have said that -- and I really agree with what Bill said, which is figuring out what the problem is. So I will say for myself, you know, there is no single problem but we have to prioritize what we think is most important. So, for me, the biggest problem that I

would like to see solved, is this one of putting ethics back into this issue because it is not in there right now.

And I do that out of the desire to have both the actual protection of the patients, and the pursuit of the research both go on, and my sincere belief is that, if we do not put ethics back in, neither will happen and we will be in big time trouble.

So that is the logic of my motivation here. So given that, that then precludes any quick fix to this problem or -- and it precludes anything but a really sort of drastic shake up of the system.

Now I am leery of drastic shake ups of anything and I would go to great lengths not to have drastic shake ups but in this situation I do not see very many other options.

DR. SPEERS: Thank you. This conversation is actually very helpful because it says a couple of things to me and to staff as we work on this. One is that of those various options, at least what I have heard from three of you here, is that you are leaning towards a more dramatic change rather than a tweaking of the system, and that is important for us as we proceed along and need to do some of the background work. And I certainly agree we do not want to move --

we do not want to make drastic change and have bad regulation.

So these two go together, these two issues of the structure, and the purpose or substance of the system and the regulations, which is where these two are moving along -- these two issues are moving along together and, hopefully, they will become very clear to you in the next few months.

And we will lay out very clearly what the problem is, what we think the problem is because we have -- you have heard testimony. We have some in background papers and then we have been hearing from IRBs. You are going to hear from IRBs -- from their perception of what some of the problems are in July.

I would like to ask for the other three Commissioners at the table if I could just get a sense of where you are on this issue of tweaking versus dramatic change.

DR. MESLIN: And as you are thinking, if Rhetaugh and Trish are still on the phone, and wish to weigh in, please let us know.

Eric Cassell wanted to make a comment.

DR. CASSELL: Well, I do not think we should tweak. I mean, we are hearing a lot of noise from -- a lot of complaints about the way it is working from

outside. We have a system that sort of came into being. We understand a lot more what it is supposed to do. We are aware that ethics is somehow dribbled out of it and I, myself, believe that we have to make major change and drastic is always -- doctors get nervous with the word "drastic."

DR. MESLIN: Major.

DR. CASSELL: Major change. I like that.

And I also feel that, whatever we end up with, that a central regulatory agency is a better one merely out of matters of power, and that is an issue that we have to consider because an agency -- a set of regulations and an agency that has no power is in difficulty and that is one of the current difficulties.

DR. SPEERS: Thank you.

DR. MESLIN: Bernie?

DR. LO: I like the idea of a major, not necessarily drastic, change. I just want to make sure we get the major change right, because the problem is when you make a major change, you can do a lot of good or you can do a lot of harm.

So I would suggest that we look at the big picture. I mean, as I sort of think about what I hear the problems are, one way to think about it is that we do not really have any assurance that the individuals

and organizations who are responsible for protecting human subjects actually do the job they are supposed to do. Just as in every other branch of clinical medicine, we are looking for outcomes, performance and things like that. We ought to hold people accountable, which means IRBs, OPRR and individual investigators.

I think another thing we keep hearing about is the -- how much of this really depends on what David calls the wink and the nod, but it is that interaction between the physician-investigator and the subject, which is so important in determining what the potential subject thinks, and whether they are going to enroll or not, which is totally different than the emphasis on consent forms.

It seems to me the inference I want to draw from that is, that education about clinical research has got to be part of your training as a clinical researcher and you do not finish a fellowship without doing that any more than you finish your cardiology fellowship without learning how to do your angiograms. You do not get an NIH grant until you show that you have understood research ethics the way you do not get the grant unless you know biostatistics.

So I think there are big picture issues that we can deal with. I am not prepared to say how you

educate, who -- what kind of model you use but I just think these notions of, holding IRBs accountable, making sure investigators really learn what we think -- what somebody thinks they should learn are the sorts of things which I think would be fairly major. I mean, this does not happen and, I mean, I -- the stuff that is on my computer, this is public -- I cannot say it is public record but there are a lot of NIH training grants and program grants that are given out that do not have in place anything more than boilerplate as to training of investigators in research ethics.

And everybody knows it, the study section knows it, the PIs know it, the people whose names are down to do the teaching know it. And, you know, that is more than a wink and a nod. That is sort of falling asleep at the wheel.

So, yes, I would go for major changes but to not be so presumptuous to think that we know all the little steps that need to be taken.

DR. CASSELL: But I did use the word "education." I just want to reemphasize that.

(Laughter.)

PROFESSOR CHARO: Diane?

DR. SCOTT-JONES: I would agree with what has been said so far. I would agree that we should think

about major changes but very carefully. I agree that we should take into account all the stakeholders, try to consider the perspectives of researchers, of people who participate in research, and I think we should give careful consideration to the social sciences. I know that Marjorie is very aware of the importance of this.

I think we should consider carefully children and adolescents as distinct from children. And I agree with Bernie and, of course, with the point that Eric often makes, that we should plan for education about any changes and educating again all stakeholders, IRBs, students, new investigators, and the public generally who participate in research.

PROFESSOR CHARO: Steve?

MR. HOLTZMAN: Let me start with the structural question first. I think if one thinks about human subjects protections, that the impetus for it starts with the word human subject. It has absolutely nothing to do with what agency is doing it. It has absolutely nothing to do with where the money came from. And the idea that there ought to be a locus that is centralized and deals with humans per se makes all the sense in the world to me, and so I would be very, very supportive of it.

I think getting it right is actually -- it is

an opportunity for it to be much more flexible and not have a single univocal sense of what are the appropriate kinds of protections but actually could work with those different agencies to say, okay, you do social science work. What kind of protections should we be evolving for that?

So, again, when I think of centralization, I think of rather something that can integrate diversity as opposed to come down with a single monolithic set of rules. So I would be very supportive of that.

And I think it would go a long way to starting to try to mend the problem of the public trust because I know for those of us who try to do it right and still get nailed to a cross, it would be nice to have a place you could go to and say, "We are doing it right."

I mean, I could point you to accusations that are now on the web about things that researchers have done, where we know OPRR investigated it and found that it was groundless, but it is out there on the web and you are getting interviewed by the Washington Post about these accusations.

With respect to the education component, I mean there the issue is what can we do other than hortatory kinds of things. But it is clearly the most important thing we could do.

Dr. Cassell, education is the most important thing.

And I was struck in the discussion earlier, that in encouraging the teaching of research ethics it is not a matter of teaching people rails or teaching people nails, it is actually teaching people how to think and bring a set of questions and considerations to their research which are not in their minds intrinsic to the research. Questions from an ethical perspective of why am I doing the research? All right. How am I performing the research? And what will be the distribution of the fruits of the research?

I think that is what we are trying to do. An education that gets people to say those questions are as important questions as questions about whether I should use this or that restriction enzyme. Okay. And then giving them a framework in which to say that that needs to be thought about and justified.

PROFESSOR CHARO: I had a few comments of my own but first let me ask if there are others who wanted to speak at this point.

DR. MESLIN: Have you heard from Trish and Rhetaugh?

PROFESSOR CHARO: Trish and Rhetaugh, are you still there? They may have gone away for the moment.

Let me intervene, and I am sure other people are going to have comments, too. We have got, by the way, about ten minutes before we have to break, unfortunately.

What I have heard people talk about today, and over time, has absolutely included public trust and I think it was Bernie or Bill who called it "uneven regulations," inconsistent regulations or simply differing regulations that make it complex. Occasional major harms, so far occasional major harms, inefficiency particularly in the collaborative research area.

And one thing that may be a little bit more controversial as a "problem", that we would have to decide if we think needs attention, is a system that is able to better influence research so that there is a just creation and just distribution of benefits as well as distribution of burdens, and that goes to the historical problems of the inclusion of women, and to some extent racial and ethnic minorities in research so that we are confident we understand how these new products operate with people whose physiology or circumstances are different.

All of which suggest to me that you would absolutely want a central authority in the Federal

Government for the purpose of being able to simplify -- first to make rules consistent as well as, as Steve was saying, to facilitate a more efficient way of amending those rules or particularizing those rules to special situations. Something that is now very difficult because of the multiplicity of agencies involved in amendments.

It also seems like it would suggest the need for such a central office to have the capacity to rapidly respond to a changing environment as to what constitutes harm. We heard that the harms that people are worried about today now focus much more on privacy than they had before and yet we do not have the capacity to respond quickly to that.

It also strikes me that ideally a system ought to take advantage of incentives and enforcement measures that go beyond simple regulatory enforcement with fines or shut downs. There are incentive schemes where, for example, accredited IRBs or licensed investigators, as if you got a driver's license, are subjected to a simplified set of rules or a simplified set of auditing procedures as compared to those that have not been pretested and found to be presumed competent to handle these problems.

And it also means that it might be worth, in

my opinion, examining the role of state governments and state law, since if we wanted to focus on major harms, which would suggest perhaps focusing more attention on major risks and beginning to clear out minor risks more efficiently from the system, there is a role in state law, which covers things like battery, the unconsented, offensive or harmful touching of somebody else, that could be called into service to provide back up for those areas where there was some retreat at the federal level, none of which would be inconsistent with maintaining a decentralized system that is, at its heart, professional self-regulation with sufficient central guidance, oversight and occasional intervention to maintain public trust.

Bernie?

DR. LO: A couple of thoughts. First, you know, I have a computer so I play around with charts and things. I think it would be really helpful if we each made a list of what we think the problem is, that we are trying to deal with, and circulated them and get a sense if there is commonality or are we just sort of all over the board here.

And, secondly, I really would like to think through the notion of professional responsibility. I mean, it seems to me, one of the things that is

different from the traditional deference to physicians and other professionals, is that we now have the ability or some ability to compare actual performance to stated expectations and goals.

And to the extent, again in the clinical arena, doctors are being held accountable for all kinds of outcomes and getting used to the fact that someone is looking over your shoulder, we should -- and there is a whole sense at least in ideal theory, if not in practice, that people ought to look at their -- take a hard honest look at what they do with a view to quality improvement as a whole and mistakes literature now.

I think we should try and piggyback on to that and say, we are not talking about trust in the sense that we know more and you should just trust and defer to us.

But trust now, I think, can be backed up with some sense of outcomes related to performance and even if it is just a procedural outcome, in terms of passing a licensure exam or certification or something, it seems to me that is better than just saying, you know, you have got an IRB that somehow has a piece of paper that gives you a Multi-Project Assurance.

So to the extent we can build in the self-improvement through looking at outcomes, that would

give people more of a rational basis to trust the investigators.

PROFESSOR CHARO: Bill, and then Alex.

MR. OLDAKER: I think Bernie's idea is a good idea to the extent that we can put out there what the problems are, but I would think it would be good, also, to have Marjorie or others put together a statement that we could look at as far as whatever those problems are.

And then we set aside two hours to really debate them because, to me, if we do not come to grips with what the problem is up front, it is going to be very difficult for us to progress to a place where we actually get something done.

So I think, you know, it is -- I think it is wonderful and it has been very instructive to hear from a number of the witnesses but I think with the diversity we have here, it would be worthwhile for us to really thrash out a common vision of the problem we are trying to solve.

I mean, just -- you know, as an over arching thing I know that we agree on a number of things but I do not know if agree that this should be a very broad and cover more areas than it currently covered or not, and I think those are the kinds of things that if we do

not touch up front, we are going to be constantly spending more time trying to figure out how to go down those alleys.

PROFESSOR CHARO: Alex?

PROFESSOR CAPRON: I concur with both of those comments. I wanted to actually raise something that we have not directly talked about in the last few minutes as an example of something else.

We have heard a good deal of discussion about the therapeutic misconception that has been raised as an example of a problem and we have heard some fairly widely differing views about that. And I was thinking as everybody was endorsing the notion of education, and I thought that both Steve and Bernie gave a nice endorsement of that, what would be the education on a topic like that.

Would investigators be cautioned as part of David Magnus' testimony this morning about the ways in which they subtle feed that, or is feeding it really quite all right because that is part of the hope that Eric Cassell talked about at one point and so forth.

I wanted to know whether it is our sense that in this report as part of the process of examining the present system we would intend to address substantive issues of that sort or whether we intend to flag those

kinds of issues, explain why they are difficult, and suggest that that is one more reason why an ongoing structure is needed, through which issues like that can be thrashed out publicly and with input from people who realize that those issues are on the table.

I do not think the average person who is an IRB or an investigator knows that that is necessarily before us, for example, but if there were an office that says, you know, this is a big issue and we want to prepare appropriate educational materials, or we want to put something in the regulations, or in the guidance documents that are given to IRBs or whatever.

So do we have a sense that in this report we are going to get to issues like that or would we get to them in this latter way that I described of sort of saying, here are a bunch of issues that are current issues, and the only real way to address them is through some ongoing process?

PROFESSOR CHARO: Let me just warn you because Marjorie needs to leave as scheduled at 12:30 that there will not be time to answer your question from members of the Commission right now.

PROFESSOR CAPRON: Just on the record.

PROFESSOR CHARO: But if Marjorie would like to have any closing comments about things people should

think about in addition to that so that when we pick up the discussion we are ready to respond, feel free.

DR. SPEERS: Thank you.

As I envision this report and the types of recommendations that will be made, I think of them as the Commission dealing with the broader issue. Sort of opening the doors that then another body, whoever that would be, can go into much more detail on it. But I do not think that we -- I do not think we have the time, the luxury of time to go into detail on some of those issues, but we can certainly open the doors.

PROFESSOR CHARO: With that, I would like to excuse Marjorie and --

DR. CASSELL: You are excused, Marjorie.

PROFESSOR CHARO: -- to turn the chair back over to Alex as we shift gears back to the International Report. As I understand, there will be approximately a 10 minute discussion on an amended recommendation.

I know that Ruth and Alice will be back in momentarily and presumably lunch will arrive at some point for everybody to have here at their favorite seat.

PROFESSOR CAPRON: Feel free to move. Why don't -- does staff know whether the food is about to

be delivered? Okay. Why don't we let people stretch their legs for five minutes and if you have not checked out, you better do so immediately and so forth and so on.

(Whereupon, at 12:30 p.m., a break was taken.)

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