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C O N T E N T S

P R O C E E D I N G S

OPENING REMARKS

BY HAROLD SHAPIRO, Ph.D.

DR. SHAPIRO: Colleagues, those members who are here, I would like to assemble and get our meeting started this morning. We are a little short of time. I want to make the best use we can of it.

Let me tell you what I propose to do this morning. I want to spend about a half hour right now on a very brief review and reaction to Chapter 1 of the Oversight Project which you have all received. I will turn to Marjorie in a moment to do that. But I would also like to ask Marjorie to indicate from her perspective what kind of feedback that she needs in order to continue to make forward progress here.

We have really quite an accelerated schedule in front of us in the Oversight Project. Our hope is that we will have four chapters available for the Salt Lake City meeting roughly six weeks from now. We will certainly have three. And so, we are going to make rapid

progress here, and it is going to be dependent on thoughtful feedback from the Commission to Marjorie. We will not have time for all that today, obviously, in half an hour.

But I do want to save a half hour before we go to the panels that are coming this morning to revisit a couple of issues in the International Report, so we can also move that forward. And in particular, with some recommendations in Chapter 5 we never got to discuss, I want to go to those. We really have a lot of information and feedback on the others which will be restructured along the lines of our discussion yesterday, because my intention is still to try to get a full set of recommendations out for public comment within the next couple of weeks. And so, we will certainly produce new drafts almost immediately after this meeting, and look forward to some feedback from you so we can then have-- these go out for public comment.

As I mentioned yesterday, the public comment session will take us beyond the Salt Lake City meeting, so that report will probably not be in front of us at the Salt Lake City meeting; we will spend it exclusively on the Oversight Project, and as you know, we have two other panels coming this morning on that.

So, in view of our tough time constraints, I

want to turn directly to Marjorie, and have her say a few words about Chapter 1, and then get some feedback from the Commission. Marjorie?

ETHICAL AND POLICY ISSUES IN THE OVERSIGHT OF HUMAN SUBJECTS RESEARCH

DISCUSSION OF CHAPTER 1

PRESENTATION BY MARJORIE A. SPEERS, Ph.D.

DR. SPEERS: Thank you. Just to remind you of what we are trying to do in this chapter, we are trying to lay out the rationale and justification for the Oversight Report. In particular, we are trying to very clearly state what the problem is, and what it is the Commission will be addressing in subsequent chapters.

In part, this chapter is before you now in response to a request that you made at the June meeting in San Francisco that we very clearly state what the problem is. So, what I would like to get from you today is, is the problem clearly stated here? Is it the problem that you think it is? And when I say problem, I recognize that it is a multifactorial problem. So, have we emphasized the right aspects of the problem, or the ones that you want us to address?

Before we do that, I wanted to just spend a couple of minutes telling you about the next three chapters that you will be getting. Again, what we are

trying to do in this chapter is very clearly state what the problem is, so that then, the next three chapters will address recommendations related to the problem, and we have conceptualized those three chapters in the following way. One of the chapters will deal with the oversight system at the national level, or at a macro level. It will be a chapter that provides a very broad perspective, and recommendations related to an entire oversight system.

Another chapter will deal with selected ethical issues, and how those ethical issues, then, are applied, or carried out through regulation and guidance. And then, the third chapter will address issues related to the local oversight system.

So, we are envision taking this problem and then addressing the solutions for it, and the recommendations that you will make, by categorizing them into those three areas, the national level, ethical issues, and then the local level. It is very likely that then there would be another chapter that puts it all together and summarizes it.

We are working on Chapter 2 now, and have a fairly good draft of Chapter 2. It was very clear in writing that chapter that everything is connected to everything in this system, and it really becomes very

difficult in some ways to write the chapters with the recommendations, because it assumes--and even to deal with the system on a national level, it assumes that you already know what we are going to say about the local level, or what we are going to say about some of the substantive ethical issues.

For that reason, it is likely that you will get the next three chapters as a package. And I know that that is a burden for you to have three chapters at once to read, or even two chapters, if we do the next two for sure. But I think the more that you have in front of you when you are looking at any one chapter, so that you have as much of the entire system before you, it will be more helpful to you in reading it. So, anticipate that that is what we are planning to do.

And as Harold said, it is our intention and goal to try to have those three chapters, plus this Chapter 1, so four chapters, before you at the October meeting. If we don't achieve that goal, then our second goal is to have three chapters before you, the next two plus this Chapter 1 as it is revised.

We will send out an e-mail to you asking you to provide your comments, particularly the ones that we can't go over today, over the next week to ten days so we can continue to work on Chapter 1.

So, what I would like to hear in terms of discussion and what would be helpful to us again, is to hear whether you feel that we have accurately described the problem, whether you feel that the balance and tone in this chapter is appropriate, and if there is anything that we have missed.

DR. SHAPIRO: Thank you very much. Let's go to the comments of Commissioners. Alta, Bernie, then Carol.

PROF. CHARO: First, let me start the chorus of praise. It is really good. It does a wonderful job, and it covers a lot of material, and it was a pleasure to see it, and get a sense of where the report is going to go. So, first, thank you very, very much.

My comments are three items that I think we might add, or emphasis somewhat differently. The first is very small, and it is on page ten, where you talk about NBAC's unique interest. I think there was an inadvertent oversight because in your list of reports there is one other official action. Our very first was a formal resolution about extending human subject protections beyond federally funded and FDA regulated, and I thought we should add that.

The second had to do with the phenomenon of state, that is, not federal or governmental in general, but actually state-level government, or county-level

government funded research. I know I have got it marked here, but there is a page where there is an acknowledgement that some research is done by state governments and less frequently counties, but from now on we will call it private sector research.

I understood that, you know, from a syntactical point of view, but actually, it allows us to slide over what is an interesting area that dovetails with one of our reports which is research with people with mental illnesses or other decisional impairments, a lot of which goes on in state hospitals, and is beyond the pale of the current federal regulations under many circumstances, and I think raises, (and this now dovetails into the third point), raises the very special issues of trust which is discussed here in other places.

But as has been mentioned in other meetings, one of the distinguishing factors of the research relationship in the biomedical context, is the subtle change of a relationship in which there is a great deal of trust on the part of the patient toward the professional into one that does not deserve exactly the same kind of trust. You might still have trust in the research enterprise, but it is not the same as the trust in your personal physician.

And I think that that issue of trust is also

profoundly altered when we are talking about governmental sponsorship, funding, and conduct of research, because I think that our historical experience has been that, when it is the government that actually seems to be in charge of the research and something goes wrong, it seems to be doubly shocking to the conscience. And I would hate to lose that, either the relational aspects of research in general as one of the reasons why we regulate research, and then, very specifically, try to find a way to pull out the role of state governments and county governments in that area.

DR. SHAPIRO: Thank you. Quite a few commissioners want to speak. Let's try to be as brief as possible since we have very limited time on this one. Bernie.

DR. LO: Marjorie, I also want to add my thanks and praise for your efforts on a very complicated topic.

My main concern is a matter of emphasis or balance. As I read this, I tried to take the perspective of a citizen who is not an aficionado of government regulations, and what I didn't find here, and what I would like to see, is a sense of what are the current problems from a human perspective or from a patient research perspective. We don't really make any mention of the current things driving the discussion, for

example, the Jesse Gelsinger case or some of the things we have considered in previous reports. So, I would like to see a sense of what are the actual--scandals is too strong a word, but the cases that made people stop and say "Whoa! If that is what is going on, there is a serious problem."

I think a lot of the first chapter really has to do with regulation issues and composition of IRB issues, that really I don't think grab the public attention. I don't want us to fall into the trap that, for instance, many scientists say that it is just a matter of complying with regulations instead of real substance.

And my second point is that I would like to, if possible, and of course, this may be asking you to predict the future, to tie the introduction into the conclusions. To the extent to which we can anticipate in the introduction some of the big recommendations we are going to make, we need to set the stage here. So, let me just take a crack at throwing out some issues I think we are going to want to make some recommendations on.

One is more attention to the consent process, as opposed to an emphasis on consent forms, and you know, to use some examples here where people just didn't understand what they were getting into, even though the consent form said it in fine print. The issue that Greg

Koski raised about the current oversight is totally driven to front-end IRB approval, and no concern about how the research is actually carried out, and how, in particular, researchers deal with unexpected issues that emerge in the course of doing research. And I think, you know, to me, that is one of the real tragedies of the Jesse Gelsinger case.

A third issue, I think, is a sense that there is too much regulation of relatively low-risk research, and not enough attention, or at least cases where dramatic research was carried out under IRB approval, that in retrospect, people said how could that happen. So, you know, to take an example from the recent past, the approval by the IRB, post-hoc though it was, of the blastomere separation experiment. You know, it was approved; it was approved after the experiment was done. But they clearly didn't (inaudible) the issues, and we need to sort of address that, I think.

And finally, I think we need to address the issue of whether we really know what IRBs are doing. There is so much emphasis on, you know, that they didn't keep minutes right or they didn't have the quorum right or the composition wasn't right. But what we really don't have, and this goes to some issues we are going to talk about later, in terms of what is their actual

performance, and on things we really care about in terms of protecting human subjects, whatever those variables are, do we really know what they are doing? And I think to the extent we are going to talk about certification and training, I think we have to try and anticipate the substantive issues.

So, if we could highlight those things, I think the report will find a wider audience than its current emphasis might give it.

DR. SHAPIRO: Thank you, Bernie. They were really very extremely helpful comments. Carol?

DR. GREIDER: I have just one comment, and then a question. And the comment is to add my voice to the others who have said that this is really terrific. I think that there is so much here in Chapter 1, and I like the completeness of it. That said, there are just a few places which I can give written editorial comments, where I think that maybe there is a little bit too much detail, and those might be put into later chapters.

But the question is, as you laid out the other chapters, national issues, ethical, and local, in the past we have tried to ground a lot of our conclusions on substantive, ethical issues, and norms, and so I am wondering why we would start with national oversight, rather than the ethical. Why put the ethical issues

second?

DR. SPEERS: In part, it seemed to me, in working with this report that in needing to start somewhere we, in part, have to do some very basic things, like define what an oversight system is, define what the components of it are, define who the players are, and what the functions are. So, it seemed to me that that would come first, and then after we discuss some of the ethical issues.

We actually toyed with the idea of doing it the other way, but I think that given that we have to jump in somewhere, we should jump in with defining what the oversight system is. So, that was the reason for doing it. I think that again, when you see the chapters, if you feel they should be re-ordered, that can clearly be done.

DR. GREIDER: It just might go to addressing some of the things that Bernie was saying, to have some of the actual cases as it relates to people. It might help in that, but I am willing to wait and see.

DR. SHAPIRO: Thank you. I do want to make a comment. David is next on my list here. But we really do want any detailed comments you have made and marked up copies. They are extremely helpful to Marjorie and anyone else involved in actually doing the text. So please,

either leave them with us or send them to us, any way you want. We surely want to get those comments. David?

DR. COX: This will be fast. It is great. Going a little bit along Bernie's lines, a feeling that is missing is that people are in control of their own protection, because there are lots of players. The system is paternalistic, and it doesn't allow the people, who are being protected, enough say in their own protection. And that came out in the testimony yesterday, and I think that it is not much of the system right now, but to make sure that those people who we are trying to protect, are seen as some of the players in the mix.

So, I don't have specific places to do that, Marjorie, but I think you understand what I mean. Because the way it was historically, and you lay out very nicely, is that it was a very protectionist, paternalistic approach, and that is really changing. In fact, it is one of the reasons that has necessitated rethinking a major overhaul. So, it was just a feeling I didn't get very much in terms of the text right now.

DR. SHAPIRO: Thank you very much. Are there other comments people would like to make with respect to the draft of 1? Understand, we are not having a full discussion now; we are limited in time. But other

comments that you think might be helpful, suggestions, questions, et cetera, to those who are going to be producing the next draft of this chapter and subsequent chapters?

All right, that is fine. But let me again repeat what I said just a moment ago. I have a very heavily marked up copy, and I am sure that many of you do, too, and they are invaluable if they are legible. I have decided I have to go back to my word processor since mine look illegible to me, but I will send them in to Marjorie, and I hope you all do the same.

Okay. Thank you very much. As I mentioned earlier on, our panels start approximately at 9:10 or 9:15, I have forgotten what the time schedule is, and since we have visitors coming for that, I don't like to delay that if we can avoid it. But we do need to spend a little bit of time, perhaps we have three-quarters of an hour, to pursue some further issues on the International Report. In particular, there were some recommendations, many recommendations that you saw yesterday, that are going to have to be redrafted along the lines of our discussion, and we don't have time to go back to that today. But you will certainly hear very quickly about this with some new proposals very shortly. But I do want to ask Eric to just go over a few of the recommendations

that we didn't get a chance to discuss yesterday, just to get a sense of where the Commission is, so as we redraft this, we can restructure these recommendations in ways that seem sensible to the Commission. So, let me turn to Eric. Eric?

DISCUSSION OF CHAPTER 5 RECOMMENDATIONS

PRESENTATION BY ERIC A. MESLIN, Ph.D.

DR. MESLIN: I won't repeat the things that we have already discussed. The recommendations that we have not discussed directly in Chapter 5 are recommendations 5.4 to 5.9 inclusive. I am going to suggest if you still have the handout version of the recommendations that I provided to you that there are some in that list which are, if I can predict what you might think, are not terribly controversial. I may be wrong, but that is my sense.

The two that come immediately to mind are Recommendations 5.6: “The relevant U.S. research regulations at 45 CFR 46, Sub-part A should be amended to include a section that addresses international collaborative research conducted or sponsored by the United States.” When I say non-controversial, that was put in as a kind of cumulative recommendation that you may wish to add at the end of Chapter 5, or at the beginning, and simply repeat or cross-reference with

those other recommendations that do have a need for regulatory change. That may or may not stay depending on whether you think it is a good idea to have such a cumulative recommendation.

Diane?

DR. SCOTT-JONES: Would that recommendation perhaps be better coming before Recommendation 5.3? Because 5.3 and 5.4 talk about issues that are addressed in that regulation.

DR. MESLIN: Right. That is one of the reasons that I suggested it may not be a controversial recommendation as much as where it needs to be placed after you have agreed on the other substantive ones.

Alex, did you want to--?

PROF. CAPRON: Well, I, frankly, did not understand what 5.6 was trying to achieve in the context of these other recommendations. Is there a way of summarizing that quickly?

DR. MESLIN: Only what I had said before. It was put in there as a way for you to decide, if you felt that a cumulative recommendation that summarized those other relevant recommendations, which in this case would probably be, depending on how 5.3 and 4 are written, should be mentioned. It is, by no means, a required recommendation.

PROF. CAPRON: So this is a statement of something that is implicit otherwise.

DR. MESLIN: Yes.

PROF. CAPRON: Oh, okay. Because I thought somehow it was suggesting--

DR. MESLIN: No.

PROF. CAPRON: --that there was going to be an additional category.

DR. MESLIN: Originally, in the form--

PROF. CAPRON: Instead of saying "that addresses", why don't we say "to include the substantive changes relating to international collaborative research contained in the recommendations of this report". I mean, that is the thrust of what we are trying to say. Otherwise, I had a sense that the implication is,somehow the present regulations don't address international collaborative research, which made no sense to me.

DR. SHAPIRO: Good point.

DR. MESLIN: Right. Thank you. We can make that--

PROF. CAPRON: This would be, if anything, the very last recommendation of the entire report, and we are in effect saying bite the bullet, and amend 45 CFR.

DR. SHAPIRO: To accommodate these recommendations, exactly as you said. That is a good way

to put it.

PROF. CAPRON: That is not the way it reads.

DR. SHAPIRO: Right.

DR. MESLIN: The other, and I said I was taking these slightly out of order, thinking that they were non-controversial, was Recommendation 5.9: “NIH, CDC, and other agencies that sponsor international research should permit researchers to request financial support for the cost of compliance with ethical requirements at the institutions with which they collaborate, et cetera.”

PROF. CAPRON: Is there any indication that they are now prohibited? Is that the present understanding?

DR. MESLIN: Prohibited from requesting?

PROF. CAPRON: Yes.

DR. MESLIN: No, they are not prohibited from-- Sorry. Are they prohibited from--

PROF. CHARO: This came up at the San Francisco meeting, as you may recall, and I think Rachel was helpful on some of the details here and came up with some suggested language, because there were different kinds of restrictions depending on which agency it is that was funding the research.

DR. MESLIN: This is the language that emerged to some extent from that meeting in San Francisco. It was general rather than-- A former recommendation had

indirect cost rates, and a number of those sorts of things, and this was made more generic.

PROF. CAPRON: Could we replace the word "IRB" in the last line with the word "review"? Because IRB is a generic--I mean, it is a specific U.S. parochial term.

DR. MESLIN: Right. Carol?

DR. GREIDER: It stood out to me that in this recommendation NIH and CDC are singled out, whereas in the other recommendations it just said "U.S agencies that sponsor". I wasn't clear as to why that needed to be different.

DR. MESLIN: No, it was an artifact of former drafting.

Other thoughts about those? Those were the two out of the six that were remaining that I thought were non-controversial, and we might want to go on to others.

PROF. CAPRON: And in light of Alta's comment, the word "request" is going to be replaced with the word "receive"?

PROF. CHARO: I don't think anybody is really confused by it.

MS. LEVINSON: I will work with Eric on this one to tweak that because, of course, they can request it, but Alta is right. There are caps on administrative costs that make it difficult to receive them, so we will

work on finessing.

DR. MESLIN: Okay. Now we are left with what I hope will be discussion. I am not sure, Alex, whether you had done any nighttime work.

PROF. CAPRON: (Inaudible.)

DR. MESLIN: Okay. Do you also have it, at least for-- Which one were you working on, so we won't go to that one?

PROF. CAPRON: Oh, 5.3, 5.4.

DR. MESLIN: Okay. That leaves 5.5 and 5.7. I would like to suggest-- And 5.8. I would like to suggest, Harold, unless there is any objection, that 3, 4, and 5 actually are seen as a cluster, depending on how the determinations of equivalent protection are made, and by whom, and with what degree of authority a central body has. It may be that 5.5. which for those who, perhaps, don't have it in front of them, "Where national laws, regulations, or guidelines have not been adopted by the host country, U.S. sponsoring agencies should recognize the host country's authority to adhere to accepted international guidelines."

The basic message behind Recommendations 5.3, 5.4, and 5.5. is how does the U.S. government, and through what mechanism, grant or determine that another country can use guidelines that are equivalent or

provide equivalent protection to those of the United States. Whether those are national guidelines of the country, or whether they are international guidelines that the country uses in lieu of national guidelines may be irrelevant once issues around who determines equivalent protection are settled. Maybe we should wait there for Alex's text to be circulated, to have that discussion.

The issues in 5.7 should be familiar to the Commission. This is brand new. It is on page 27 of the longer text, or just the bottom of page 2 of the handout. Formerly, there was a recommendation that encouraged the old OPRR to use other mechanisms in addition to the SPA process. Because we are aware that the assurance process is under revision, and there are new proposals for how the assurance process will work, both simplifying and shortening, et cetera, it made sense to us that NBAC would be wise to make this type of recommendation, rather than to just simply encourage them to do something else. Let's see how well the whatever else they are working on is doing. So there is no editorial pride in the language. The essence was that this process should be evaluated after a period of time.

Bernie?

DR. LO: Eric, to pick up on a point you just

made, I am wondering if somewhere there should be a recommendation that we support and encourage the simplification and, you know, lessening of the burdens of obtaining these assurances. I mean, many of our recommendations, it seems to me, are secondary to the primary recommendation that things have got to be simpler and, therefore, better. So, not just the 3, 4, and 5 that go into who gets to determine what is equivalent and, therefore, simplify, but also, this recommendation which has to do with seeing whether those goals are achieved. We need, I think, to declare our support for those goals somewhere as a recommendation.

DR. MESLIN: Bernie, were you suggesting that that would be part of what is now 7, or a separate--?

DR. LO: No, I would like to see that as a high-up recommendation, that we want the simplification process simplified and made easier, while still assuring adequate protection.

DR. SHAPIRO: I think that is, actually, an important point. I haven't thought through exactly where it should come, but I think we often overlook that issue in some of the things that we discuss, and that is one of the criticisms of all this, that things are unnecessarily complicated. Some things need to be complicated, but some things are unnecessarily complicated, and prevent,

you know, ethically quite appropriate research from going forward, just because the bureaucracy gets in the way. And that is a point we need to make, and it is a high-up point, as you point out.

DR. LO: But also, it is an assumption that underlies a lot of our other recommendations. I just think we need to make it more explicit.

DR. SHAPIRO: Right. Alex?

PROF. CAPRON: Well, you know, the urge to say we should back off of all of this, I sympathize with. It is, however, true that on the domestic side, while this is a time when, I think, Dr. Koski and others have an opportunity to rethink the entire mechanism, (and I take from his testimony yesterday that he plans to do that), at the moment, any thought that there should be less oversight of, less encouragement to good practices in, and so forth, IRBs either domestically or internationally, strikes me as, perhaps, getting the cart before the horse.

I mean, we do not now have a system which has been able to uniformly provide, even at very good institutions, a commendable implementation of the expectations for ethical human subjects research. And while I do think that, if there are countries which have systems in place, that there is a certain, to use the

word Alta used yesterday, need for comity in treating their systems, the notion that what we really want to do is get all the regulations out of the way, and make this just as simple as possible, I don't have the sense that around the world, anymore than around the United States, we would be happy with the results that would flow from simply stepping back.

Now, maybe I have misunderstood your urge--

DR. LO: No, I think that is a good point, because I didn't state what I wanted to say clearly. I think what we want to simplify is the assurance process, not back off on sort of oversight. I think, you know, you are right, that we need to be very careful about the language we use, but I am talking about what now is, generally, I think conceded to be a very cumbersome special assurance process that is very burdensome, but doesn't necessarily provide substantive protection.

PROF. CAPRON: May I, Mr. Chairman, respond to that?

DR. SHAPIRO: Yes.

PROF. CAPRON: In that line, I would agree, but it would seem to me that the major thrust of what we are talking about is something that will come up, really, in the report domestically, because most of the research that we are still talking about occurs domestically, and

a change in the assurance process domestically ought to lead to simplification and have better mechanisms for encouraging the right outcomes, and so forth.

I would, therefore, think that we should refer readers, as it were, to our forthcoming report. In other words, here, rather than having a major recommendation, it would be a matter of saying we note the plans for revisions that are underway; we encourage and applaud efforts to simplify the assurance process; certainly, that should have an impact internationally as well as domestically, particularly making the assurance process more relevant to international standards, rather than solely the language and procedural expectations of the domestic system which we know is a stumbling block for getting those assurances. And the notion that that whole mechanism, including its international side, ought to be evaluated after several years.

But I would not be comfortable going much beyond that, because we really haven't explored what it would mean to have something in place of the present assurance system. We just had hints from Dr. Koski yesterday about what he was thinking of.

DR. SHAPIRO: Other comments? Alta, did you want to--? David?

PROF. CHARO: David was ahead of me.

DR. COX: So, I am sort of in between on this, and let me just tell you the feeling that I get from reading these recommendations is that I don't want to be there, because it sounds like government, you know, bureaucracy. That is what I see Bernie responding to. On the other hand, I agree with what Alex says.

So, what one can put in the recommendations that is not there at all is some clue to the process of how we are going to do this, and the way we are going to do it is that there are going to be some overriding principles on which one makes these kinds of determinations. Now, I know that that is obvious to us around the table, but it is not obvious to a reader that reads these recommendations, because we just say do it, but we don't give any clue to a structure behind how it is going to happen.

So, how does one figure out what an equivalent protection is? Well, it is because we have certain principles that we hold fundamental, some so fundamental that we won't even let research be done in a place, you know, if those principles are violated. So, that tone doesn't come through these recommendations at all.

Now, I realize this isn't very helpful in terms of the specific, you know, word-smithing of them, but I think it is that lack of that feeling that is causing

this, I believe, discussion between Bernie and Alex.

DR. SHAPIRO: Well, look, if we can find appropriate-- I don't want to take any longer on this particular issue because we have to get on, but as I tried to say carefully before, if there are things we can see that are unnecessarily complicated, not because we want to relieve people of burdens they need to carry; we want to relieve people of burdens they needn't carry. Then, we ought to be sensitive to that. What we will find, I don't know.

So, let's go on, because we just have not got very much longer.

DR. MESLIN: Do you want to go to Alex's? Because he has done some work on 5.3 and 5.4.

DR. SHAPIRO: Okay. Has everybody got a copy of that? People all got a copy? Just raise your hand if you don't have a copy. Thank you.

Alex, why don't you--?

PROF. CAPRON: Well, let me just tell you the intention. The intention was to summarize in one sentence, the first sentence of 5.3, the notion of the process, led by OHRP, and involving the other agencies that would lead to the policy guidance, and move forward the process of equivalent protection. By the way, I make no promises about that being the right section. It is

what I got out of reading the report, and I may have misread it. So, please, someone-- I didn't have the regulations at hand.

The second sentence is intended simply, really almost descriptively, about the effect of a determination under that policy guidance, and it is there-- It is in the passive voice. The intent is to say once such a determination has been made, then the federal agencies treat the IRB, or the review body (I tried to avoid the word "IRB") as equivalent.

Then, in 5.4., I took the next step to try to say what is going to happen if there is a problem with this implementation process, and OHRP becomes explicitly the lead agency on this. Now, that we had talked about, but I don't know that I summarized everybody's view on that. I thought we needed something to shoot at. So, that is what 5.4 tries to do.

Two steps then, policy and implementation.

DR. SHAPIRO: Thank you very much. Let's just discuss this. Carol, and then Bernie.

DR. GREIDER: I just have one question about 5.3. It doesn't seem to me that it says who is making the determination. The first sentence just talks about setting forth criteria and a process, and the second sentence says "once a determination has been made", and I

ask, "Made by whom?"

PROF. CAPRON: This is what I tried to address right now. This is, in effect, a description of the effect of such a determination. The "made by whom" is 5.4, and the reason for doing that-- The second sentence could become commentary, if you are more comfortable with that, and probably as commentary it could be massaged even into several sentences. I mean, why do we need such a thing? Because if we have it, then once an agency has made a determination-- Now, we could just say that "once an agency has made a determination", if that language would make you more comfortable.

DR. GREIDER: Could you put the second sentence of 3 below 4?

PROF. CAPRON: Well, the idea was what does this policy guidance do? Policy guidance means that if implemented, there is an equivalency of the review bodies that have been found by that country to meet its system with our own MPA-qualified IRBs. And as I say, it may just be that that sentence really should just be descriptive commentary, because it is-- Or maybe not. Or, to follow my general sense, and the point you are making, maybe I should have written it in the active voice, and say, "Once a federal agency has determined--" Would that make you--? I mean, I could certainly say--

DR. SHAPIRO: Let's-- We certainly have some options there, but let's try to focus in our discussion here on the substance, the principles behind this which I think are really quite clear the way Alex has written it although, you know, perhaps it could be improved.

I have a number of people who want to speak. Bernie, Steve, Alta, and Larry.

DR. LO: I think these revisions are very clear, and I like them. Again, I am concerned about trying to step back a step, and it seems to me that a basic problem is that the current existing authority to declare that another country has equivalent protections has not been acted upon. And I think what we want to say is, alot of countries out there may well have policies in place that are equivalent, and we haven't declared that, and as a result, they have to go through--you know, people doing research in those countries have to go through an incredibly cumbersome process, and that whoever has the authority to do that ought to get on the ball and look at these things, and say these countries have equivalent protections, and make it easier to do research, because we think subjects are being protected. It seems to me that is the preconception to which Alex's two revisions give a very clear laying out of how to do that.

DR. SHAPIRO: That is very helpful. Part of

that, but not all of it, is in the text, and I think that will help us think--

(Simultaneous discussion.)

DR. LO: And I tried to-- Did I give you something on--

(Simultaneous discussion.)

DR. SHAPIRO: Yes, I have that right here.

DR. LO: Okay. That tries to--

DR. SHAPIRO: And that will be helpful. Steve?

MR. HOLTZMAN: Yes. I would like to second Bernie's motion there, that the focus should be on the substantive end that we are trying to achieve which is, effectively, a certification process of other nations, right? Because the rest of this is just because of the way we currently have a system with different agencies.

Alex's draft of this that OHRP coordinates-- And we could go stronger, and say it is important to get to the substantive, and OHRP take the lead, and we recommend other agencies follow their lead. We could go that way.

DR. SHAPIRO: Alta?

PROF. CHARO: I think that what has been drafted here works very well, but it is necessarily tied to the current system, and as it has been mentioned, that may be in flux. So, it is possible that this would be helped by

having a recommendation next to it that anticipates its goals, but doesn't specify the mechanisms so precisely.

It is, I think, a little bit of what Bernie was saying, if I may, something that goes something like "The federal government should encourage and facilitate international research to that end. It should help U.S. researchers to identify sites and collaborators where research can be conducted in a manner that satisfies the following core ethical and procedural values". And then begins to pull out a list, so that we get to this question of what constitutes substantial equivalence without using that language, and without tying it to current regs. And on the list is things like independent prior review, minimization of risk, favorable risk/benefit balance, ideally, adequate compensation for injury, individualized informed consent from all competent adults if the research is more than minimal risk, things like that. And in that sense, set the stage. And then, with some text saying if we were to do it under current rules, we would recommend that this be the way you do it, and I think, then, Alex's language gets very nicely to how we go about it. But it sets out the over-arching goals should those current rules change, and if the system moves toward registration instead of assurances, et cetera.

DR. SHAPIRO: Okay. Helpful comment. I hope you will give us the--so we can at least review it carefully.

PROF. CAPRON: Can I just suggest--? I think that is a very helpful comment, and in a way, it is a framing comment for the whole report, and I would put it right up at page 3 of the first chapter. I mean, it is at that point that we recite those three basic principles, and an over-arching recommendation that recognizes that the system is in flux, and this report contains a number of specific recommendations framed within the present system, but the goal is to-- And just take the transcript and take Alta's paragraph and plug it right in there, and make that a recommendation right at the first chapter. And that is, as you say, an orienting, or framing--

PROF. CHARO: We would need collectively to make sure that we are comfortable with the particular list of things we have now identified and announced as core.

DR. SHAPIRO: That is always a problem whenever you construct a list like that, but we can find ways to deal with that that don't focus on, you know, whether we left out one, or forgot one, or something, and so on. So, let's have the text, Alta.

Larry?

DR. MIIKE: Wait long enough in this group, and you don't have an original thought.

DR. SHAPIRO: That is my strategy.

(Laughter.)

DR. MIIKE: I was going to comment basically what Alta said, because if you look at the chapter, and not the list of recommendations, these are obviously tied together, and it needed some-- Since many people are just going to look at the recommendations, they needed something, and a statement such as what Alta said needs to be done.

On Alex's two clarifying changes, I agree. But Alex, why did you put the weasel word "endeavor" in there?

DR. SHAPIRO: That is an editorial comment.

DR. MIIKE: You sort of let the agencies out by saying they should endeavor, rather than they should do it, uniformly.

MR. HOLTZMAN: It is a recognition of human imperfection, Larry.

(Laughter.)

DR. SHAPIRO: Including our own.

Okay. Tom?

DR. MURRAY: It is going to be hard to follow that colloquy. This has been a very good discussion.

Thanks to Alex for drafting, and Alta for her useful additions. I am now getting a little less clear what the status of Recommendation 5.3 would be. Would it--? If we are going to keep it as a recommendation, I would still revise it in the sense that I would put-- We now have two sentences, I believe? I would start with a sentence that frames the broad principle that we want to, you know, respect other nations who are, with integrity, attempting to protect their own subjects. So, we want to do something that frames it broadly. And then, probably use a version of the current first sentence which says under the current system, this is how we would do it.

The third one reads like a legal contract, and I think it would be at most--could be broken up and just added as commentary later on.

DR. SHAPIRO: Okay, thank you. And I do want to-- It is helpful that when these things are inserted in text, it is hard to know whether you want that introductory language in the text or in here, but that is something we need to work on. But I think that is helpful.

DR. MURRAY: I think in the recommendation the first sentence ought to be an enunciation of the general principle.

DR. SHAPIRO: No, I understand.

DR. MURRAY: Not introductory text, but actually the language of the recommendation.

DR. SHAPIRO: Okay, last comment on these, because then we just have to go on.

PROF. CAPRON: Stimulated by Carol's good remark, let me suggest to you that if we have anything like this, the second sentence of 5.3 might read as follows: "Once a federal agency that sponsors international research has determined, pursuant to this policy guidance, that a nation's human research guidelines and procedures provide quote 'equivalent protection', review bodies established or accepted by the appropriate authorities in that nation may be treated by the agency as equivalent to a domestic IRB possessing a valid federal MPA."

DR. SHAPIRO: Okay. If you would just give us the language, we will continue to work on the language, and I think we understand the general point.

I would like to spend-- (So, you will get that language from Alex.) I would like now to move on to the other recommendations we haven't even touched on, there are only one or two, and just get some initial responses. I mean, we can't resolve all of this today, given our time, but just get some initial responses to it. Eric?

DR. MESLIN: Believe it or not, we have

discussed all but one remaining of the recommendations, and that remaining recommendation is 5.8: "Independent review of proposed research must be conducted by an unbiased, competent body in the country where U.S.-sponsored research takes place. In addition, independent review must also occur by the sponsor. In the case of U.S. sponsors, this review should be conducted in accordance with U.S. research regulations, or those deemed to provide equivalent protection to participants." And then, we reference other recommendations. "Researchers should include in the research protocol plans for facilitating communication between or among IRBs in the United States and collaborating countries."

The principle that this recommendation is supposed to illuminate is how many IRBs does it take--

DR. SHAPIRO: To change a light bulb.

(Laughter.)

DR. MESLIN: --to allow research to go forward, and which IRBs should they be. The first part of the recommendation says the host country's IRB has to review this. How many others, and which others, have to review it is the question that this recommendation is supposed to answer. The last sentence just makes sure that everybody is talking to each other.

Now, just-- Go ahead.

PROF. CAPRON: It seemed to me that the phrase "U.S.-sponsored" in the second line is too narrow. I would suggest that after the word "research" in the first line, we add "subject to U.S. regulations."

DR. MESLIN: Right. That is-- Yes.

PROF. CAPRON: And then, drop the words "U.S.-sponsored" and just replace it by "the". At the end of the last full line, add "review bodies in". So, it says "between or among IRBs in the United States and review bodies in collaborating countries." Again, not assuming that IRB is the right way to describe them.

DR. SHAPIRO: As Eric has said, the issue here is what do we feel are the minimal requirements. Obviously, people will have their own view as to whether they want to involve their IRB in a lead or subsidiary. I mean, there are all kinds of views individual countries might have, but the question is, what do we feel is the minimal requirements to assure the ethical conduct of the trial.

One recommendation here is it has got to take place at least in the host country. That seems pretty straightforward, and I don't think any of us would disagree with that. The question is what else we want to put in as minimal requirements.

Steve, then Alta.

MR. HOLTZMAN: Question of clarification. I think the paradigm in mind here involves a U.S.-based investigator with a foreign collaborator. Are there cases where, first off, there could be direct federal funding of investigators none of whom are in the United States, all right? In which case, who is the relevant internal review body in the U.S.that we are referencing? And second, to the extent that we want this to reference outside of federal funding, and as a suggestion, for example, to the private sector, or (inaudible) FDA-mandated again, is there necessarily a domestic nexus for this in the U.S.?

DR. SHAPIRO: Alta?

PROF. CHARO: I am going to take the case of the publicly funded research first, because it is a little bit easier. I would say that the answer to how many IRBs it takes to change a light bulb is two: one in the country where the research will take place, and one here in the United States, so that we have both local conditions, and interpretation of U.S. regulations adequately covered by respective bodies.

With the private sector--

MR. HOLTZMAN: (Inaudible.)

DR. SHAPIRO: Touch your button, Steve.

MR. HOLTZMAN: --stay on the feds. So, is a

direct funding where it is the investigators, there is no local investigator, no U.S.-based investigator.

PROF. CHARO: So what you are contemplating then is that having determined that there is a collaborative site in Rwanda that we have come to know is reliable and well-staffed, and has all the capacity necessary, we would fund researchers at the University of Rwanda through a federal grant, and have only the Rwandan university's own local review board go through it, just as if you were funding research at the University of Wisconsin.

PROF. CAPRON: That is not collaborative research. There is no collaborator from this country, just money from this country.

(Simultaneous discussion.)

MR. HOLTZMAN: Assume I am really dumb for a moment. I am asking a question of whether there are any cases where the United States funds research, human subjects research, where there is no U.S.-based investigator involved.

DR. SHAPIRO: The answer to that is yes.

MR. HOLTZMAN: So therefore, who is the relevant IRB, who is the U.S. IRB, that is involved? That is my question.

PROF. CAPRON: What would be the U.S. IRB? If

there is no U.S. collaborator, if it is just U.S. dollars, then it would-- But the same is true today. I mean, if CDC-- Not CDC. If the Cancer Institute gives money to the University of Wisconsin for research, the Cancer Institute doesn't run an IRB on it, they expect Wisconsin to do it, and if it is the University of Abadan, and they are not sending U.S. investigators from Wisconsin over there, there is no reason for the Wisconsin IRB to be involved.

DR. SHAPIRO: I think there is some--

(Simultaneous discussion.)

PROF. CAPRON: --someone who qualifies for Cancer Center money, but they happened to be based in Africa.

DR. SHAPIRO: I think if I could just ask Steve if I get the point he is making. The second sentence here is what Steve is focusing on, I believe, and correctly so. That is, the way this is written, it assumes that there is a collaboration, and Steve is correctly pointing out that that is not necessarily the case. My understanding of the way things currently stand is in the case that you pose, that takes place in the IRB in the country where this is taking place. And so, you are quite right to point to that, that we have to accommodate that.

MR. HOLTZMAN: Right. And so then, what Alta gave was an in-principle argument about why there had to be domestic review in the U.S.--

PROF. CHARO: It was assuming a former collaboration that was not present--

(Simultaneous discussion.)

DR. SHAPIRO: I agree. You have made a good point here. I agree.

Tom? Excuse me, Alta is next. You are on my list then, Tom.

Did you make your point already? I can't remember?

PROF. CHARO: Who knows?

DR. SHAPIRO: Tom, let's go.

(Simultaneous discussion.)

DR. MURRAY: You can follow on whatever I am going to say, Alta.

Imagine the headline: "American-- U.S. Company, Pharmaceutical X, Pays for Research for Its New, Dangerous Drug in Country Y Somewhere in the Developing World". Company X's spokesperson says, "We didn't have an American investigator. We relied on local people for the work, and so therefore, all of the review and other requirements of this commission report are irrelevant to us."

PROF. CAPRON: No, they are not. They would have to be relevant.

DR. MURRAY: I am just telling you what the spokesperson will say. I am not saying that it is all correct.

PROF. CAPRON: But the FDA--

(Simultaneous discussion.)

DR. MURRAY: But there would be no U.S. IRB review. Would the FDA require a U.S. IRB review? I don't think so.

PROF. CHARO: The FDA wouldn't require a U.S. IRB review. It would require that whatever review process was used was one that met the FDA's standards which we, in an ideal world, know would incorporate all of the brilliant recommendations that we have made here.

DR. SHAPIRO: And maybe some of the ones that aren't so brilliant.

DR. MURRAY: So, that is how we would catch them. If they wanted to market it back in the U.S.?

DR. SHAPIRO: That is right.

DR. MURRAY: If they want to market it back in the U.S., then we wouldn't have that--

(Simultaneous discussion.)

PROF. CAPRON: That is true today.

DR. SHAPIRO: True today. Still true.

Okay, any other comments? I still want to focus on--

Sure, Tom?

DR. MURRAY: I was just struck by the phrase which would have--in the second line of the recommendation, that the review "must be conducted by an unbiased, competent body in the country", and who could disagree with those words, that the review body should be unbiased and competent? A cynical person in another country could say, well, you know, U.S. committees are generally the creation of the institutions who are getting the money to do the research. Are they unbiased? So, it could be turned back against us. And secondly, I think if we were going to say this, we need to somewhere in the report elaborate what we mean by unbiased and competent, or else it will be taken as a kind of arrogant claim by a country that may not be so clean on its own regard.

DR. SHAPIRO: I guess-- I am sorry. David?

DR. COX: This is on a different question, so did you want-- Go ahead and make your point.

DR. SHAPIRO: Okay. I am wondering if the Commission has-- There is a kind of multi-center trial analogy in international collaborative research to the multi-center trial issues that we have in this country

regarding whether or not there should be lead IRBs, or how many IRBs you need; does everyone have to have their IRBs, and so on. That whole issue just plays out again here. It is really in principle the same issue.

Do any commissioners feel that issue itself, in the context of international collaborative research, that we need, or should, say something about that? Do we have anything to say about it? Is that something we should try to work on?

David?

DR. COX: So, this had to do with my point. My answer to that question is yes. And the part of this recommendation that says "researchers--", and I have made this point in previous meetings of the Commission, "researchers should include in the protocol plans for facilitating communication amongst IRBs". How?

You know, I mean, I have been in that situation. It is almost impossible to do. So, that is putting--you know, requesting researchers to do something without giving a plan of how they are going to accomplish it. So, it falls into exactly what you are saying, Harold, which is that you want to facilitate all these different things, but that it is not clear the process by which you are going to do it at all. To me, at least.

DR. SHAPIRO: Larry?

DR. MIIKE: Well, the last comment that Tom made raises some issues for me on this recommendation, because if we look at it in light of the discussion we had on 3, 4, 5, and 6, I believe, 3, 4, 5, and 6 look toward assuring that the IRBs in the foreign country, the host country, does meet this criteria of an unbiased, competent body, yet I assume that we still conduct research in countries where they may not have that, and that there is a body there that reviews it, and there is a body in the United States if it is a sponsor that does it. This recommendation puts us in a dilemma then, because how are we going to proceed with research in those countries which have not met the test of our prior recommendations, and still come out with ethical research?

DR. SHAPIRO: I presume we do it, the last couple of years, through the Single Project Assurance mechanism, which I believe could allow that to go ahead if a particular location can convince us that they--

DR. MIIKE: All I am saying is that the way it is currently written, following those other recommendations--

DR. SHAPIRO: I understand.

DR. MIIKE: --would naturally follow that they have met these, and so we are going to--

(Simultaneous discussion.)

DR. SHAPIRO: I understand.

Bernie?

DR. LO: I think the issue we are running up against is the different levels of review we want to see in place. On the one hand, we are saying countries should have policies that are equivalent to the U.S. policies, or adopt international standards, and that, I take, is what 3,4, and 5 are about, certifying the country's sort of ethical principles, so to speak. There is a whole other issue of what is the IRB going to do in a country that has good principles. Is the IRB going to apply them with wisdom and discretion the way we would hope an IRB in this country would? And here, I think we have to say there is a real issue, that we may think the principles are good, but we have no evidence as to whether IRBs any place in the world, even in this country, are really doing a good job working at those principles.

And so, you know, we are talking about certifying IRBs in this country somehow; we don't know how we are going to do it yet. Given that skepticism about how our own U.S. IRBs work, it seems to me one could have similar skepticism about IRBs in other countries. And see, that, to me, is where the rub is.

Even if you know that the country's principles are good, you have just certified the country. You haven't certified the IRB in any way, and that is where, I think, Tom's headline will cause troubles, because there are going to be allegations raised that the IRB was pretty naive, and inexperienced, and not very good at doing its job protecting subjects.

Because of that concern, do you want to put on an extra sort of over-the-shoulder second opinion look in a foreign country, where you wouldn't necessarily do it in this country unless there was sort of cause directed at the institution?

DR. SHAPIRO: Alta? Then we are going to have to close this discussion.

PROF. CHARO: Bernie, I think the difficulty you raise is extremely important. I think it also dovetails with yesterday's conversation about what recognition of a foreign country's policies really means, because the notion of comity is that, once you have recognized that government's authority, you have recognized their authority not only with respect to their principles, but with their ability to implement those principles.

Now, in the United States, we put down certain kinds of procedural requirements with regard to the IRB operation so that there is that second level of

protection, and those procedural rules include things like adverse event reporting, and continuing review, and then all the paper work requirements that annoy people so much, the minutes, and the quorum votes, and all that stuff. And we can certainly list those things that we think are essential procedural safeguards that help to ensure that policies are implemented most of the time in a way that is acceptable, but I don't think that we want to be in the business of not only having to recognize a foreign government's approach to human subjects protection, but also in individually certifying each individual researcher, because like I said, it is like recognizing New York State's ability to marry people, and then having to individually interview all their judges. I mean, you will never simplify and streamline the system if you are going to go that route. There has to be some degree of trust in the other government, and that is what the capacity-building recommendations are all about.

DR. SHAPIRO: It really is an issue, and I don't know that we will resolve that issue, but it is an important issue. We have to find some way of highlighting it, focusing on it, not letting it pass us by, even though we may not be able to fully resolve it.

Okay, we are going to have to end our discussion on this particular topic now. Why don't we take a five

or seven minute break before the panel-- Yes, Eric?

DR. MESLIN: Since this is the last time at this meeting we are going to talk about the International Report, I just wanted to give you the timetable and homework assignments, lest we forget them. If you have marked up, edited copies of the chapters, please hand them to Alice or me or the staff before you leave today. If you have them elsewhere, send them immediately.

Secondly, we will be sending around the proposed edits to the recommendations for 4 and 5 that we have been discussing the last couple of days. We will try and do that within the next 24 hours to you, and please let us know if they meet your approval. And then, you will see revisions to the text of 4 and 5, hopefully, within a week or so, with the goal of getting these five chapters and recommendations into the public comment process within, as Harold said, 10 days plus or minus a few days.

I can't give the public who is here the exact date that the public comment period will start. It will, hopefully, start, you know, on or about the 20, 21st, 22nd of September, which is 10 days from now, but understand that it may take another couple of days, but our process will kick in 45 days of public comment as soon as we are done.

And that is all.

DR. SHAPIRO: Okay. Let's reassemble at 9:15.

(Whereupon a brief recess was taken.)

DR. SHAPIRO: As soon as everyone is stoked up with an adequate amount of caffeine, we will get underway.

PROF. CHARO: No such thing.

DR. SHAPIRO: It is probably not strong enough for you, Alta, right?

We have two panels that we are going to hear from this morning which are dealing with subjects which are directly relevant to our Oversight Project, one dealing with privacy/confidentiality, and the other dealing with quality control, and with respect to the first panel which we are going to turn to right now, you have also seen papers which have been presented to us, and we want to welcome back Professor Sieber who has been before this commission before. It is marvelous to have you here again. Thank you very much. And also, of course, Janlori Goldman, welcome. It is a great pleasure to have you here this morning.

So, let's just launch directly into the panel. We have scheduled-- Again, we would like to keep this to about an hour, so I will ask you to keep your presentations in that context, since we do want to leave

plenty of time for commissioner's questions that they may have. And I think the way we will proceed is that we will start with Professor Sieber, and then I would like to go directly to Professor Goldman, and then we will go from there, because I don't want to use up all our time on one of these things, which can happen.

So, Professor Sieber, please. Press the button. Oh, you want also the overheads. They have to be reloaded, I am afraid, or something has to happen. I can turn my glasses backwards. Maybe that will--

(Simultaneous discussion.)

PROF. SIEBER: They need to go in upside down and backwards.

DR. SHAPIRO: My students once pointed out to me that I could only misplace these slides so many different ways, and I said that is true, providing I don't repeat the same mistake an infinite number of times.

PANEL II: PRIVACY/CONFIDENTIALITY

PRESENTATION BY JOAN E. SIEBER, Ph.D.

PROF. SIEBER: Okay, well, let me begin, and presumably my slides will catch up with me quickly.

Good morning, and thank you very much for inviting me. It may please you to know that I am not going to summarize the whole paper. Rather, I am going to summarize the main problems and the recommended

solutions, and then, within the solutions which I won't go into in detail are really all of the elements of the paper.

As you know, my emphasis is on the need for clarity and for education. I have tried my recommendations out on many IRB members, and all agree that researchers and IRBs need more education, not more regulations. And I would like to add that they have all told me that they are so concerned that they feel micromanaged, that common sense has gone out the window, because so frequently regulations do not really fit the specific circumstance.

(Slide.)

The Common Rule does not define-- Ah, good! Progress!

DR. SHAPIRO: Caught up.

PROF. SIEBER: The Common Rule does not define privacy, although it has a section called "Definitions". The IRB Guidebook, in Chapter 3, page 27, does a halfway good job. It defines privacy as having control over the extent, timing, and circumstances of sharing oneself physically, behaviorally, or intellectually.

But it is naive and ethnocentric in instructing. "Decide whether there is an invasion of privacy by basing your decision on your own sense of propriety, and

the circumstances of the study." This advice is sometimes okay, but it is pretty amateurish. It presumes more sophistication than the IRB may have. But this is understandable. Before Web-based education, the task of communicating in detail with researchers and IRBs about judging privacy interests of others would have been really daunting.

(Slide.)

Presumably, everyone knows what privacy is. It is a word we toss around a great deal. The existing regs and guidebook offer no suggestions for helping a researcher who seems insensitive to the particular research populations' sense of privacy. There are tools for learning what is private to others who are situated differently from oneself. If a researcher's seat-of-the-pants judgment about invasion of privacy fails, the IRB needs to require the use of relevant tools. If the IRB and the researcher lack such tools, both subjects and the research may be at risk. Even the researcher may be at risk.

(Slide.)

When a subject responds to something that he perceives as an invasion of privacy, there are various things that he might do. We all have ways of protecting our privacy. He could decline to answer, which we have

told him he can do. More likely, though, if he wants to appear polite, he will lie, which provides great data, of course. He may be evasive; he may quit the session; or he may reveal more than intended and then worry about it a great deal.

The researcher would do well to respect personal privacy.

(Slide.)

But that is not easy. Let's look at our own sensitivities. What is private to you here today at the Commission differs from what is private to you elsewhere at another time. It depends on where we are on an issue, on our mood, on our recent past experience, and so forth.

These unpredictable and sometimes ephemeral individual differences are handled through informed consent. Where privacy is an issue, relevant attention should be given to the way informed consent is worded, and more importantly, how it is delivered. We all keep saying informed consent is not a consent form, and you bet it isn't. It needs to be delivered with a real understanding that you may be dealing with very personal sensitivities, and there is nothing in the regs that talks about your body language, comprehension, and so forth.

(Slide.)

Apart from our own individual idiosyncratic senses of privacy, there are major differences between populations in what they consider private. And as it says on the slide there, gender, ethnicity, age, socioeconomic status, education, ability level, social and verbal skill, health status, legal status, nationality, intelligence, many things relate to what we consider to be our privacy interests.

There are many tools for finding out what these interests are, but those tools are rarely used.

(Slide.)

Thus, researchers and IRBs often rely on their own sense of propriety. And I really want to emphasize, this sets an ethnocentric, capricious, and inconsistent standard for respecting privacy.

(Slide.)

A useful definition of privacy in the regs is one that is really quite general and simple. It might be-- This would be in the definition part of the regs. "Privacy refers to persons, and to their interest in controlling the access of others to themselves. For example, via informed consent." This definition suggests the dynamic and subjective nature of privacy interests. The regs should refer readers to other sources for

further elaboration on how subjects and researchers regulate access.

(Slide.)

People regulate the access of others to themselves irrespective of whether a researcher is sensitive to their privacy, but they don't always do it in a way that protects themselves, or that fosters valid research. So, the researcher has a very important role to play in providing and communicating the appropriate respect and appropriate protections.

(Slide.)

As detailed in the paper, there are many ways to learn about and respect the privacy of subjects, and I won't go into detail here. But they include, of course, informed consent, knowledge of the subject's culture, rapport, and sensitivity to the individual, having research associates from the culture that you are studying who can be really good informants on cultural determiners of a sense of privacy, and extensive consultation with appropriate professionals and peers of the subjects.

(Slide.)

Now, here is the real clincher. Most research methods courses do not teach this material. A critical problem is that most research methods courses and

textbooks don't teach you how to understand privacy, or to assure confidentiality. Many scientists still take the "get data" approach that ignores the subjective sensitivities of subjects, and so, of course, then, the data they get isn't very good. Textbook publishers focus on what professors want. The relevant literature that researchers need in order to know how to protect privacy and confidentiality happens to exist in rather out-of-the-way applied research journals, and a few really excellent books, the very best of which currently is out of print, and that is Boruch(?) and Cecil *Assuring the Confidentiality of Social Research Data*.

(Slide.)

In short, the regs are no help, the IRB Guidebook is naive, and research training is inadequate.

(Slide.)

But there are solutions in sight.

The Common Rule also does not define confidentiality. I will be briefer here. The problems are much the same as for privacy.

(Slide.)

The Guidebook assumes, or hopes, that there is IRB expertise concerning mechanisms of assuring confidentiality. I have given a lot of IRB workshops,

and I have never quite found that member who knows a great deal about this.

(Slide.)

The Guidebook does not even hint at the multitude of techniques for protecting confidentiality, at their advantages and limitations, how they are applied, or how some of the more sophisticated methods which are fairly arcane, just might come in very handy. One is left thinking that there is just a handful of common sense techniques when there is so much more.

(Slide.)

The literature on these techniques is scattered in applied research and applied statistics literature, so the poor IRB chair, or staffer, who seeks to find these literatures, interpret them, and make them available to the IRB and to researchers, just can't do it. They need a lot of help.

(Slide.)

There are other complications. There are continual changes in issues. Let me just mention three. Electronic media rapidly change and challenge confidentiality. Keeping pace with this is a big job, and this isn't the kind of literature that the average researcher or the average IRB member readily reads or understands.

Relevant state and local laws are rarely tracked or interpreted by most IRBs.

Also, increasingly, data sharing is being urged, and data audits are occurring. These need to be planned for in special ways, and each researcher shouldn't have to reinvent procedures of planning for these.

(Slide.)

Let me give you a suggested definition of confidentiality. "Confidentiality is an extension of the concept of privacy. It refers to data, (that is, identifiable data about a person), and to agreements about how data are to be handled in keeping with subjects' interest in controlling the access of others to information about themselves."

As you will see, this definition is further enhanced when we get to the informed consent requirement that I am going to recommend.

(Slide.)

The proposed definitions of privacy and confidentiality bring with them a need for changes in informed consent requirements, and also, a need for educational resources that would be available in a user-friendly form on the Internet, kept up to date, and tailored to each institution by its IRB.

(Slide.)

Informed consent is integral to privacy. Hence, regarding privacy, the informed consent element concerning risks would be modified as follows. In CFR 46.116 (2) in parentheses, "A description of any reasonably foreseeable risks or discomforts to the subject--", then we would add "including possibly unwelcome seeking or presenting of information or experiences; that is, possible invasions of privacy."

(Slide.)

Regarding confidentiality, the consent statement would be changed to--just entirely changed. It should direct the researcher more exactly. Since anonymity is highly desirable where possible, it needs to be specifically mentioned. The recommended new element would read: "A statement of whether and how data will be rendered anonymous, or a statement describing the conditions of confidentiality of identifiable data, who will have access to such information, what safeguards will prevent or reduce the likelihood of unauthorized access, and what unavoidable risks of disclosure may exist."

That definition doesn't let the person think that confidentiality is just promising you won't tell other people. It implies the more sophisticated issues.

(Slide.)

The educational resources would be on Web pages. They would be formatted with the help menu, much like the help menu on your word processor, so that information would be found via a table of contents, and an index.

There is a big Web site and a little one. The big page would be a user-friendly resource for everyone, researchers, IRBs, and teachers of research methods who wanted to turn it into curriculum for their courses. It would be user-friendly, and also, I really want to emphasize my recommendation that it be non-regulatory, though the IRB could treat parts of it as requirements at their discretion. The rationale for this is that institutions are irrationally--(well, not irrationally given the penalties), are very fearful that they will inadvertently do something that will get their research closed down by OHRP. They are motivated more by fear of violating a regulation than by a sense of ethics and intelligent interpretation. They have a sense of ethics; they are not allowed to use it. This must be avoided.

(Slide.)

The initial contents of the big Web page would be all the topics included in my paper, perhaps, would be how to handle informed consent with links to relevant topics, how to develop a protocol with links to relevant topics, and any other topics deemed appropriate.

(Slide.)

Just to give you some sense of what some of the contents might look like, there would be guidelines for "ethical proofreading" of case study material to prevent harm, assuming that your cover is blown, that all of your efforts to mask identity get seen through. How do you limit any harm? Something like how to obtain a certificate of confidentiality, and what that covers and doesn't cover. Federal laws governing school research; tips on respecting privacy and ensuring confidentiality in Internet research; uses and methods of inter-file linkage; tips on handling mandated reporting issues. Just as examples of some topics.

(Slide.)

Very briefly, the developers of this document would be experts, researchers from various disciplines, and experienced IRB folks, with input from this commission, and OHRP. The work would be commissioned, overseen, and edited by a standing committee of specialists and representatives of this commission and OHRP. There would be a Web master appointed to create and maintain the Web. As it approaches completion, it would be reviewed by IRBs and researchers who volunteer to be involved.

This would be an iterative process. Issues

change, technology changes, and improvements would be suggested. The Web would always be a work in progress, an evolving document.

The little IRB Web page would instruct each IRB how to tailor the big educational resource to their institution by putting local information on their own Web page, and linking it to the big Web. This would be mandatory. While the big page would not be considered regulatory, I would propose that IRBs be required to use the big page, and to tailor it as suggested on the little page.

(Slide.)

(Slide.)

The little Web page would provide guidelines on how the IRB might appraise its need for local expertise, develop workshops and materials for its clientele, select and develop new resources for its clientele, organize and format the local Web, and communicate with their institution's Web master, and update the local Web.

(Slide.)

The overall goal here is to provide the resources, guidelines, and context for IRBs, researchers, and students to engage in rational, sophisticated approaches to respecting privacy, and assuring confidentiality.

(Slide.)

And as befits professionals, without fear of violating, or seeming to violate, federal regulations.

(Slide.)

Thank you.

DR. SHAPIRO: Thank you very, very much. We will come back in a few moments with questions.

I would like now to turn directly to Ms. Janlori Goldman. Once again, welcome. We look forward to your remarks.

PRESENTATION BY JANLORI GOLDMAN, J.D.

MS. GOLDMAN: Thank you. Thank you very much for inviting me to be here this morning, and I want to also thank the commission for commissioning a paper from us. It forced us to sit down and do a rigorous study which we had meant to do for a while, and there is nothing like having a deadline to get you to do that.

I want to acknowledge Angela Choy who is sitting here to my right, who works at the Health Privacy Project, and who is the co-author on the paper, and who serves many different functions in our organization since we are only about four folks, as a senior researcher, and Web master, and field director. And when we have a chance for some give and take, she may be able to answer your questions better than I can.

Before I get into talking a little bit about what we did in our paper, I wanted to just talk a little bit about the Health Privacy Project which I direct, and which I created a number of years ago, and which is housed at Georgetown University. The project is essentially focused on trying to ensure that privacy is protected in order to improve the quality of care, and access to care, and we have been involved in a number of studies that look at exactly what Dr. Sieber was talking about, which is the impact of not protecting privacy in the health care environment, what are the consequences.

And so, we have seen that there is a direct impact in terms of people being afraid to share openly with their health care providers, that people are giving inaccurate information in order to shield themselves. In some instances, they are obviously paying out-of-pocket to avoid having a claim submitted, and in the worst case scenarios, they are avoiding care altogether. I am sure that many of you are already aware of this in terms of anecdotal, but what we have tried to do is to create an empirical basis for understanding this so that we can then use that in making some policy decisions down the road.

In our paper, we essentially surveyed the law related to research and confidentiality. We looked at

policy and ethics, and we made a number of recommendations. I think that a number of things that have already been said this morning are important here, but I want to just elaborate that when we are talking about confidentiality in research, there is very little guidance in the Common Rule itself, and some guidance in the OPRR Guidebook. But essentially, the Common Rule was not written with an eye toward addressing confidentiality and privacy concerns. So, whatever is in there, I think we are trying to read between the lines, we are trying to pull something out of it that doesn't currently exist.

So, we not only have a lack of guidance in the regulations, we also have a lack of expertise and resources at the IRB level, and at the association level, because there has been no incentive to develop it. So, it is not necessarily that people are insensitive, or that they are intending to do harm, or that there have been mistakes that are being pushed aside. It is that there is no legal incentive even if there is an ethical incentive to address confidentiality.

Now, in a clinical context we have seen that it is addressed probably to a greater extent, to a more thorough extent. But in just participating in an Institution of Medicine study that was chaired by Bernie

Lo, in looking at confidentiality in health services research where you don't necessarily and don't usually have direct contact with individuals, and the use of the information for research is secondary, confidentiality is not addressed. It is not addressed by institutional review boards; it is not addressed by researchers in any kind of a comprehensive way. And it is certainly not addressed, I think, sufficiently by those that are giving the information out for health services research.

So, I would argue that we do need regulations in this area, not because I am necessarily a proponent of the heavy hand of government coming in and telling researchers and institutional review boards what they should do, but because that is the necessary trigger to begin to develop the resources, the guides, the rules, the training that has to happen in order to begin to address confidentiality.

Now, because the Common Rule had not been written, obviously, with an eye towards confidentiality, and this has been an emerging issue in the last few years, the Congress and the Secretary of HHS is attempting to craft a set of rules that will change the way that institutional review boards address confidentiality, and we do go into this in our paper, but I want to spend just a few moments on it.

In about three or four weeks, maybe five weeks, depending on who you talk to, the administration will be issuing a set of health privacy regulations. They will be the first ever nearly comprehensive privacy regulations to be issued at the national level. And while they do many things, they essentially will cover health plans and health care providers as they use identifiable information. And they will affect directly researchers that are getting access to identifiable information from those providers, and from those plans. Researchers that are acting independently, and gathering information in an independent context, in other words, not with a dual role as a health care provider, or not as receiving the information from what is being considered a covered entity, would not be covered. But let's put that aside for a moment, and just talk about what changes may occur, because I think they may-- My hope is, anyway, that they will have a ripple effect in the research community.

What the administration is proposing in its draft regulations is to do two things: one, to expand the scope of coverage of the Common Rule; that it will no longer only apply to federally funded research, but will apply to all research, regardless of the source of funding. And the second major change is to add four

additional criteria to the Common Rule to specifically address confidentiality. And while you could argue that the existing criteria that are there that need to be applied by the institutional review boards in the event that informed consent is waived, and the four criteria there are what need to be waived in order to justify waiving informed consent, the additional four criteria are meant to address confidentiality specifically.

And I just want to quickly go over them, because I think that they are important in trying to understand what it is that the administration is trying to do here. Now again, these are draft proposals, and we don't know what the final wording will be. But to add to the existing four criteria the four new criteria, the proposal is that the IRB would look at: whether or not the research could not practicably be conducted (and again, that word "practicably" is consistent with it being used earlier in the Common Rule) without access to and use of the protected health information (the IRB would have to assess that); the research is of sufficient importance so as to outweigh the intrusion of the privacy of the individual whose information is subject to the disclosure; there is an adequate plan to protect the identifiers from improper use and disclosure; and there is an adequate plan to destroy the identifiers at the

earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers.

Now, I do not expect that if that is finalized, that IRBs and IRB members will look at those new criteria and say "Ah! Here are some new criteria. Let's go through and check them off." There is going to have to be, I would say, very substantial training, resources developed. I am hoping that OPRR would take the lead in that, but that the associations that work with researchers, and work with IRBs, will be very involved in developing a set of consistent resources and guidance in terms of how to apply the new criteria.

One of the other things that is interesting about what the administration is proposing is to allow, particularly for non-federally funded research, to allow something called a "privacy board" to essentially mirror or replicate the institutional review board. There has been some resistance, as you might imagine, on the part of the private sector to always having to go through the formal IRB process, and so, there is something called a "privacy board" which would be allowed to be developed by that private sector research institution to review the confidentiality concerns.

I think that there is a weakness there in that

that entity would only be constructed to assess privacy and confidentiality, and so, the other ethical issues, and the other issues of protecting human subjects, would not be addressed by that privacy board, and would fall by the wayside. So, it would essentially create two different systems of review. But that may be where we are going here.

The recommendations that we make in our paper in terms of how privacy and confidentiality can be better addressed hit a number of points that have already been made by other committees, commissions, by the administration. Some of them are already embodied in the IOM report that was just released on health services research and confidentiality, and by a report that we did last year on best principles for health privacy. Thanks to Bernie who chaired that, we were actually able to find some common ground among some pretty diverse groups on where to go in the confidentiality area as it relates to research.

But essentially, our recommendations are focused on having privacy and confidentiality be considered a central element in the designing of a research protocol, and in the initial review by an IRB, as well as the ongoing review; that the issue should be front and central along with a number of other ethical issues that

are already being addressed, and it should be built in to the proposal, and built in to the review.

We, obviously, and I have said this a couple of times, but I think it is critical to the success of having confidentiality handled in the research context, we need resources for training, for support for technical assistance. I am hoping that this would come, again, from OPRR, that NIH would be directly involved, that the associations would do this.

But I would recommend something a little bit different than what you heard earlier. I think that the guidance in this area, and the technical assistance, needs to be uniform; it needs to be consistent. I think that one of the problems that we could run into is allowing institutions to develop their own unique type of guidance, and type of regulations in this area. We really need some consistency and uniformity, and we need to encourage individual members to develop expertise in these issues so that it is not just are you keeping the records in a locked filing cabinet, but that someone has some expertise in talking about removing identifiers. What does it mean to create non-identifiable information? That is not a simple issue. It is not easy to develop expertise in that area, but there are resources available that could guide someone in that process.

I think the greatest benefit to having this front and center is that the question will need to be asked by researchers, by IRBs, by individuals looking to participate in a research project: Do you need identifiable data? We don't ask that question now. There is no legal incentive (and again, I focus on that because that is often the incentive that works) to ask do we need identifiers for this particular project. And if we don't, let's have them removed before the information is received. Or if the resources aren't available on the part of the disclosing entity, then once the information is received, let's remove the identifiers that are not needed for the project. You minimize risk in that kind of a situation, and you don't then have to worry about how the information might be used later, once it is out of your hands if, in fact, it is ever out of your hands.

One of the things that I think has been very troubling for the public, and has certainly been troubling for us in looking at this is that we don't question the intentions of researchers or institutional review boards that are assessing confidentiality. I believe that people want to do the right thing in this context, and that everybody has altruistic motives. But what we have seen is that once information is gathered,

and it is available in an easy to use form, and electronic form, that it is organized, that the researcher has done this stellar job in making the information usable across the database, or across the file, it becomes extremely tempting to use it in another context. And we have seen that with the Framingham study, that those individuals that gave their consent to participate in an ongoing research project are now being subjected, and may be subjected, to having their information used in a different context. And it is an afterthought to suggest that we are going to go back and get consent, and that we are going to try to remove identifiers, but we are not really sure what that means, and that these issues have to be addressed at the outset, and not after the fact once we have decided that this is in some ways an irresistible temptation, and we want to be able to use the information for another purpose.

And so, that is really, I think, the larger piece that is missing from this debate, is that we haven't yet institutionalized a way of addressing privacy and confidentiality up front. I am hopeful that once we do have a set of enforceable rules, and that they are applied across the board, and individuals don't worry is this a privately funded project? is this a federally-funded project? do the rules apply? do they not?, that

they will have some assurance the information is going to be held in a confidential way across the board, and they won't have to worry about whether to be honest, they won't have to worry about whether to share information fully, or that it might be used to deny them insurance, or employment, somewhere down the road, that it might become an irresistible temptation, and that we can then have better confidence in the integrity of the data.

Right now, where people are leaving information out, where they are failing to participate, where they are providing inaccurate information to researchers, we don't know where that information is unreliable. We have no way of measuring where people at the outset, either with their doctor, or with their health plan, or with the researcher, where people are afraid, and where they have skewed data, or where they have just left something out. This way, we can encourage people to much more fully participate in their own care, to get better care at the outset, and also, to provide better information down the line for research and for public health.

Thank you.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: Thank you very much. Thank you both very much. I am sure there are a number of questions from the Commissioners. I have some questions,

but let's go to commissioners first.

Alta?

PROF. CHARO: Some fine points, if I may. Ms. Goldman, both you and Dr. Sieber have frequently used the words "identifiable" or "anonymous". Now, in the context of our report on research with human biological materials, we struggled to come to an agreement about how to use those terms, and we settled on an interpretation which is the same as the interpretation that NIH's former OPRR had recommended be used. And that was that identifiable information is not only information that is tagged with a name and an address that is obvious the person using it. It could be tagged with any number of obscuring identifier links, such as codes and such.

So, first, how are you using the word "identifiable", so that we can then continue the conversation all talking about the same thing?

MS. GOLDMAN: It is an excellent question, and I have struggled with it as well. Let me tell you where I am at on it.

We look at information on a continuum. You are not talking about information which is either identifiable, or non-identifiable, or anonymous. Information is very identifiable. Maybe it has been a little identifiable as you remove certain pieces of

information, and on the far side of the spectrum, on the far side of the continuum, you have anonymous information, which is there is no way to then re-identify. Anonymous information for the most part, I think would be extremely difficult to achieve, and maybe not as useful, whereas identifiable information, obviously, is the richest, most layered data.

The proposed health privacy regulations actually create a definition of identifiability, and say that any information which is identifiable comes under the scope of the regulations, and the way you determine if it is identifiable is whether or not 19 different data elements are included. If any of those elements are included in the record, the information is then considered identifiable. And that includes both name and address, as well as, you know, Social Security number, zip code, birth date, phone number, certain demographics data, race, age--

PROF. CHARO: Let me give you a little quiz then. So-- No, so, I mean, I just really want to understand how it interacts with our report, if I may, with your permission.

In our report we said, okay, imagine a researcher has a piece of tissue that has nothing but a code. It is just a series of random numbers that have

been assigned. But far away, in a locked safe, exists a code-breaker. The researcher may not even know the name of the person who is the code-breaker; there may be three intermediaries. But there is a code-breaker, and so, in theory, with enough collaboration, the code could be broken so that the tissue could be matched to a specific individual. Would that be considered identifiable or not under the proposed privacy rules?

MS. GOLDMAN: I would say that it would be considered non-identifiable under the proposed rules, because if the information as it sits in front of the researcher is non-identifiable, the prospect that somewhere it could be re-identified is not enough (this is, again, my opinion; it may not be the opinion of the administration) is not enough to render it identifiable. However, if the information is then re-identified, it then triggers the regulations. If at some point, somebody does match it with information from another place, and it is then re-identified, it then triggers the laws.

PROF. CHARO: So, it is non-identifiable so long as it is not being used in certain ways, but-- So, the information collected from me will be considered non-identifiable because it is being collected with all these coding routines, and then, 20 years from now when

somebody comes back and says, you know, we chose to re-link everything because we decided there was a reason for re-linking, it now has been transformed into identifiable information. From my perspective as the source of information, the status of that information changes over time.

MS. GOLDMAN: That is right. And there may be prohibitions, there should be prohibitions, on re-linking. It is not just that there is the possibility of doing it, and maybe it will happen. The idea of having a federal scheme in place is to give guidance that this is not appropriate, that the re-linking is not appropriate by the researcher. It may be appropriate in some treatment context, just as an example. But this is an issue that has to be determined early on, that we are not saying it is non-identifiable today, but 20 years from now maybe we will decide to re-link, that we need to make these decisions early on, and to create some prohibitions and limits.

PROF. CHARO: Last question. At the time we did the HBM report, it was my impression that not only OPRR but NIH as a whole had endorsed the version of identifiable which we used in our report, which is somewhat more solicitous of individual privacy. Has NIH changed its position, or was its position overruled by

the Department?

DR. MESLIN: I wonder if we could go and maybe ask Julie Kaneshiro, who I believe is here from NIH. Julie, are you prepared to respond to that question from Alta, and maybe just give an update on what the status is? Just come on up to the table, and take a seat at the microphone, and push your red button. Thank you.

MS. KANESHIRO: Hi. I would just say that the NIH is currently considering the NBAC's report on human biological materials through a working group that is run at the Department level, so we are considering it in collaboration with the multiple agencies within the Department, and are coming up with a formal response. So, I would say that the activities of developing a final rule on privacy, and also considering the Commission's report on biological materials is happening concurrently. So, at this point, I would say that we have not reached a conclusion about the issue of identifiability.

PROF. CHARO: But there was a prior position? Or was I misinformed?

MS. KANESHIRO: There were comments that we submitted to you in response to your draft report which did indeed, you are right, support the Commission's interpretation.

PROF. CHARO: Thanks. I just wanted to kind of

get everything straight.

DR. SHAPIRO: Okay, thank you. Thank you very much.

Tom?

DR. MURRAY: This is also for Janlori Goldman, and hello also to Joan. Janlori, first of all, let me commend you on trying to make an active and widely understood principle that when there must be identifiable data in research, that it should be only as much as is necessary, and only for as long as is necessary. Those are very important principles. Some of us have tried to honor them, but they really need to be made an active part of the consciousness of researchers and IRBs.

But then, let me ask about the Framingham study, because I started scratching my head and wondering just what you were asking us to do. As I understand the Framingham database, and other large, longitudinal databases, the whole point of creating them is that we do not know when we begin just what questions we will want to put to the data in the future. And one of the glories of those databases is that they allow us to later on frame questions that we didn't even imagine we would be interested in asking.

So, what would you have us do then with the people who contribute to those databases in terms of

protecting their privacy adequately?

MS. GOLDMAN: Well, I hope I am not going out on a limb to suggest that my unease with what has happened with the Framingham study is that it is going to be in the hands of the private sector, and that it is going to be--that we will not necessarily have the same-- I don't really know what the future is of it. But let me say that it puts it into question, and I think that it raises ethical issues, it raises some legal issues, and I think that it creates unease on the part of those initial participants. Because while, yes, it is a rich database that you want to be used over time, so that as you ask and answer certain questions it opens other doors and makes that information available for other purposes, there is a sense of trust that it will never be used in a way that could harm individuals, or that could be used to deny them certain benefits, or to expose them in any unwanted way. But that has always been in some ways a matter of delicate trust, and not necessarily one of legality. And so, as we are seeing more and more the information being sold, or made available for other purposes, it raises this issue of initial control. And it is the second, and third, and fourth uses of the information that were gathered for an initial purpose that raises concerns on my part.

DR. MURRAY: Just a brief follow-up. I think I hear two different threads of potential objection here, maybe three different threads. One is the privacy issues, which is what we are putatively talking about this morning, and I have never heard people--I have never heard sustained complaints about privacy concerns for the, you know, follow-up uses of the databases, even though they may have been uses not contemplated before. So, I am not sure that that is the central issue. It seems to me the two other issues are, number one, privatization of the database, marketing of the database, that that is something people-- And related to that, the understanding that people at least implicitly may have had when they agreed to participate in the study decades ago, that it would be used for certain kinds of purposes and not others. And the issue here is not personal privacy, but sort of respect for the subjects' wishes in terms of what uses might be made of the database, even if privacy were totally protected. I think those are all on the table right now. I just want to make that clear.

DR. SHAPIRO: Okay, I have quite a few commissioners who-- I will recognize Professor Sieber in a moment. So, I would ask commissioners and respondents to choose their most important question, and also, make it brief.

Professor Sieber.

PROF. SIEBER: I think it is important that we also, however, figure out ways of honoring commitment to data sharing. I think that most subjects are willing to be subjects because they want to help science, not a particular scientist. And I think also that the cost of research, and the uses of research, is really helped greatly by figuring out the best ways to organize data sharing.

If we are concerned about privatization, we might then be concerned about some of the organizations such as
Sociometrics that gets very worthwhile social and behavioral databases, cleans it, documents it, and then sells it to institutions for educational purposes. I think we have to be very careful to protect those interests.

DR. SHAPIRO: Thank you.

Alex?

PROF. CAPRON: I would like to thank both of you for one of the most informative and concise presentations of a difficult issue we have had in our work as commissioners. I would like just to get your help, Professor Sieber, on the definitions that you put forward, because I think it is helpful to us to think

about them as contributions that we could make in gaps in the present federal regulations. And I just wanted, if you could, to explain, on page 90, where you give a definition of privacy, why you state that privacy refers to, and here you underline it, "persons and to their interests", rather than saying "privacy refers to persons' interest in controlling access". And on page 91, if in your description of the addition to risks and discomforts, it would be adequate to say "including possibly unwelcome attempts to obtain private information". Just those two questions to you about your suggestions. Use your microphone, please.

PROF. SIEBER: Thank you. My underlining of "persons" is to indicate that this is not about data. It is about people. And I think that to say that one has an interest implies something cognitive and active, and I might not think about my interest in something, but I may come from a subculture in which, after I reveal some information, others of my kind would say, well, that was really dangerous, or stupid, or you are very naive. And so, I want to take it out of the exclusively cognitive realm when we talk about an interest. I don't think it is strictly an active thing.

Now, Alex, your second question was about--?

PROF. CAPRON: The second question-- You used

the phrase "including possibly unwelcome seeking or presenting of information or experiences, i.e., possible invasions of privacy", and you seemed to use the word "invasion" of privacy in a situation in which you would include authorized access to that information, whereas I think in ordinary language, the word "invasion" suggests some unwanted intrusion. And so, I was wondering whether the idea would be conveyed by simplifying it, and simply saying, as I think your point is, that you can feel stressed or discomforted by a possibly unwelcome attempt to obtain private information.

PROF. SIEBER: I like that.

PROF. CAPRON: Okay. Thank you.

DR. SHAPIRO: Okay. Thank you.

Steve?

MR. HOLTZMAN: This is a follow-up to Alta and Tom to Ms. Goldman. First off, a quick clarification. I thought I heard you say that identifiable in the new proposed regs, that there are a specification of 19 different criteria, the presence of which, any one of which, would constitute identifiable. One of those was zip codes. So that is this record said the following information about me, all this generic information, but said 02139, that would make it identifiable?

MS. GOLDMAN: Well, the way--

MR. HOLTZMAN: I think that is what I heard you say, but is that--?

MS. GOLDMAN: The way the regulation is written, and I know that sounds--the way that you have posed it makes it sound very far-fetched, but what has happened is that the way that they have tried to write it, and again, it has come under quite a bit of criticism, is to suggest that if zip code is attached, and then you have a diagnosis, and you have a diagnosis and maybe an age, or a diagnosis and maybe an employer, there are opportunities in certain areas to identify individuals. And so, they are trying not to make a hard and fast rule, but to suggest that the presence of certain identifiers--

MR. HOLTZMAN: Okay.

MS. GOLDMAN: It is just the way census data-- It is a very similar way that census data is handled.

MR. HOLTZMAN: So, but very specifically, I thought I heard you say that any one was sufficient, but what I am hearing you saying is the reg is basically saying look at these, and make a judgment, or--?

MS. GOLDMAN: The way it is written as a proposal, and I think we will see some changes, is that the presence of any one of those is sufficient to make it identifiable, which means that it is covered, which means that you then have to follow a set of rules in handling

it.

PROF. CHARO: I am sorry, but I find this so odd, because if there was a code that could actually be broken and lead you to the name and address of the person, that is not identifiable because that is a prospective use, but if there is a zip code that somebody might possibly in the future try to correlate with something else in order to be able to figure out the name and address of the person, that is identifiable, even though it is not a current use. I am just very puzzled about the hierarchy of concern.

MS. GOLDMAN: Well, and I think many people were exercised about it, and so it probably will change.

DR. SHAPIRO: The analysis of these proposed drafts we ought to stick away from. You can ask specific questions, but we will wait and see what these things look like, and worry about it at that time.

Steve, you had another follow-up question?

MR. HOLTZMAN: Yes, I just want to make clear if you think about something like Framingham and the whole-- I think there is a red herring introduced when there is private sector involvement. One of the things we are concerned of in the private sector is for the majority of our research, we don't want to know the individual. We are very, very happy to go through coded information.

What we do want to have is follow-up information with respect to the condition that is being studied. This Commission-- That requires at least a one-way code. There has to be a logical connection, even if in our hands we don't know, and couldn't possibly but for breaking a code, access the individual. This Commission took the position that that should have, as it were, the ontological and moral status of identifiable information with everything that goes along with that in terms of consents, et cetera. My understanding of where the proposed regs were going were saying something different, that that would not be considered identifiable, and hence, a lot of the apparatus about respect for autonomy would not go into place. Is that a fair interpretation?

MS. GOLDMAN: My understanding of what the proposal seeks to do is to say if a code exists somewhere else, if it is not within the control of the entity that has the data, that that suggests that the entity that is holding the data is not holding identifiable information, that it may be re-linkable if they then hook up with the disclosing entity, for instance, or the trusted third party that is holding the code, which is, I think, where we are going to end up going in this area, because you do, for certain purposes, want to be able to re-link, and

the suggestion here is not that you should never be able to do it, but there are certain kinds of information that would be outside the scope of the regulation, and certain that would be within. And being within doesn't mean you are prohibited from using it. It means that you have to follow certain ethical and procedural rules.

So, the idea that who is controlling the ability to re-link, that is an important question. And at the point at which information would be re-linked, it would then trigger a review and examination, the application of the rules.

DR. SHAPIRO: Okay. I have a number of Commissioners on my list, and if anyone asks questions that are too long, I will hold you responsible for having other commissioners left off completely when we adjourn this session. So, Diane, you are next, and then David, then Larry.

DR. SCOTT-JONES: I am sure Harold didn't mean to make that comment just before I started talking.

(Laughter.)

DR. SHAPIRO: You are right about that.

DR. SCOTT-JONES: Okay. I have a question for Joan.

Joan, you have been very helpful in helping us think about how the social and behavioral sciences need

to be included as well as biomedical research, and my question has to do with that, and it is also related to what Alex asked earlier about your definitions of privacy. You made the point in your paper for us that it is important to focus on education, and not just more regulation, and you pointed out how the Common Rule defines private information, but not privacy itself, and that it doesn't really define confidentiality, but merely interchanges that with privacy. I would like you to say a little bit more about how we in our report might attend to the social and behavioral sciences, so that whatever we recommend is appropriate broadly for research, and not remaining focused on biomedical research only. What are some specific steps that we might take as we work on the report?

PROF. SIEBER: Well, one of the things that comes to mind immediately is that the issue of personal privacy having to do with emotional and social features of one's life is so central to social and behavioral science, and I think, incidentally, most of what I have said is relevant to a lot of practice of biomedical science, and certainly epidemiology, which fits between the two categories.

I would like to take your question under greater consideration and get back to you. I don't think I can

give you a good capsule answer that I would be happy with tomorrow.

DR. SHAPIRO: With apologies for imposing upon you, that would be extremely helpful to us as something we are struggling with, and you have a lot of experience in this area and have thought about it carefully, so that would be very, very helpful to us. I would appreciate it if you could possibly take the time.

PROF. SIEBER: Maybe we could take a little time after this session and discuss the points that you have in mind. You have criteria that I might not think of. Thank you.

DR. SHAPIRO: Thank you.

David?

DR. COX: So, I have a question for Ms. Goldman, and a straightforward one. As you might have gotten the drift, a number of Commissioners may have a different view of what identifiable is than what you are presenting. So, in the spirit of not killing the messenger, but finding out who they are actually delivering the message from, could you clarify precisely the body, and even the person who is making this--

(Laughter.)

DR. SHAPIRO: What could you possibly have in mind, David?

DR. COX: --making this particular suggestion--

(Simultaneous discussion.)

PROF. CAPRON: Who may then become a body if we get our hands on him.

DR. COX: --so that NBAC would be in a position to maybe make a comment to that body or individual?

MR. HOLTZMAN: You can use one of 19 different identifiers here.

(Laughter.)

MS. GOLDMAN: I am going to give you a serious answer, but you won't like it, so you will continue my role as the messenger that is getting shot.

When the administration proposed the health privacy regulations in November of '99, they opened up a public comment period, obviously, and my understanding is that NIH and a number of others were involved, and that we, obviously, submitted comments. There were about 55,000 comments that were received; about half of them did come from consumer groups. And one of the issues that was highly contentious was this issue of when is information identifiable. It took a lot of heat. The public comment period closed on February 17th, so there is no one that you can call or talk to who is going to listen to you in any official capacity.

However, I think there are people who are

continuing to struggle with this issue, and continuing to try to write something that is both privacy-protective, and workable. I think that is the goal, to say in their defense, that is the goal, and hopefully, they will achieve it. So, I think that it is a proposal that is in flux. I can't speak to, you know, it any more than that, because I don't know. I am like you are, on the outside looking in, wondering what they are going to do.

Does that help? Sort of? Not really.

(Laughter.)

DR. SHAPIRO: Larry?

DR. MIIKE: I am sorry to end this on a more sobering note, but Dr. Sieber, you mentioned something that is really not important in the greater scheme of things, but it pushed a very hot button on me, and that is about talking about ethnic differences in the sense of privacy, and you used an example, ethnic Japanese who don't want to look you in the eye, and then you say, "especially in Hawaii", as a treatment of disrespect, but you give no references, and I would say that if researchers came to Hawaii from California with that in mind, a whole bunch of their research subjects like me would say, "Those are really weird researchers. Not one of them would look me in the eye. I am getting the hell out of this project!"

(Laughter.)

DR. MIIKE: So, I guess from my side, you inadvertently made your point, but not in the way that you intended.

PROF. SIEBER: Well, I think it is true. In giving IRB workshops in Hawaii, I have often been told that. However, it is a very good example of how generalizations never work, and I think that for the purposes of the paper--

DR. MIIKE: Give me the names of the people in Hawaii--

(Laughter.)

PROF. SIEBER: This is some group here! I thought you were kind of mild-mannered, intellectual academics. Everyone is taking names!

PROF. CAPRON: We are known as the Bioethics Enforcers.

DR. SHAPIRO: Larry, I think we will--

DR. MIIKE: Zip codes won't work.

DR. SHAPIRO: That is right. And you don't want just a number, right?

Thank you very much.

I just want to-- We have to bring this session to an end because we have another panel about to start.

First of all, I want to thank you both for very

helpful papers especially, and for your presentation, and also your presence here today. We are very grateful to you. I want to pose a question. I don't want to get a response now because we just simply don't have time, but one industry that has collected very personal and private information for a very long time is the insurance industry. And they have very sophisticated ways of sharing that data amongst each other, and they have a whole organization which, as far as I know, has done its best to protect the privacy of this information, but I don't have any direct knowledge, but that is my understanding. It seems to me to be a very good case to look at, and if on reflection either of you have any observations, or any place you might send me to look and read about that, I would appreciate it, because a lot of the health data we are considering now is really for the first time being collected and used and so on. So, I would appreciate that, any reference you might send me to, or any body you might send me to, that would be very helpful.

PROF. CAPRON: Mr. Chairman, I don't think we should end this discussion without noting for David Cox and other members of the Commission, that we did respond during the public comment period.

DR. SHAPIRO: Yes, we did.

PROF. CAPRON: All right. Because it sounded as though you thought--

DR. COX: No, no.

PROF. CAPRON: All right.

DR. SHAPIRO: So, once again, thank you very much. If the commission is agreeable, I would like to go just directly into the next panel. So, thank you very much for being here today, and I will try to get our next panel to join us immediately.

We are running a few minutes early right now, so let's take a bit of a break, because some of the panel members are not yet here. Let's just take a five or ten minute break.

(Whereupon a brief recess was taken.)

DR. SHAPIRO: Thank you very much. Our final panel today, as you know, deals with quality control, assurances, site inspection, accreditation, certification, licensure. I mean, those are all items that are up there in the air being talked about, and which we are going to have to be considering in one form or another.

And first of all, I want to welcome back Dr. Koski who was just here yesterday. Thank you again. I think we have used up 39 percent of your total time on the job in the first few days, and it will not continue

in this manner is the only thing I can assure you. But thank you very much for taking time again to be here today.

We also have Dr. Lepay is with us here, and of course, Michael Hamm, and you have seen some of the materials that he has provided us with before our meeting today.

So, I will turn directly to the panel, and start with Dr.-- I will just go across this way, and start with Dr. Koski.

PANEL III: QUALITY CONTROL: ASSURANCES, SITE INSPECTIONS, ACCREDITATION, CERTIFICATION, AND LICENSURE

PRESENTATION BY GREG KOSKI, M.D., Ph.D.

DR. KOSKI: Thank you very much, Dr. Shapiro. Thank you, Commissioners. Nice to be back.

Trying to catch my breath. I am sorry to be a minute late. I got off at the wrong Metro stop. I am still learning Washington. And I am sure that is not the only lesson that I will have to learn.

Let me just, before I begin remarks let me acknowledge my colleague, David Lepay, in his new role seated here to my right, because David and I are going to be working very closely together on a lot of things, and I am sure he is going to be a good partner, and he is going to be playing a very important role in the things

that we all have to do. So, David, it will be nice to work with you. Thank you.

I guess with respect to the question before us on this broad topic of quality assurance, quality improvement, licensure, certification, accreditation, and so on, it may be useful to at least give a few kind of broad comments that sort of focus on my own perspective on this.

I think that if we simply look at the activities that go on in the world around us in almost any specialized field of endeavor, no matter what it is, there is generally an expectation that the practitioners of that particular endeavor will meet a certain standard for performance, and that they will have a certain fundamental knowledge base, tool set, if you will, for performing those activities. And we see that in every facet of our lives, whether it is in our schools, in our drivers, as well as in our professions. So, it is certainly an important part of the way we operate. And in general, many of those licensing or certification activities result from the fact that there is a certain expectation from society that people will be performing at a certain level of proficiency.

Now, we see this particularly in the professions, whether it is in the medical profession, or

law, or other professions. Certainly in medicine, since the time of the Flexner Report, we have seen a radical change where medicine has changed from what was an apprentice system to one that used rigorous curriculum for education of the practitioners, as well as certification, licensing, examinations. I think that it is fair to say that probably none of us would knowingly, willingly, send our children to an unlicensed medical practitioner, because we know that if they are licensed, at least there is a higher probability that they will be performing to the standard that is expected.

My own feeling is that clinical research, particularly all research involving human subjects, has reached the point where it needs to undergo a similar transformation in that the apprentice system that has generally been the operating model for much of the clinical research that has been done is probably no longer up to meeting the challenges before us, and that it is time to recognize that we should have appropriate standards, requirements, for education and training, as well as performance. And that includes, I believe, not only individual practitioners, but also the various entities that are involved in one way or another, be they IRB committees, or data safety monitoring boards, or institutions, corporate sponsors.

As I mentioned in the model that I proposed in my comments yesterday, this subject-focused collaborative model, each and every one of the parties engaged must know what their responsibilities are, they must be properly trained to execute those responsibilities, and there needs to be some, I believe, objective means to assess and document that, in fact, they are prepared to do that. So, I think that sort of covers the sort of basic layout.

To go into a bit more specific detail, it would make sense to me to have a uniform set of educational requirements, or expectations, standards, again, for all of the individuals participating in clinical research. Although there are, as we mentioned yesterday, separate regulatory authorities for the various agencies within the federal government which to a very large extent either fund or regulate most of the research that is done with human subjects in this country, it seems to me that it should be possible through the acceptance of standards at a high level by all of those agencies for there to be independent application of those within their own regulatory framework, at least as a starting point, recognizing that it may be necessary to move further toward rules and regulations in the future, in order to ensure that all of the agencies are able to meet their

specific regulatory requirements.

So, I believe that starting with individuals, laying out clear and uniform standards for the training and education is an important start. I see absolutely no reason why an individual who is doing research under corporate sponsorship that is regulated by the FDA should have any less training, or any more training, than anyone who is doing research for another federally-funded project. A clinical investigator who is working with human subjects, in my mind, is pretty much the same across the board, and those requirements should be uniform.

I believe that OHRP in its new configuration is well-suited to helping lead the effort to establish those uniform requirements, and we look forward to working with the other federal agencies, both within HHS and outside of it in order to do that.

With respect to the entities, I believe that, again, institutional review boards and data safety monitoring boards should have specific standards that they should work to. There already, as you are well aware, is an effort ongoing with strong support from AAU, AAMC, PRIM&R, and other organizations to begin to establish standards for IRBS.

In the current world, it is entirely possible

for a small start-up company to find a group of five qualified individuals and establish it as an IRB as long as they meet the requirements within federal regulations. That may not be the standard that we want to apply. It seems to me that an IRB that is constituted for a short period of time in order to approve a couple of studies and then abandoned is not the way to go, so that having standards that will apply, again, for all institutional review boards is, I believe, a critical step forward. Those standards would need to be established and recognized by the entire country, and hopefully, we would be able to even achieve international standards for institutional review boards, since as was discussed yesterday, there is an increasing amount of research that is done in the international domain. Applying those standards through a publicly accountable accreditation process is an important step toward bringing all of the IRBs up to a level of function that we can be proud of and comfortable with. Clearly, we need to do that in order to establish the trust that is so important for the biomedical research endeavor.

Finally, I believe that, you know, just as industries currently will proudly display their ISO 9002 certification on the side of their buildings, it is important to recognize that there is a powerful motivator

here for all industries and all institutions to adopt these standards in all of the research that are performed at their institutions, or supported by their institutions. It will actually facilitate the conduct of research on all fronts by letting everyone know that it is being done at the highest possible standard. And so, there is value to, you know, industry as well as the academic institutions to making appropriate assurances that they are going to use accredited institutional review boards, and have work performed by certified members of the research team.

There is a long way to go to bring all of this about, but you have to start somewhere, and I think that this is probably a good time and place to start.

DR. SHAPIRO: Thank you very much. I would like to follow the practice we have set. We would like to hear from each of the speakers before we go to questions.

So, Dr. Lepay, thank you very much for coming. I think, in addition to many other distinguished aspects of your career, your title is one of the longest we have had to type down here, to my recollection. But anyhow, welcome--

DR. LEPAY: Thank you very much.

(Simultaneous discussion.)

DR. SHAPIRO: --in the FDA. Yes.

PRESENTATION BY DAVID A. LEPAY, M.D., Ph.D.

DR. LEPAY: I want to thank Greg Koski, also, for the introduction this morning. We certainly do look forward to working together very closely, particularly over the next several months where there is a lot to be done.

(Slide.)

I am going to be very concrete today, because the charge that was given to me by the Commission was to, in fact, address FDA's inspection program for IRBs as it exists. This sounds like a fairly straightforward task, even given the time constraint of about 10 minutes to do it, but in fact, it is not all that simple a task, especially when one of the goals, I would imagine, of the Commission is to compare and contrast systems, and to develop some recommendations from the results of their analysis.

And I think what makes it difficult, in fact, is that the clinical trial process is a very complex one with a large number of players, a large number of shared responsibilities between these players, and a very large number of interactions that go on in implementing these responsibilities. And in fact, I think the best analogy may be one of neuroanatomy, and that is the one I will

propose here, namely, that you have to initially get some kind of handle on each of the individual components. You have to learn each of the individual pathways, but it is not, in fact, until you are at least familiar at some level with all of the pathways that you can begin to make some sense of the specifics of any one given pathway. And in fact, from that standpoint, I will say that the whole may be greater than the sum of its parts.

So, in fact, and in dealing with a few opening perspectives here that we are going to project, I think there are a couple of points that need to be raised right from the start about FDA's--or about any oversight system, but FDA's in particular. First of all, we have to avoid taking up IRBs as independent of the other parties that are involved in the clinical trial process. Fundamental. We have to avoid from FDA's standpoint, the possibility of taking up on-site inspections independent of FDA's in-house review process. This is a process that, in fact, is going on in real-time, involves several thousand people in Rockville looking at protocols, receiving and analyzing safety reports, and following trials through all phases of drug development.

A third point that I think is important to address is we have to avoid taking up FDA inspections independent of discussing a sponsor's responsibility in

the FDA system for real-time monitoring and auditing. It is often very simple to say FDA is not out there everywhere in real-time, but in fact, we have a system of shared responsibilities in place that put some of that burden on sponsors to be out there in real-time.

We have to also avoid taking up U.S. GCP standards and implementation without considering the interrelationship of U.S. and international GCP standard-setting, the various international regulatory cooperative activities that have been going on for the past decade, and the fact, indeed, that harmonization is leading to improvements in the clinical trial process globally.

And I think the fifth point I want to take just as an opening perspective is that we have to avoid looking at data quality and integrity as separate or isolated from human subject protection. And this is a very important point. We have to look at data from the standpoint of what it is. Data that is generated from a previous study is going to be used as the basis for decision-making about whether a new study should proceed, whether indeed, data has to be taken into account in the process of initial review. Data that is generated during the course of a study is going to be important to analyze in continuing review. So indeed, that is part of a public protection.

And finally, data that is submitted at the conclusion of a study that is submitted for marketing purposes is going to form the basis for labeling of that product, the way it is going to be used in promoting the public health as well as a public protective measure in conveying risk. It is going to be used in the scientific literature as a basis of influencing medical decision-making, and ultimately that data from any particular product is going to be used as the basis for decision-making on the next set of clinical trials when you have to decide what control arm you are going to use, and how you are going to appropriately use it.

So, I think it is very important to keep all of these points in mind, and not simply focus on one particular element out of context. And that is where I am really going in these opening perspectives. Very quickly, as we say here, the point being that good clinical practice, that which we are trying to achieve in FDA, is a system of shared responsibilities in which there are defined responsibilities for each of the participants.

(Slide.)

Additional points that I, hopefully, have made is that each party involved in clinical research has responsibility for human subject protection under FDA

regulations. Human subject protection is not solely the IRB's responsibility; it is the responsibility of all four parties, and this is written into our regulations.

Human subject protection is also, as I mentioned, a component not just of on-site inspecting, and we don't want to restrict ourselves to say FDA oversight is only what we do on-site, or at an IRB. In fact, the in-house review component is very critical to human subject protection at FDA. And the integration of review with inspection is also a fundamental tenet of how we operate.

(Slide.)

Each party involved in FDA-regulated research is subject to inspection. It is not just the IRB. There are programs for all of these parties, and human subject protection is addressed in inspection of each of the involved parties.

(Slide.)

So, very quickly, I am going to go through in a very few minutes what the nuts and bolts of our inspection process is. Our inspections are, in fact, conducted according to protocol; SOPs are compliance programs. They are available publicly. They are known widely through industry, among IRBs. They know what we are going to look at, what we are focusing on. Our

inspections are typically pre-announced, but we do have the authority to go in if conditions should warrant in unannounced inspections. And the way inspections are developed, they are assigned by offices in Rockville at headquarters in conjunction with our review division, and are conducted by field investigators located in locations across the United States close to the site of inspection.

(Slide.)

Our inventory. We have about-- At the moment, the way we develop our inventory of IRBs is based on investigator statements. It is a requirement of investigators, at least in drugs and biologics, to sign an FDA form 1572 which includes basic information as well as commitments as to what that investigator is agreeing to in taking on the responsibility for an FDA-regulated study, and one of the pieces of information that is required of investigators is identification of their IRB. And from that information, we within drugs and biologics have a database that currently contains 1573 IRBs that we know are doing FDA-regulated work.

When we choose among these to inspect, obviously we have limited resources, and we have to be able to prioritize. And our priorities as we have set them up in our stratified schema is to look at the three areas that are indicated here, first and foremost, that is, new

IRBs, IRBs for which we may have information of problems, either through our review division or outside complaints that we have received, as well as if we have inspected previously, we have cited deficiencies, we need to go back sooner, of course, to confirm that these deficiencies were corrected.

(Slide.)

The inspections take typically two to five days, conducted by a single individual, in work hours about 58. And indeed, right from the start, the focus of our inspection program as it is stated in our compliance program for IRBs is that the inspection is there to provide on-site information and guidance to IRBs. Obviously, there is a compliance process associated with this. If we do see serious problems, we have the ability to impose administrative sanctions. But our inspection program for IRBs is designed with the concept that IRBs are allies in the process of assuring human subject protection, and we are out there to be on-site to provide information and guidance.

(Slide.)

It is a process-oriented inspection, and this has been discussed, I think, at various levels both here and within the Inspector General's office. But of course, in designing an inspection program, we have to be

guided by our regulations. We are a regulatory unit, so therefore, of course, we have to build into our inspections what we are supposed to do, and look at by regulation. And indeed, this is how we have developed.

We do, in fact, choose current as well as recent representative studies when we go on-site to IRBs. It is not necessarily or, hopefully, not frequently done where you are just going after a study that is three years completed. The idea is to identify with the IRB the current inventory, and to follow through, to track through how an IRB has handled the oversight of this particular study, as well as the paperwork that is associated with it. The inspection does include interviews as well as examination of procedures and records.

(Slide.)

So this is what is in the compliance program. This is what is examined. Basically, very quickly, looking at IRB membership, looking at the written procedures that are out there, following through with current protocols, initial and continuing review from the standpoint of authority, process, frequency of continuing review.

(Slide.)

Our regulations require documentation. That is

a regulatory authority. So, certainly, we have to be out there looking at documentation and record-keeping. This is a focus. We are looking at a systems approach here. We are looking at how IRBs interact with the clinical investigators, and with the institution. We also are out there looking to see if they are properly using expedited review, if they are properly using emergency review, and that can be review for emergency use, or under waivers of informed consent for emergency research. And we are out there also acquiring representative informed consent forms, looking, indeed, whether the informed consent forms meet the basic elements of the regulation, and also, enquiring about the process by which consent is being obtained. And that is an important component of what we do on interviews during inspections.

(Slide.)

The follow-up to an inspection. At the end of the inspection, there is an exit interview, and at that time, if there were any inspectional observations, and observations have to large--at least what is printed, what we write, has to be built on regulatory requirements. We may discuss practices, we may discuss what we have seen that may be different from guidance and so forth, but ultimately, we have to focus in on what we have regulatory authority over. And from that exit

interview, from any observations that are taken, those are the observations of the investigator on-site.

He or she will develop these into a report including exhibits, documentation of what was observed. These will then be forwarded back to the assigning office at headquarters where they will again be reevaluated. There will be a final classification, and a close-out letter, as well as if there are any needs for initiation of compliance actions, that is when it will be taken.

(Slide.)

I think we have gone through these at times before, but it is useful to remind. What are our authorities as far as compliance actions against IRBs? With IRBs, we are not necessarily--or we are not talking about rejection of data. Most of our inspections are, in fact, voluntary action inspections, and the corrections are typically achieved quickly. The official actions that we can take, however, include warning letters, include the withholding of approval of new studies, include the withholding of enrollment of new subjects. We can terminate ongoing studies, and we have the authority, at least, to take both administrative procedures toward disqualifying an IRB, as well as criminal procedures where that might be necessary, including injunction and prosecution.

(Slide.)

It is a due process system. The IRB can respond, as can any inspected party. They can respond to FDA at any point during, after the inspection, and indeed, those responses will be reviewed when they come back to us. If we have them at the time that we are making our assessment, all of that is taken into account in developing our regulatory communication, and in developing regulatory action.

We also do exchange information, and certainly, that flow has improved greatly in the recent past between ourselves and OPRR, now OHRP, in the exchange of regulatory communication, our close-out letters, and we receive copies of OHRP's regulatory communication.

(Slide.)

So, what are some of the limitations? We said that we have an inventory of about 1573 IRBs out there. We have the resources, what we are given the resources to do is about 250 to 300 IRB inspections per year. Of these, from FDA's perspective, about four to five percent of these result in official action. The official action is most typically a warning letter with corrections very quickly put into place by the IRB. They respond very fast to warning letters in just about every case. In three cases in the past fiscal year, we had to impose

sanctions, and those sanctions were limiting new studies, and limiting enrollment into new studies.

(Slide.)

The problems that we see when we have to take actions, they are not isolated, single problems with, indeed, a piece of paper that wasn't flowing. If you look at these, of the 15 warning letters that were issued between January of '99 and March of 2000, you will see there is tremendous overlap in problems. Fourteen of the 15 have problems with procedures; 13 of the 15 also had problems with documenting activities; 10 of the 15 had problems with continuing review; nine of the 15, problems with expedited review; seven of 15 with problems in informed consent and meeting the requirements of informed consent.

We don't take official action lightly. We are looking, in fact-- We are trying to approach this from an education and corrective stand. However, when you see multiple problems as you do in these 15 cases, that is where we go in with action, and that has typically been our approach.

If I can have the next slide--

(Slide.)

It is not to say there are not a number of areas, in fact, that do evoke voluntary action, and where

we have to work to identify and educate correctable process deficiencies. And many of these, again, deal with documentation, but they are fundamental. Eight percent dealing with problems, even the performance of continuing review.

So, where does that take us? If I can go to our last slide.

(Slide.)

Obviously, this is a dynamic process. I think it is a mistake to look at any inspection program as simply a static process that goes unchanged, that does not take into account emerging problems in clinical research or emerging technologies, and certainly, we have to take those into account ourselves. And over the past four years, in my work in DSI, certainly we have tried to look at ways that we can improve the process within the framework of our regulations.

And for us, where we are going right now, certainly we are focusing much more on the informed consent process versus the form. We are very interested, again, within the capacity that we can define it within our regulations, into enquiring about the qualifications of those administering informed consent. And particularly, if those are not the physicians who are the clinical investigators themselves.

We are looking at subject recruitment, and subject recruitment in our eyes, in our regulation, is the beginning of the informed consent process, and this is, of course, an area that we need to reaffirm with IRBs, and we need to move forward and put attention to.

As we look to how we can improve IRB performance, one of the key issues in IRB performance is access to information for subjects, and this is something we are looking to increasingly enquire about. Are those numbers that are given real? If somebody dials a number, a contact number, are they getting the contact they wish? Are they getting the information out of it that they wish? These are things we can approach, and we are moving toward.

About four weeks ago, of course, the Department sponsored a workshop on conflict of interest. This is still a very active comment period extending until the end of September. We expect that as those comments come in, as we have dialogue across the Department, that will be a direction as well that we will be pursuing.

And finally, responsiveness to complaints. And when I say that, I am speaking of both responsiveness to complaints by IRBs, as well as by each of the processes in regulated research, including ourselves. This is something we have to build into the system. We talk

about real-time, we talk about real-time protection. One of the best ways of assuring real-time protection is to be responsive quickly to problems as they occur, and that is certainly a focus right now of FDA's inspection program.

I thank you very much for the time.

DR. SHAPIRO: Thank you. Thank you very much for those very helpful remarks.

Let me now turn to Mr. Hamm for his remarks, and then we will go to questions.

PRESENTATION BY MR. MICHAEL S. HAMM

MR. HAMM: Okay. Thank you for inviting me to address the Commission.

I am a consultant for certification and accreditation organizations, and organizations interested in developing these programs, so I am approaching this as a lay person from your point of view, but I can address questions regarding these organizations and what they do, how they operate.

I thought I would just give you a little overview of the accreditation/certification world. The first thing I always address with crowds that are somewhat new to this are some definitions, because the terminology has been somewhat of a problem.

Generally, I refer to accreditation as a process

to evaluate an organization or a system, whereas certification is a process to evaluate the knowledge, skills, or abilities of individuals, and unfortunately, for various reasons, some organizations prefer to use one of the terms just because they think it sounds better, and there is a fair amount of confusion there, but that is always an issue. I have to ask when someone says "We accredit or certify", you always have to ask exactly what they mean, because the terminology is used in various settings in different fashions.

I guess the issue of why it is important to government, when I hear of government approaches, regulatory approaches, I think of this as the club or stick. Voluntary certification/accreditation are more the carrot side, although having said that, there is shades of gray. I guess I would have to say as accreditation/certification programs evolve, in terms of their relationships with government and other stakeholders, they also have a little stick, too, and sometimes that stick is growing. So, there is a lot of overlap, and in fact, some attorneys have even described some of the more powerful accreditation programs in the country, such as the Joint Commission for the Accreditation of Health Care Organizations, as quasi-regulatory bodies. And it is an interesting

concept, because even though it is voluntary, frankly, from the point of view-- I come out of a hospital background, and the reality of it is, in 2000, if you are a tertiary care center involved in research and teaching, accreditation is not voluntary; it is mandatory. So, I mean, that is some of the dynamic that we are dealing with.

But in terms of the things accreditation can do, and I will start out with what I think is the most powerful impact, both accreditation and certification have the power to improve the performance of individuals and organizations, and that is the bottom line. That is why I deal with organizations, sometimes looking at their strategy or mission. I mean, that is really the essence of it. And they can achieve this in kind of an interesting fashion, not by forcing something, but by letting the peer pressure, and building this philosophy of self-improvement, and that is really powerful. To me, I like this much better than regulatory approaches because I have seen the whole change that can take place in an industry when there is this philosophy of self-improvement, like we would rather do it ourselves, set the standards, and try to live with them, than have someone else impose things.

I realize, of course, in every field there have

to be requirements, too, but certification and accreditation can complement regulation. In accreditation in the field you are dealing with, federal regulations have to be a major component of it. So, I think the two fields are complementary, but the important thing is the voluntary, private accreditation efforts actually have that potential to sort of improve through changing the whole mind-set about improvement as a responsibility coming initially from the organization.

The other thing I would say is from a government point of view, this saves money. These are very cost-effective. To have another organization take on the role of developing the standards, building support for them, measuring compliance with them. If a federal agency were to fulfill that requirement, it would be a whole new regulatory initiative. So, many agencies look at this as a way of, basically, extending the impact of the government through a private sector initiative.

And also, the standards, as I mentioned, there is interchange. The accrediting bodies can use government standards; government agencies will be looking at the accreditation standards, and certification standards. So, there is an exchange of the information, although this is a little bit dangerous at times. I guess one of the fears, occasionally sometimes a

government agency will use an accreditation standard for a purpose it wasn't intended for. I will give you one example.

In another life, I was working with an organization, the Accrediting Commission for Graduate Medical Education, ACGME. At one point, one of the federal agencies decided that maybe they could use accreditation systems to rank residency programs, and decide who should be funded. Well, there is an example of something that may have looked very nice in terms of a way to have somebody get some information that could help achieve another agenda, but I can tell you from the point of view of an accrediting body, that was a kiss of death. And of course, they backed off from that. That is the danger, though, of misrepresenting sometimes what is the purpose, or the results.

And both certification and accrediting bodies have to be very careful about how they represent what their achievements mean, and how they are used. Sometimes, for instance, a danger in certification is people equate certification with competence, an overall definition of competence, and I am always warning people, it is just one part of it. Competence is more than passing an exam showing a minimal level of knowledge, skill, or ability. There is a lot more to it. You have

to be very careful, because sometimes employers or other stakeholders assume, well, if someone is certified or licensed, they have been blessed. There is nothing more that you can expect. And that is wrong.

And again, it goes back to that question of asking the questions of the quality of the certification program, or accreditation program. There are very good programs, and there are some very bad ones. Fortunately, by and large, in certification and accreditation, most of the organizations, because of the very nature of this business, are interested in doing a good job. This is not a field where a half-baked effort has any benefit. Most of the organizations, before they get into these fields, realize they are making a commitment to quality, and they are coming up with, basically, the best programs they can. But it is not easy. Certification and accreditation are expensive activities. They take a lot of time. And they are very controversial, too.

One of the interesting things is that the sponsors of most certification and accreditation organizations in the United States are non-profit associations, professional associations, 501(c)3 and (c)6 organizations. One thing that comes as a little surprise to these organizations when they get in the accreditation business, all of a sudden they are in the discrimination

business, and this comes as a little shock. Whereas, normally an association can be helping its members by educating and training them, giving them all sorts of benefits, now, all of a sudden, you are saying, "You are in, and you are not in". And that results in lawsuits, legal challenges, ill-will.

So, as a result, many of the certification and accreditation bodies look toward an administratively independent structure, sometimes separate from the organization, and that is another sort of a good practice in both certification and accreditation. But the dilemma of that is that it costs extra money, it is harder to put together, so many of the organizations have to start out within an association very close to it, but hopefully, moving toward an independent structure which is frequently more acceptable by other stakeholder groups such as government, the public, et cetera.

Just a couple of trends in accreditation/certification you might be interested in. The number of certification bodies is growing fairly rapidly. I wrote an introduction to a directory about five years ago that listed 1600 certification and accreditation bodies. It is well over 2000 now, and growing. Far more certification than accreditation, although there is growth in accreditation, too.

The quality of certification and accreditation bodies is improving. The staff, the structure, the funding, I see definite improvements, although there are not any national or international bodies that set a minimum standard to be an accrediting or certification body. So, literally, any organization can put together a certification or accreditation program, and sort of it is let the buyer beware. So, there is questions you always have to ask as a third party, sort of looking at how valid and reliable the process is.

Other trends. Government is increasingly interested in both. I see sometimes certification used in bid specifications in the health care field. Health care has embraced both the certification and accreditation. As I mentioned, Joint Commission for Accreditation of Health Care has a major role in establishing quality standards, not just for hospitals now, but for a variety of health care organizations. They even have the concept of deemed status which is interesting, saying that if you meet the private, voluntary accreditation standards, you are deemed in compliance with Medicare conditions of participation. So, this is a strong link between government and a private standard-setting initiative.

Another example where you have this link is in

education. The U.S. Department of Education, the Secretary of Education sets standards for academic and educational accrediting bodies, and in fact, the reality of it is, those standards are so powerful now, they drive a lot of the practices in academic accreditation. It is not an option, frankly, if you are accrediting institutions.

So, there is a lot of interest, and in fact, there is even a national commission looking into standards for certification to be used in bid specifications. I think it is primarily of interest to the Department of Defense, but I think that will also probably affect other government agencies.

So, those are some of the things that are happening, and I think should be of interest.

Some of the concepts that I think are important to keep in mind, accrediting bodies are given a fair amount of leeway by the courts. They still can get in legal trouble. The greatest danger for accrediting bodies is anti-trust, or restraint of trade issues. They have to be very careful to make sure the standards really don't have the impact of discriminating against a certain class of provider, and frequently the challenge is in size. The smaller organizations are challenged.

When I worked for the American Hospital

Association, sometimes I used to deal with the Joint Commission for the Accreditation of Health Care Organizations, and my test was, if that nine-bed hospital in Jackman, Maine, can do it, I will feel comfortable with it. And that is a challenge. That is not easy to do. And I will have to tell you, when you look at that book of requirements for accrediting health care organizations, that is a constant source of tension. But it is one of the biggest challenges. And you can always go to court if you feel the impact of the standards is some form of discrimination.

The other thing is marketing challenges, and this is somewhat of a dirty word in the standard-setting, but the reality of it is new certification and accreditation efforts have to sell themselves, especially if they are not mandated, and that is not easy, when you think about it. Who gets excited about taking a test, or being tested? You remember the reactions you had about tests. It is not something that people have a warm, fuzzy feeling in their heart about. It is generally something you do because you feel it is important to your career, your profession, an employer encourages you. But it is not easy to sell these things.

The same thing with accreditation. Applying for accreditation is an expensive process. It is a major

decision for an organization. They have to weigh the pros and cons. So, marketing is a major issue.

Some of the ways that-- I don't have much time left here, but I will just give you a few of the benchmarks I use to evaluate certification/accreditation programs. Probably the most important is the standards themselves. Are the standards valid and reliable? Valid meaning, do they measure what they are supposed to measure? Reliable meaning, can they do it consistently, looking at different applicants and organizations? So, those are sort of the gold standards. And those things are not easy to measure, but any organization looking at an accreditation or certification process needs to ask that question.

The other thing, a trend in both, primarily accreditation, but certification, too, is getting away from looking at the structure and process, and more the outcomes. Outcomes is sort of the major movement in the accreditation world. This is hard to do, but it is something most accrediting bodies are looking at, and the issue being is somebody may have all the pieces in place, have nice sets of minutes, comply with all the regulations, but if the outcome isn't what you want, they really haven't achieved the goal of the process.

For instance, in educational accreditation, (I

have served on an educational accrediting body), when all is said and done, you go out and talk to the students. You know, you can look at papers, minutes, accounting records until they are coming out your ears, but what is it all about? You have got to go out there and just measure exactly what did it achieve. And sometimes it is actually talking to the students, talking with the patients, things like that. And putting the burden on the organization to say what was your objective, and how did you meet it? Because sometimes the accrediting body really can't decide that. It is going to differ from one setting to another.

But at any rate, those are a couple of the key things. I think I will cut it off here. It is bad to be competing with lunch, too, I guess.

DISCUSSION WITH COMMISSIONERS

DR. SHAPIRO: Well, thank you very much, and thank all of you for keeping your remarks exceptionally coherent, but also, within our time frame.

Let me just begin by turning to Marjorie for a second. She wanted to ask a specific question of Dr. Koski, and then we will go to members of the Commission.

DR. SPEERS: Dr. Koski, my question for you is, could you, in just a few minutes, tell us what is the status of your office's revision of the current assurance

process? We have heard that that process is being revised, so we would like to know the status of it, and it would be helpful for us if you could address it, both in terms of domestic assurances, and international assurances.

DR. KOSKI: Thank you, Marjorie. The assurance process has had an enormous amount of effort put into it, headed up primarily by Tom Puglisi and Cliff Scharke, and basically, they are pretty much on the launching pad with the simplified assurance process that was recommended, and our hope is-- I mean, the original target was to be able to roll it out yesterday. We missed yesterday, but the pressure is on to continue to get that, you know, completed as soon as possible, and right now I think the target for that would probably be October 1.

So, that process is one that accepts the recommendations that have been made to simply have a single standard assurance. There are some challenges with respect to implementing that for the single sites we have called Single Project Assurances, but again, we will continue to work on that. But basically, that part is ready to go.

And there is a Single International Assurance also. I have spoken with the team about actually rolling those two together into a single process. We think that

this may not be the time to do that quite yet, but indeed, I think that yesterday there were citations of some of the international standards that have already been established with the CIOMS, or the ICH GCP guidelines, as well as others that are there. There is even a set of international operational procedures and guidelines for institutional review boards that I believe were-- I saw the book waved around at the front table yesterday. So that simply, again, by recognizing those, having a standardized international assurance should also be possible, and that will be rolled out concurrently with the other. But for now, we will keep the-- Because there are some subtle differences between the international guidelines and those that we use in this country, we will probably keep the two separate for now.

I hope I answered your question.

DR. SHAPIRO: Okay. Thank you very much. Let's go to questions from commissioners. Bernie, then Larry.

DR. LO: I first want to thank all three of you for very useful and concise, lucid comments.

I want to try and take some points that Michael Hamm raised, and ask Dr. Koski and Dr. Lepay how that might play out. I mean, it seems to me in any accreditation or certification process, the choice of standards, or variables to look at, is key. And Mr. Hamm

correctly pointed out that ultimately we are interested in outcomes, rather than structure or process. And as we all know from clinical quality improvement initiatives, it is much, much easier to look at structure and process, and in many ways, that is the bedrock. If you don't have a quorum, you know, how can you do anything?

But as I think about the kinds of issues that have raised the substantive concerns, the consent process. Dr. Lepay mentioned that. But it is not just the qualifications of the people getting consent, it is-- You know, the form was right, but what was said contradicted the form, or gave the wrong impression, or somehow at the end of it, when you talked to the patients, studies show over and over again they don't understand what they just consented to.

And as I think about medicine, we have been lucky that for many things we care about, there are measures that are easy to collect, that everyone agrees are important. You know, post-op complications and morbidity, you know, we want to reduce those.

Where do we get standards that are valid, reliable, ethically meaningful, and easy to collect, so we are not sort of imposing a whole new set of data-gathering activities that sort of aren't worth the cost of collection? It seems to me, those are challenges, and

if you folks could give us your thoughts on that, it would be helpful.

DR. KOSKI: Well, I will just jump in. I will tell you that we are currently engaged, and have been engaged in a process to deal specifically with the challenge that you mention.

Establishment of standards, as Mr. Hamm pointed out, is something that must be done with sufficient input from sort of all of the stakeholders in the process, as well as the experts, that what comes out of that process is something that is going to be universally recognized as being both valid and reliable, so that they can be applied, essentially, by any, you know, body that chooses to get into the accreditation process. And we are currently working on doing that, and I think that what we are trying to do is to capture the value of the work that has already been done to try and leap-frog this process, and move it forward as quickly as possible.

Actually, I will be announcing specific details of this soon, but I am not at liberty to do that right now. But clearly, this is a very, very high priority, and I think I wish that I had said everything that Mr. Hamm said, because it clearly, I think, lays out very clearly what the challenges there need to be.

With respect to the quality issue, that is, you

know, the Holy Grail. How do we really get there? Are we sure that we are doing what we want to do? And there are no easy answers to that. Again, as you pointed out, sometimes you have to go to the people who, you know, if the goal is to protect human subjects, then you may have to go to the human subjects and find out, okay, what is the incidence of their actually understanding what they got into. What is the incidence of people actually being harmed in research?

I actually met last week with John Eisenberg from AHRQ. They are trying to develop appropriate methods to validate quality of care, and so on. John seemed very enthusiastic about bringing the intellectual resources of his organization to bear on this process as well, to try and define the, you know, what quality would be.

The process that we are moving forward with is one that incorporates into it not only the establishment of standards that could be used for accreditation of institutional review boards, but also, as a second part of that effort, a definition, an analysis and definition, of what appropriate outcome on quality measures would be, so that when we look at what we have done two years from now, we will be able to make an objective assessment as to whether or not we have accomplished our goals.

DR. SHAPIRO: Thank you very much. Larry? Oh, sorry--

DR. LEPAY: Again, this is an area of certainly very active conversation in Dr. Koski's three official days on the job, my 13 in trying to coordinate some of these efforts across FDA. We have had now two conversations that have dealt very much with this particular subject, and clearly, it is very clear as we discussed it internally within FDA, that we have to find a way to engage stakeholders in this discussion. And we have to make sure that all stakeholders are, indeed, represented. We can't simply just go to the IRBs, or to their administration. We have to make sure, in fact, that the academic medical centers and their administration is tied in, as well as a recognition that more than half of FDA-regulated research is now performed outside of the academic medical centers.

So, it is really getting this dialogue going, and then trying to, in fact, systematically sort through the recommendations that are given to us, and we are certainly looking at ways of soliciting those recommendations.

DR. SHAPIRO: As I looked at some of the overheads that you projected of what you did in inspections, and people you spoke to, I understand it was

a summary; it wasn't meant to be fully detailed, and so I just want to ask a question. Would any of those inspections ever speak to human subjects, people who are actually participating? Is that ever part of the effort?

DR. LEPAY: It is not a routine part of the effort. I mean, typically, we have gone to speak with subjects when, in fact, the subjects themselves have come to us with complaints. We have gone in cases where we have seen particular issues that, in fact, require our resolution with individual subjects. I think, as was discussed yesterday, in fact, when we are talking about IRBs, most IRBs themselves do not have contact with subjects. So consequently, going to an IRB, we do sit in on meeting on occasion, but going to an IRB is not going to be a source of contact with subjects, and being able to pursue from that end.

DR. SHAPIRO: Thank you. Larry?

DR. KOSKI: If I may just add one quick comment.

DR. SHAPIRO: Yes?

DR. KOSKI: It may well be that establishing simple mechanisms for the public, for the subjects, to actually get in touch with those people who are responsible for the oversight, where we could even, for instance, track the number of, you know, calls of concern, or complaints, or whatever, over a period of

time-- And one of the measures of effectiveness that you could imagine was to see a decrease in the numbers of problems that are reported. You could even count news stories in the media for that matter. But I think looking at various indices that provide some real evidence that at the point where protections are supposed to be having their benefits are actually working, will serve us well.

DR. SHAPIRO: Larry. Sorry.

DR. MIIKE: Listening to the discussion on accreditation and certification, it seems to me that (and I know we can't get into it over here) is that it is not just an add-on. It is going to change your whole way about how research is done, who is eligible. And say, for example, you are certainly not going to be able to come out with a Single Project Assurance accreditation, and things like that. So, it is going to change the whole way in which the research is going on, especially as it seems to be decentralizing more and more.

But my specific question is for Dr. Lepay. You mentioned that in your oversight of the research that is undertaken, you look at the researchers, you look at the sponsors, you look at the contracting research organizations, you look at the IRBs, and the human subjects, however adequately or inadequately, is

addressed in all those issues.

Now, what we hear over and over again is that the kind of routine examination of IRBs you do is exactly like what OHRP does in the process side. Have you folks ever examined the information that you get across the project in these different areas? Or alternatively, is that information available and subject to analysis so that you can give us a more systematic overview about here is the IRB, here is--well, actually what you find out in these other areas? Where is the disjoint in there? And where is the information that supports it?

It seems to me that your information is something that can start to help address that question without having to undertake a whole, brand-new approach to that. And I know there would be issues of confidentiality, et cetera, but you can certainly do an across the board group analysis of that, and it probably would be helpful to Dr. Koski's organization. But have you done that? Any of those kinds of things, and try to improve your examination of the IRB process in the FDA oversight?

DR. LEPAY: Well, I think this is something we are talking about, certainly as we look into more scientific approaches to be able to get information from our inspections. And indeed, you know, it has only been

the past few years where we have really started--two, three years, because that was an interest of mine, into even developing some basic metrics. I think now we are at a point where we need to refine what those metrics might be, and how we can use them. I mean, we have tried to develop them from a standpoint of sponsors, what they do in monitoring, get some basic information. But certainly, these are areas we need to-- We need to look at how the data that we have in-house can be better utilized to, indeed, look at trends.

And in some cases, I need to also mention, when we give figures here, we are talking about metrics, and not statistics, if you will. And I think one of the approaches we need to look at as well, and maybe we need to target from year to year in different areas, if you will, looking at what the status of that particular entity, or what that particular area happens to be at that time, do some more focused statistical sampling at that point, and be able to use that data in a more meaningful way.

DR. MIIKE: But let me-- Don't you now-- It seems to me that you would, logically, instead of doing these site visits, and taking them as individual site visits, and continuing to do what you do all the time, that you would look at what you have collected to change

the focus when you go on into future site visits directly inspecting-- You know, you shouldn't be looking, concentrating, so much in this area now. So, if you have done that, then you have already got the basis for starting to take a look at the relationship between what the IRB knows in an institution, and what has been going on.

DR. LEPAY: I think I would have to say we have done that in areas broadly across the program. We saw problems over the past several years, going back when I first started looking at metrics, in the informed consent itself, in the informed consent process at the clinical investigator's site, and we have directed a lot of our attention, as we train our own investigators, into putting more focus in this particular area, and we have actually seen, again, not metrics but statistics. We have seen some improvements there.

Right now, we are having some issues that are coming up about adverse event reporting, and meeting FDA's requirements as far as safety reporting is going. We are getting that out at clinical investigator sites. We are putting more emphasis in the training of our inspectors in what we are requesting individually of our inspectors to look at based on those particular metrics.

But again, you know, these are just loose trends

that we use as a basis to be able to guide where we are next going. We also have started placing more emphasis, if you will, on what is happening in CROs, what is happening in monitoring programs, because indeed, that was not a focus of FDA's inspectional attention back three, four years ago, and as we started looking at it, approaching it first from the clinical investigator site, we developed certain concerns, and there was a lot of public attention at that time to what some of these concerns might be. And as a result, we have refocused our program in that direction. We need to be able to do more of that. And some of that can come--

You know, again, we have to see ways of leveraging our resources to be able to pull more information in, so we can use our resources more appropriately, to direct them to what really needs to be handled, and what needs to be improved.

DR. SHAPIRO: Thank you. Yes, Dr. Koski?

DR. KOSKI: May I comment? Obviously, one of the problems with any statistical approach, while it helps to target areas of concern and all, is the fact that in order to get the statistics, things have to already have happened. And so, one of our challenges is to find out, you know, how to get closer to where things are really happening.

And I want to emphasize something that David said, that the FDA has been very good at this, and working with industry. There is a requirement for ongoing monitoring by study monitors who come in and look at studies while they are going on. And by and large, that has focused on sort of the, again, the integrity of the process. But there is a real opportunity for us to work to incorporate more protections for human subjects in that part of it as well, so that if deficiencies are noted in the first monitoring visit, and there may be multiple visits during a trial, we should be able to utilize that information in a real-time feedback process, to apply it to protection of human subjects, rather than waiting until the study is done. And that is not currently something that has happened.

Even at institutions where, you know, they know that there is monitoring going on, there is no requirement that information from those monitoring visits go back to the IRBs. And indeed, it should. In fact, the Association for Clinical Research Professionals, ACRP, has implemented a certification program for research coordinators, and they are building into that process, you know, increasing amounts of information about the protection for human subjects, so that, indeed, people like the research coordinators at a site could

play an effective role in protection of human subjects, again, in real-time, as could data safety monitoring boards. And linking the adverse event reporting process into all of this gets to new ways to take what we are already doing, and applying it in a manner that is going to improve protections for human subjects.

This is one of the great opportunities that we have, synergizing, using those things that we already know are in place and working, and taking advantage of them in new ways to make the process better, and I think we will see some progress in that area.

DR. SHAPIRO: Thank you. Alex?

PROF. CAPRON: This is an enormously exciting time for the field of the protection of human participants in research, and I think that, you know, it is no secret that those on the Commission, as well as off the Commission, have been somewhat frustrated with the speed with which we have addressed one of our central mandates, which is this question of the oversight provided by the federal government for research. But I think as it is turning out, Mr. Chairman, we have the opportunity to come at this critical juncture, and I am enormously impressed and pleased to hear, both from Dr. Koski and Dr. Lepay, the sense that the process is being fundamentally re-examined.

I would urge staff to come back to us as soon as possible with a set of preliminary recommendations that we could, given the time it takes us to get through recommendations and refine them, that would address this issue of accreditation. I think there is, from what I have heard in the several years that we have been thinking about this, and talking about it, widespread support on the Commission. There is agreement, I think, on the objectives of an accreditation process for the review procedures that are used, IRBs or otherwise, looking first at risk reduction. That is the safety issue, the protection of human subjects, both from physical and non-physical risks. Second, quality assurance and quality improvement. Third, a system that provides predictability. That is, after all, the very idea of the assurance system itself, assurance that you will follow federal regulations. Fourth, consistency. That is to say, reliability across organizations. And fifth, independence, the sense, as we were talking today in our International Report, that there is a reason that these determinations have credibility.

I want to raise three problems with the whole panel, and ask how you think we can address them. The first is, achieving standards and processes that appropriately combine substantive knowledge about the

field, (that is to say, the field of human subjects research), and expertise in assessing the structures and processes, and measuring outcomes. Those are two separate things. And my sense is, from what I have seen happening, partly in response to, I think, a call from the VA, is that some groups that have some knowledge about accounting, and measuring, and so forth, that is on the measurement and the process and outcome side, may be weighing in, and other groups that have knowledge about human subjects regulation are weighing in, and do you think it is going to be possible to marry those two?

The second problem, or question, is how do we satisfy stakeholders with potentially conflicting, or at the very least, different interests. On the one hand, we need public accountability. But we also need, as several of you have said, acceptance by the field, which by itself is made up of researchers, the reviewers, the IRB members, institutions, and sponsors of research. And they may all have different interests.

Within the Joint Commission, it has seemed to me that, putting aside those of us who are public commissioners there, that even within the organization, there is a good tension, because on the one hand you have the doctors who want standards to be high because they want to do the right thing for their patients, and on the

other hand, you have the institutions who, of course, want good reputations, but have to worry about how do we pay for all this? How do we organize it in a way that is feasible? And so, there is a natural tension, and the joint aspect of the commission represents that.

How do we achieve a similar balance here? How do we have the public's interest in high standards matched with something that will have appeal to the people who will really be paying the price, the customers as it were, who will have to pay for a process if it is a process of private accountability?

And third, what about the problem that Dr. Lepay just addressed, which is the growing use of non-institutional settings to conduct research? And again, some of this is research which may already be reached by the FDA, but our Commission early on reached the conclusion that we favored a system of federal oversight that would reach non-federally-funded, and non-FDA-reviewed instances in which human subjects are used. And how do you adopt an accreditation system that can reach those non-institutional settings? Because as Mr. Hamm said, when we speak about accreditation, we usually are thinking of institutions, as opposed to a certification of individual investigators.

Those are three problems that I hope we will

address, and I would like any help we can get from the panel. Specifically, I would also love to know from Dr. Lepay, since we heard a little bit more enthusiasm from Dr. Koski, whether you think there is any possibility that given the relatively small resources you have, (from what you said, the ability to look at an institution probably once every six years, roughly, given the numbers you gave us), about using this kind of public/private mixture that accreditation is, do you think there is any possibility that part of your process would be a deemed status relationship with accredited IRBs? Is that in the cards, do you think, for the FDA?

But I would like response on the three problems and the objectives from any of you, but that is a specific question for Dr. Lepay.

DR. LEPAY: Yes, let me start with the specific question, because I am not sure I have good answers for the first three.

I think very much we are looking for ways, as any inspectional system would, or any regulatory agency would, to be able to leverage resources. And ultimately, the way we have to do that is to look at approaches, to ask the question is inspection the only way out there that we can, in fact, achieve what we need to in this process. And we already recognize that the answer to

that is no. We recognize it even internally within FDA in the way we collaborate between our review process and our inspectional process. We recognize it in the collaborations as they have come increasingly to exist between ourself and other federal agencies in sharing information. In fact, from our standpoint, we have different leveraging points in the clinical trial process than perhaps OPRR formerly had. We are not directed-- We are directed toward IRBs, but we are not specifically directed toward institutions.

Our basic leverage point, or our most fundamental leverage point outside of the clinical investigator, is the sponsor themselves. The sponsor is not--is typically a leveraging point for federally-funded research. So, in fact, there are ways in which we already recognize that there is the ability to complement the kind of information we have, and we have to be able to find ways of being able to share that information, and to be able to leverage.

I think when we start talking about accreditation, I think that this is something that can move forward within the FDA framework. That is not to say that we have any anticipation that FDA would run an accreditation program. In fact, I think quite to the contrary. I think it is the way that we have worked with

other certification programs. We have worked with a number of organizations that were mentioned out here today, and we have worked with them, so far, in an educational setting. And that is not to say we cannot work with them in other capacities as well, recognizing at the moment at least, we don't want to endorse any particular certification program. But again, as we start to talk about more widely accepted standards, that may become less of an issue as time goes by.

And I think that comes back to your first three questions, how do you achieve that kind of standardization, and how do you get that kind of agreement, and how do you identify the stakeholders, and getting them all to participate. And as I say, I think it is an area-- Of course, we are going to you as well to try to provide us with some guidance in that regard. And we are discussing within and among ourselves. I can't say that I have any immediate silver bullet at this point, but it is something we are talking about very actively. And hopefully, it is something that we can talk about quickly.

DR. SHAPIRO: Mr. Hamm?

MR. HAMM: Just if I could comment quickly on several of those. There is not any short, quick answer, but if I could go through each of them.

On the standards. Good accreditation programs use consensus standards with input from basically all the stakeholders, and that is not saying that one stakeholder group is going to prevail, because it is a balance. Obviously, if it was just the federal standards, it turns into a regulatory process. So, you have to balance.

But the good accreditation programs, they are consensus standards, and the standards, before they are finalized, are passed around to every group, literally, that has an interest in them. And they are ongoing; it is dynamic. They are never carved in stone. That is the other thing that is a key. So, I mean, the potential is there, but it takes a lot of time, a lot of effort. It is not easy building good standards, but that should be the goal, is to come up with a standard that will address the perspective of the multiple stakeholders.

Also, stakeholder representation. Good accreditation programs are not going to be governed by just IRB members, or one segment. It should have representation from the different parties that have an interest. Again, with balance, an incredible balancing act. If you have got 12 seats on the board, you have got to make sure that no one group has the power to dominate it.

In terms of looking at entities other than

institutions, here again, the accreditation world has a tremendous opportunity, because sometimes the private sector is most interested in having this recognition. It helps sell the effort with their stakeholders. So, accreditation is definitely flexible enough to look at various settings, including the private sector. And just--I thought of an example of the FDA process of perhaps a look every six years. An accreditation program in this field could set any time period they want, three years, five years.

The other thing accreditation programs do generally is have an annual report. Even though you may be accredited for a three to five year period, and usually that annual report is hunting for the incidents, or anything that requires some immediate attention. So, I think it would be very complementary to the regulatory process by having another peer group have a mechanism in place where they can go in if there is evidence that something is out of line, and take action.

So, the accreditation process is flexible enough to, I think, address your needs, but it takes time to develop them. The standards are, as when groups start out, I hear people say, well, can we have a set of standards in a year? And the answer has to be, well, it depends. If you have been working on it for maybe a

decade, and you have already got a lot of interest, you can do it. But generally, to start out building these from scratch takes quite a bit of time, and especially the outcomes. This is the hardest thing in most fields.

And sometimes, one strategy that I encourage in outcomes is to put a little bit of burden on the applicant organization. For instance, I use the academic model. Some universities, their strategy may be targeting people in certain fields, and in a geographic area. If that is one of their outcomes, they should declare that, and they should be measured by that. And some of the process may be educating the human research protection programs to set some of their own outcomes, and be held accountable for them. That may be one of the most important impacts of the accreditation process.

DR. SHAPIRO: Dr. Koski, you will have the last remark, because we are going to have to--

DR. KOSKI: Yes, I know that our time is up, but I want to thank again Mr. Hamm for making his comments.

I will say, although I am just new on the job, I have actually been working as a consultant with OHRP since its inception back in June, and almost all of my efforts during that time, and apart from doing the necessary hand-holding or shaking, has been to work on

this issue of coming up with accreditation standards. I can tell you that we have been actively involved in discussions, okay, with you know, an organization that would be recognized as being impartial and of sufficient stature to bring this process together. And I think, clearly, all of the stars are aligned right now, okay? This is probably the one opportunity that we are likely to have, and we must take advantage of it.

But yesterday, after my comments, I was approached by representatives from the biotechnology industry, from the pharmaceutical industry, as well as from the patient protection advocacy groups, all of them saying sort of "Let's go". And I think that represents the enormous energy that is really behind this right now.

There is work that has been done for more than almost two years now already out there that can help to leap-frog this effort toward accreditation standards for institutional review boards. There must be a level playing field. There must be buy-in, and I think by simply having the different parties engage in the process, as Mr. Hamm pointed out, is certainly the way to get there.

So, this is a high priority, fast-track initiative that we must move on, and I think that this has been an extremely valuable discussion for helping us

get there.

DR. SHAPIRO: Well, let me thank all three of you for being here today. We very much appreciate your presence, and your contributions to us. Sadly, we have to adjourn. So, thank you very much. Thank you, Commissioners.

DR. MESLIN: One brief announcement before we leave. Just for the public who is aware, the Commission next meets in Salt Lake City in October.

And I wouldn't want commissioners to leave without being made aware that today is the last Commission meeting of one of our most cherished staff. Stu Kim is going to be moving on to a position in the private sector at a law firm, and I know the Commissioners, and certainly all the staff, have been very grateful for Stu's contribution. He leaves on the 6th of October, but I wanted to let Commissioners and the public know how much we appreciated his work.

(Applause.)

DR. SHAPIRO: Thank you. Good.

(Whereupon, at 12:07 p.m., the meeting was adjourned.)