

DR. SHAPIRO: We're going to have a small change in the agenda. I'm going to turn to Eric in a moment to discuss two of our proposed future projects: one which we call international research, and the second, federal oversight of human subjects, which, of course, covers a project which is partially done already but not completely done. And then, rather than go to the capacity draft right after that, we'll go back to yesterday's discussion and continue that somewhat further on the draft of human biological materials and see if we can resolve a few more outstanding issues before we turn to staff to produce the next draft. And then we will return to the capacity draft itself.

Jim feels that we ought to be able to deal with that in three hours today, given the status of that document. I think that's probably correct. Of course, that's already out for public comment. We have not received all. The 30-day period we allowed is certainly not over. We've begun to receive some comment, but those comments and the comments that come from our discussion today will have to be incorporated in the next draft in some appropriate way. So we will turn to that.

I should mention one other thing. Mary Claire King will be here somewhere between 12:00 and 1:00. She's scheduled at 1:00 to talk to us about genetic research and families and so on, which also of course will be part of the discussion on material we're going over right now.

Let's turn, first of all, to the international research project. Eric?

DR. MESLIN: Just very briefly before I let Alex Capron say any words. The Commissioners have had a 2-page draft, a proposed outline for this project for a couple of meetings. Regrettably, we've not been able to discuss it. It's under Tab 4.A in your briefing book.

Principally, this has been a proposal that we have been developing that focuses the Commission on the idea of whether existing rules and regulations within the federal oversight mechanism would either need to be amended, or altered, or revised to take into account developments in international research that the United States conducts or sponsors in other countries.

I'll let Alex say a few words. The only other thing to add there is that we've already begun on the staff side to be gathering information and developing some of our research background, so your discussion to go forward has not prevented us from at least familiarizing ourselves with the issues.

Alex, did you want to add anything?

MR. CAPRON: Obviously, this is something which is getting attention in other international fora. You have newly before you the agenda for the international summit in November, where the topic is the proposed topic for the delegates. I don't have anything to add beyond that.

DR. SHAPIRO: Are there any comments, questions, concerns, ideas people have, with several having read the outline which, of course, has been before us quite some time now although we've not had time to discuss it? If there are, this would be a good time, because otherwise, unless there are some concerns, we will go ahead and begin developing the materials and so on.

Jim?

DR. CHILDRESS: I like this very much. Do you want us, in terms of additional issues we think perhaps ought to be included, to raise some of those now, or send them to the staff?

DR. SHAPIRO: Yes.

DR. CHILDRESS: It seems to me that under Part 1.A, how the research is conducted, it would be useful to have some better sense of the kind of negotiation that goes on, not simply in terms of the collaboration in design of studies, but negotiation with all the parties involved.

And over under 2.A, it seems to me it's not merely protection from harms, but also the broad sense of protection from wrongs. A person might be exploited, for instance, without being harmed: one taking advantage of the person's situation. But it seems to me we ought to develop a broader heading for that, harms and other things we would consider to be wrong. And there ought to be some attention perhaps to consent under that heading as well.

With those few additions, it seems to me this is a very good plan.

I guess the second question would be, and maybe I missed this when it was presented earlier, but at this point what is the tentative plan for going about this? Are we going to have contract papers, commissioned papers, any thoughts so far from Alex or Eric?

DR. MESLIN: The plan now is that I have been in a bit of a holding pattern pending the Commission's agreement. I've identified a potential Project Director for this who we would bring in, presumably on an institutional arrangement from another university, who has already expressed some interest. We would, obviously, be delighted to have some commissioned papers that in consultation with Commissioners and staff, we could commission fairly quickly. But the plan is to make this a wholly contained project with the project lead and staff in place.

DR. SHAPIRO: Alta?

MS. CHARO: Although it's implicit in some of what's already in the outline, it would be good I think to pull out more explicitly issues about justice and equity in the sharing of the results of research. This has been a particular issue not only in the pharmaceutical development, but in the area of population genetics, which is one of the "frontier" areas of collaborative research where you have both the concerns about the ultimate products being shared adequately and, an additional concern also comes to mind that's not explicitly brought out here, and that is notions about collective ownership, referring back to yesterday's discussion, of certain kinds of resources including the resources of our own bodies and knowledge about our genomes. That might be a nice thing to bring out more fully, since I think that's also the way it's discussed in the international arena more so than in the U.S.

Once again, though, I would love to reiterate my desperate desire that we finish the current projects before we devote lots of resources to any new projects.

DR. SHAPIRO: Bernie?

DR. LO: I also like this a lot. I think it's a very important topic. Two comments, one in terms of suggesting additions. Under 2, we really are focusing primarily on the idea that we want to protect people from harm, and just as Alta wants us to pay attention to issues of justice, I think issues of beneficence are important. I think we need some discussion of what is our obligation to try and address pressing problems in other countries that don't have the technological resources to just conduct these studies on their own. I think there are issues that have to do with what the researcher's obligation is in planning a study to have thought about the availability of not just the results, but the interventions that are proven effective. I know it's a big topic in the international sphere, but I think there has been very little attention given to the role of the researcher. I think we should be looking at whether researchers, by virtue of wanting to study questions like HIV prevention in the developing world, [have] an obligation to start getting involved in these kinds of discussions, which may be a significant change in the role many researchers see.

My second comment has to do with making sure that we carve out a niche. There's so much else going on, as Alex pointed out, around the world, and I think we need to make sure we don't duplicate a lot of the things that are going on elsewhere but focus on what we uniquely can contribute and keep ourselves disciplined to look at that. It's going to be so tempting for us to try and rewrite CIOMS or Helsinki or something else, and that's not something I think we would be fruitfully doing.

MR. CAPRON: Certainly, one thing that came out of the meeting a couple of weeks ago on AIDS vaccine trials in Geneva was the sense that the CIOMS international guidelines do need to be rewritten and the willingness of CIOMS to put together a good international panel to do that with the encouragement and support of people from the WHO UN structure and perhaps from industry as well. So, I agree, we should not take on that task.

My sense is that Alta's concern is absolutely right, we have projects we have to finish. But there is also a pipeline effect. We need to have some of the beginning work done even if it doesn't take up Commission hearing time for another six months. It is just much more efficient to be prepared.

DR. SHAPIRO: David?

DR. COX: Very quickly. These remarks actually come from reading about that meeting in Geneva. I'm very keen on this issue of justice that Alta brought up. I think that without solving all of the different problems, that's an issue right now that, at least with respect to American involvement, U.S. involvement in research in other countries, is very poorly defined and could lead to some clarifications. Not that people aren't talking about it, but it's a very clearly defined issue on which there is little resolution. I think although I want to see us get our projects done now that we're working, that's one that I think I'm very interested in.

DR. SHAPIRO: Rachel?

MS. LEVINSON: I think we need also to consider within that the role of the U.S. government and possibly private sector and define those, delineate them.

On Bernie's first point, in addition to the resources, you should also think about the framework for decisionmaking in the host country, not just international standards but the standards in that country.

DR. SHAPIRO: Other issues?

[No response.]

DR. SHAPIRO: This is an area, of course, where there is a lot of attention now and there are a lot of other people, as Bernie and others have said, that are looking at this and we do want to find something we can say. One of the reasons for this, it came up in a conversation I had with Alex last night, is that this thing really generates hard dilemmas and it is not exactly easy to resolve them. So there is going to be ongoing discussion for a long time. This is something just by the nature of it that generates very serious dilemmas no matter which way you take it. And so I think it's an interesting but demanding topic despite all the attention that's been given to it.

DR. COX: But maybe the advantage, Harold, is that it will make tissue sample stuff seem simple and we can actually get on with it.

[Laughter.]

DR. SHAPIRO: Okay. Any other?

[No response.]

DR. SHAPIRO: Let me just ask a question, and I think I posed this question last night in some informal conversations, whether these various groups that have been looking at this have really thought carefullyXthis is a question, I don't know the answer to thisXabout the alternative set of what is it that generates the interest in doing this kind of work? That is, do people really analyze why it is that Company X goes there or Researcher Y goes there? And I just, while there's a lot of speculation about it in the newspapers and so on, I really haven't seen any really thoughtful analysis of that. I think myself, my own view is that that may have some clues in it which would help us think this through. I don't know, it's a provisional notion.

All right. We are going to go ahead in a preliminary way. We understand what our priorities are. Our priorities are to get these reports done. But we do need to get started and arrange for it. Any other questions on this?

[No response.]

DR. SHAPIRO: Okay. Let's spend a few minutes on the federal oversight of human subjects.

Eric?

DR. MESLIN: Very briefly, we first mentioned this idea in our Los Angeles meeting where we would combine some of our existing work, which includes the completion of the federal survey report. We will have an initial staff summary of that made available hopefully within the next couple of weeks, and then it is our intention to share that with the client agencies who were participating in that, and then use that material as part of a more broad project which combines not only some of our structural questions about the system, but also some of the enduring questions that have arisen as a result of the two IRB studies that have been put on the table, on the 11th and 12th of June, respectively, the Office of the Inspector General Report and the NIH evaluation.

The 1-page proposal you have before you is really a way to put together into one place a project that sort of synergizes what we've been talking about, and that by next April or May would be a report that provides NBAC's perspective on how the structure of the federal oversight system adequately functions and what needs to be done to keep it in good health for the years to come.

As I say, the first part of that is complete. We are writing a staff summary. We have already commissioned three papers for the second part. You have heard from both Dr. Charlie McCarthy and Dr. John Fletcher; their position papers were presented to you and are available. The third commissioned paper, by Tina Gunsalus the first draft has already been submitted to staff. Comments have been given back to her and the Commissioners will see the first draft of that paper probably within the next three weeks. So we will have three major pieces of workX

DR. SHAPIRO: What's it titled? What's the subject of that?

DR. MESLIN: Her paper is looking at alternative structures that might be available to usXus, being those who are considering this issueXmeant to supplement what McCarthy and Fletcher have done.

MR. CAPRON: I thought her paper originally was looking at the industry side.

DR. MESLIN: It is including both. By alternative structures, it includes what ought to be done with respect to private research not currently defined. So, is it possible for us to include a structure that would involve both. And we would invite her to come to the September meeting in Washington along with federal agencies who would have a chance to review some of that material. Staff is already engaging in a comparative analysis of the OIG reports and others.

So there is a lot of work already being done, and it is our hope that we will be able to have our staff be led by a Project Director on that as well. I am confident that that project, which really is a kind of capstone to the two case studies of human biological materials and research on persons of mental disorders, would be completed by April.

DR. SHAPIRO: Alex?

MR. CAPRON: I just have a question. I think that the plan sounds excellent and, in an ideal world, should be the way we proceed. My question is only the first part of this was the part that, of course, had been begun before we existed because of the requirement after the radiation report for all the agencies within that year, and we found out that not all of them had done this before we got started, to report in about what they were doing. And it took up a good deal of our time prior to Dolly.

I have gathered that some of the agencies, since that's their major contact with us, have been unhappy with our lack of product on this particular area. Are we confident that through OSTP and so forth and the Science Council they will be persuaded that our plan of action of pulling that component in with these other two on IRBs and the whole oversight structure makes sense so that we don't get backbiting on this. Because this is certainly the right way to proceed but not if we're going to have incredible political headwind. In which case, we could issue the report in three pieces because, certainly, that first part is now much further along.

DR. MESLIN: I may want to let Jim Childress say something about that. But we have had a lot of conversation with federal agencies in the interim and presented a version of this plan to them. At this point, they seem to be very pleased with this kind of arrangement.

But, Jim, you may want to say something.

DR. CHILDRESS: Having taken part in one of those discussions, there was actually general enthusiasm about this, particularly because there's another component that Eric has mentioned before but perhaps wasn't as clear today, and that's not only that they would receive materials and then give feedback in September, but also the possibility of interaction with staff and any Commissioners who would be available prior to that. And that gives an opportunity for clarification and understanding.

DR. MESLIN: Rachel may want to add.

MS. LEVINSON: I think that's correct. I think that their concern wasn't the lack of product but the lack of interaction on development of the product. And we worked on trying to correct that in giving them the opportunity to review material that they hadn't seen previously. And there will be an ongoing effort to brief NSTC member agencies as this and other products come along and give them the opportunity to interact. The September meeting also provides that opportunity.

MR. CAPRON: Thank you very much.

DR. SHAPIRO: Okay. Any other? I find this is a very important project. I think this is a critical project for us. I will, before we meet next time, appoint one of our Commissioners to really head this from our Commission's point of view, quite aside from the staff work, because I think we really want to drive this forward. I think it's an extremely important aspect of it. And I do want it done by the middle of next year so that we'll have to go quickly on it. But I'll keep everybody up to date in the next few weeks as those arrangements are developed.

Let me return now to, although I said I was going to do this later, let me just try to get it off our agenda and we'll return back to the human biological materials.

I've been thinking about the comments made yesterday on the proposal we had before us regarding Belmont revisited. If I understand the comments that the Commissioners made, people were very concerned about using up staff time on this in view of other kinds of projects that we have in front of us, and I certainly understand that. On the other hand, my own view is we should not let the 20th anniversary go by without participating in some way.

So my proposal will be that we continue to plan something, but it will have to be something in conjunction with others and something that does not use our staff time, so that we don't pay that particular cost. And so we'll perform some kind of convening measure but rely on resources supplied by others as well to get this done. But I just don't think it's quite right to let the moment pass. So, with your permission, I'm going to pursue it with the understanding that this should not be a sink to use up staff resources, because I think that point was very well taken yesterday and I think it was pretty important, so I agree with that. But I don't want to abandon it, is my point.

Now there were Roman I and Roman II, and different views as to who was interested in I, if II follows, and so on and so forth, different combinations of interests. For the moment, I will proceed with I in conjunction with others. Of course, any Commissioner who wants to participate in this is more than welcome to do so. I don't mean to be excluding anybody from this.

Whether we, in fact, proceed to Roman II I think is still an open issue. We're not going to resolve that today. I don't want to take time this morning to talk about it.

So I will proceed, together with Jim, if he's willing, to consider just what kind of framework therefore we should use to mount such an effort, obviously in conjunction with others and having other sponsors as well.

Yes, Arturo?

DR. BRITO: I thought about this last night about the Belmont Report and revisiting it, and I think it is an important decision to make and I think it is important to revisit it. But I don't necessarily agree with what Alex was saying yesterday about having necessarily to do Roman numeral II because of time constraints. Ideally, it would be nice to do it, but I think it's more important looking at how Jim went up the three proposed parts of Roman numeral I. That number two in those three parts I would like to see a heavy emphasis on that, basically, interpretation, use, and the institutionalization of the principles of the last 20 years.

Because I think over and over we keep hearing this recurring theme from guest speakers and, honestly, from my own perception what a lot of problems are. It's nice to have principles, it's nice to have rules, but one of the problems we keep hearing over and over is that the implementation of the rules there's a problem with that. I think we would have a lot to add if we could just find out where the problems are—we know where some of the problems are though when implementing these universally agreed upon principles, where the roadblocks are. I think that's how we could contribute and I think that's something we could probably do in the amount of time we have, still looking at the history of the ethical decision made to make the Belmont Report, et cetera, but with the focus on number two under part one.

DR. SHAPIRO: I just want to make clear, in case I wasn't before, we're going to plan this within the context and constraints of not using a lot of our own resources to do it. Therefore, just what will come out of this will be a matter of negotiation between ourselves and others who will participate in this. But those comments are very helpful and we'll try to incorporate them.

Okay. Any other questions? Yes?

MR. CAPRON: Arturo has put a view on the record. I would like to be on the record on this issue.

DR. SHAPIRO: Sure.

MR. CAPRON: I think if we're going to spend any time doing one, it makes sense if it's connected with having an objective, and I don't know by what date, doing two. I also go back to Al Jonsen's statement that spending some time, the National Commission spending time on their principal discussion and getting a framework of Belmont on the table helped them in their other work. And I think we've gotten to the point where Belmont is not only a research document, but is a document the principles of which get cited more broadly. So that to the extent that we have a broader agenda, it would be relevant. And I think it would be a shame not to think about how we would go about number two. And this is not me volunteering, despite the way it's put here, to do it in any principal way.

I just think that just having a celebration of the history of Belmont and its significance and so forth, while it's fine, if Princeton University Press wants to convene something so that they can publish a book or something, we should attend and maybe our name would help getting some of the fundraising for it. But I think that ceremonial aspect would be a lost opportunity for this Commission if we didn't go on to do it. I'll just put myself on the record that way.

DR. SHAPIRO: Thank you.

MS. BACKLAR: I want to second that, because I brought this up yesterday. If we're going to do it, I would like it to be useful.

DR. BRITO: Well, I didn't imply that it is just to be a celebration. What I'm saying is that I think there's heavy focus on the second part of the first Roman numeral, the implementation and what the problems have been.

DR. SHAPIRO: We will not engage in anything that is not useful.

MS. BACKLAR: Thank you.

[Laughter.]

DR. SHAPIRO: All right, if we can, then let's go back to the issue we were discussing, the set of issues we were discussing yesterday when we began to deal with issues of identifiability. And we had a rather long and very useful discussion regarding issues of community, community harms, and how that would relate to IRBs and the obligations it would have and so on and the obligations on investigators. We will, on the basis of that discussion, begin to rework some of these recommendations, expand them, fill them in, get them a little denser, so to speak.

But I'd like to move for this moment right now to the top of page 5 in the accompanying memo which deals with what is called here "Guidance 3." As I understand this issue, it raises the concern about whether we think anything further needs to be said in this context regarding the issue of minimal psychosocial risk. Is that something that we want to say anything about, should say anything about? I think it's here because not a lot is said about it in the current context, in the current regulations and so on.

The question is, in my mind, one, are we talking about risk to individuals or, again, are we talking about risk to groups? And in either case, whether we're talking about one or the other, is there something we think that we want to say about this? Now, the way it's written here is we're just saying someone else should start thinking about this, right, is what substantively that statement says. But that's just a convenient placeholder here.

The real issue for us is to think about psychosocial risk, is there something in the context of this problem that we want to raise? And this could be a recommendation, it could be an exhortation, it could be anything. But the question is, should we take on the issue?

David?

DR. COX: I feel very strongly that we need to take on the issue. And I'll start off by making a statement and then seeingXwell, I doubt people will be shy about it. There are two extremes by which one can look at minimal risk with respect to the genetic information in tissue samples. One extreme would be to say that all such research is minimal risk. And the other extreme would be to say that no such research dealing with genetics is minimal risk. I would argue that neither of those is a tenable position.

And so, what it means is that genetic research or research involving genetic information is situational in its character and to use some examples of those situations where we would say in this situation a particular type of risk is deemed minimal, but the same type of research in a different situation is not minimal. Use specific examples. So that's my suggestion of what we could do as a Commission.

DR. SHAPIRO: Bernie?

DR. LO: I agree with that very strongly. I want to sort of flip it around and ask David if he can give us two examples; one, an example of genetic research on existing samples that is commonly thought to be minimal risk that he thinks is not really minimal risk, and the other way around, examples of commonly designed studies where the risk truly is minimal.

DR. COX: This is tough, Bernie, because I was thinking about this this morning. I'll say at the outset that I don't have the appropriate cases nailed down yet. But I can give some general trends in that regard.

So, some research that would be viewed as not minimal risk because that family member involved in a research study comes to you, is very interested in being involved with the research, and, in fact, volunteers his or her family members for this, but it turns out that for those other family members it basically destroys their lives to be involved with this because for psychosocial reasons they don't want to know what the answer is. And so in that particular family context, this isn't minimal risk. It has to do with the family dynamics and the family structure.

Now, that's straightforward. This is faced in genetic counselling all the time. The question is, how the hell is an IRB going to deal with that kind of an issue? So this is why I have no problem defining that contextual situation of not minimal risk, but is it relevant to IRBs. So I need a better example.

On the flip side, something that would be viewed that may be not minimal risk that could be minimal risk is this information of coded materials. Coded means identified. So does that mean that all research done with coded samples has the same risk? If, in fact, there is no intention and it's very difficult for people to go back and get information through the code, then that's a very different type of risk than if the code leaks like a sieve. So those are two situational examples. But I think we need much better ones than that that can be very precise. And I think they need to be directed specifically to how IRBs would adjudicate or consider the issue.

DR. SHAPIRO: Alta, then Arturo.

MS. CHARO: I find myself thinking about what Allen Buchanan said yesterday. And among many things, he reiterated a very commonly understood notion; that is, that risk is not simple harm, it's harm times the likelihood that the harm is going to come to pass. And I think that makes it possible. I'm watching your face, Diane, only because it's you know, if you have a terrible thing that's only got a one in a billion chance of happening, it's not considered to be as risky as if it has got a one in two chance of happening, right?

The reason I think of this as being tremendously important is because this is where I think that the discussions about coding can be brought back in in a much more robust fashion now that we've lost some of their value in the discussion about identifiability. Because there are three kinds of harms that we worry about here primarily. There's kind of a "peeping Tom" invasion of privacy harm, there is a backflow of intermediate ambiguous information harm, and there's a kind of breach of confidentiality stigmatization/discrimination type harm.

And this is where if samples that are being used by researchers are coded, we have substantially reduced the likelihood that there is an actual invasion of privacy in the form of "peeping Tom" because the researchers at least do not have any way at the time they're doing the work of linking what they're seeing to any particular person.

And this is where David's long-ago-made suggestion about some kind of filter or filtering group that can regulate the backflow of information should some findings that might have clinical significance be developed becomes very important in trying to regulate the flow of information back to tissue sources should there be some inclination to do so. A researcher sees something that looks like it might be of clinical significance but it's ambiguous enough that it might just be aggravating, and rather than making the decision on his or her own to not go or to go and to wrestle with that alone, there's a filtering group, whether it's the IRB or another, that helps to decide if this is finally the appropriate moment to send information back down.

So that in the discussions about minimal risk, I think we'll have a great deal of difficulty in coming up with some nice hierarchy of which harms are significant and which harms are not. But what might be easier to do is to come up with a set of procedural devices that can reduce the likelihood of any of these harms coming to pass. So that in many, many cases it will be possible to conclude that overall a protocol is, in fact, a minimal risk because the likelihood of any harm, substantial or otherwise, has been minimized so substantially.

DR. SHAPIRO: Alex?

MR. CAPRON: I think that's a very sensible way of proceeding. I wonder whether the reluctance to address the magnitude side is because we don't think that there really is some kind of a metric; if not very precise, at least sort of these kinds of things are more risky than others. And I can understand the conclusion, well, it's very hard, it's so much a matter of opinion. But then I come to the problem of the way in which this is simply then put off onto the IRB.

And my current thinking about IRBs is they are a pretty weak read for doing a lot of that work, not just because they're overworked and so forth, but because it's an extremely difficult thing to have an issue like that thrown at you if you're an IRB that hasn't spent a lot of time. Now, maybe the IRB at Stanford, if David's doing a lot of research of this sort, sees these kinds of proposals all the time and becomes quite expert, the same way we know that some become expert on research with the mentally impaired. But for a lot of them it is going to be out of the blue.

And if we can't at least develop some discussion I'm not talking about regulatory language where you would say if it's this it's automatically hot but some illustration of well, if it's research on a disease that is treatable and where it's familiar to people and so forth, it's this kind of thing; if it's research on something which is lethal and untreatable and where the fact that you have this could be devastating psychologically and in terms of ability to get insurance and so forth, that's different; if it's research on sexual orientation or alcoholism or something that's very socially fraught.

These are the kinds of things where I think we need to ask somebody to talk to geneticists about examples and have real-world examples and have some discussion of it so that we provide some help to the people at DHHS, if this is maybe going to be illustrations in the official IRB guidebook or something, assuming that IRBs may not all read this report. But somewhere along the way, I'm with Trish, we want to be helpful with these documents. And if we don't think that there's any way of saying much about it, what are we thinking the IRB is going to do about it?

MS. CHARO: Just by way of clarification, I was never suggesting we don't try to look at the other side. But I just want to emphasize that the Mayo Clinic approach, described last time, in which every form of genetic research is non-minimal risk is one that has the advantage of simplicity and it certainly gets high levels of compliance because everybody knows that they have to go to the IRB and they can't waive consent and it's done. But I don't think it accurately reflects the real level of risk out there that could be achieved.

MR. CAPRON: Well, I wasn't thinking I was disagreeing with you, Alta. I was in part responding to the combination of your comments following David's, the argument that the probability issue is something which we can highlight and discuss and show how lower probabilities reduce the sense of "risk," and I agree with that.

But I didn't want to leave David's sense, well, he couldn't think of anything off-hand and his answers were all on the probability side, too, to say that we can't provide some guidance. Once the IRB at Mayo or any other place gets these things and they are weighing potential harm against potential benefit, one of the issues is, well, what is the harm? And just giving people some sense so they'll be familiar with it. That's all I was suggesting.

DR. SHAPIRO: Eric?

DR. MESLIN: This issue was raised at the last meeting in Cleveland. And in the revised staff draft, we took some time to identify cases in the material. It appears beginning on page 230 and goes on for another three or four pages. These were cases that were constructed, with David's input and others, that attempt to identify those sorts of examples. One possibility for Commissioners to consider is to review those cases and give us staff some feedback as to whether they would appear to be the kinds of cases that form the boundaries that you're describing, David. They can certainly be supplemented by others.

DR. COX: They do sort of. But I'm actually very much in favor of combining, and I think this is what Alex is saying. The problem with those cases right now is that they're just sort of there floating and it doesn't have the principles of which the cases illustrate. So I hear Alta saying let's have some principles and then here's the application of them to real cases.

The fact that we may not have those cases perfect right now doesn't mean we can't get them. I'm quite convinced we can. But what I haven't heard us do is really articulate the principles yet. Alta started. We don't need a lot of those. We say this is a hard problem, here are some guiding principles and then here are some cases that they're applied to. Because if you just have the cases, it will be like Al Jonsen spoke yesterday, this wooden interpretation, it's going and trying to fit everything into these cases. We need the principles.

DR. MESLIN: That was one of the reasons why the revised chapter 3 was placed where it was. Pedagogically, we might want to move it and provide that backdrop for the case analyses.

DR. COX: Yes. I actually think that these principles are woven through a lot of our discussion and a lot of the text now. But what we need to do is extract them. And so we have this thing "Principles for Idiots," and we say here it is, three lines, here they are, these are the principles. That way, for busy people at IRBs or doctors or researchers, they can carry around a little card in their wallet to remember the principles.

MR. CAPRON: Maybe the idea without having the title printed on it.

[Laughter.]

DR. SHAPIRO: "Dummies" is the more common title these days.

Let me ask a question. What's wrong with the idea, which I take it doesn't have any support here, of saying that there is no minimal risk, everything is more than minimal risk? Now, I understand that makes a lot more review cases. I understand that technical issue. But is that a serious objection? It does have the benefit of being very simple; it's probably therefore wrong and not very helpful. But I'd like to hear some comment about that.

DR. BRITO: I think what Alex was saying, that it puts the onus then on the IRB to make that decision because then everything has to be reviewed by the IRB.

DR. SHAPIRO: Alta?

MS. CHARO: Actually, everything would have to be reviewed by the IRB anyway. The key here is whether or not you could waive consent, because to waive consent you have to show both that it's minimal risk and that you couldn't practically get the consentXand we'll deal with practical later, which I think is even more of a morass than this.

MR. CAPRON: And expedite review.

MS. CHARO: Yes, although that's really in some ways maybe it was a poor choice to highlight that as much as we did because it's really just a matter of whether it takes a whole committee or one committee member to get the thing through.

The simplicity is actually a huge advantage because it takes away so much uncertainty and it simplifies life tremendously for the IRBs. All they've got to say is fine, get consent, come back when you have. But the reality I think is that many collections are going to have samples taken from people who have long ago moved along, and the United States is a tremendously transient population and some people will have died, others are just unlocatable.

And it not only reduces the universe of samples that you can use in an absolute sense, it changes the statistical validity of the samples that are left if one suspects that there are some in fact selection factors in who has died or who has moved on which might make the remaining samples that are useful in the sense that you could get consent still useless from the point of view of scientific validity.

So an insistence on a consent requirement without exception has the potential for being a tremendous obstacle in the research endeavor and it's not an obstacle to be placed there lightly.

DR. SHAPIRO: Just to push it one tiny step further and before dropping it. I think those points are extremely well-taken, especially if there's no exception to the consent. But we have examples of other cases where there is exception to the consent, they're not practical or whatever issues like that.

MS. CHARO: But to get the exception to consent you have to show that it's minimal risk. So if you say nothing is minimal risk, then no exception can be made.

DR. SHAPIRO: That's the currentX

MS. CHARO: Except for totally unidentifiable anonymous samples, absent minimal risk, there's no exception to the consent requirement.

DR. SHAPIRO: Right. But that's the current regulation.

MS. CHARO: That's true.

DR. SHAPIRO: One could use thatXwell, I'm not sure, I haven't thought this through to be honest, I'm just sort of raising the question. I will think about it more carefully.

DR. COX: Harold, this is my concern, and I can certainly see how people may minimize what I'm going to say. I don't think it's on really strong grounds but I feel it strongly. And that is that by doing that, by basically having nothing "minimal risk," what you basically do is take any responsibility off the researcher because then the researcher says, oh, all of this stuff somebody else has to figure out what's risky and what's not.

That's the situation that we're in right now. And that anything that we do that makes it so the researchers become less invested in this issue of figuring out what is risky and what isn't, I'm against.

Now, I realize that from a regulatory point of view this is a very appealing fix. But I think part of the problem with these complicated problems is that unless people get engaged in them,

what we are going to have are regulatory fixes and we will never solve the problem. So that's my concern, but maybe it's too ethereal.

MR. CAPRON: I would like the Chair to follow up on what I found his very helpful intervention in this discussion just now. When are we going to see language that would suggest that on the flow chart if the answer is initially yes, this may involve more than minimal risk, you have a chance to revisit it on the same kind of practicality grounds, because the practicality grounds are not unconnected with the risk.

I have Dr. Hook's slides from the last time, and looking at the risks, if you're thinking about a situation of the type that Alta describes where the problem is you're dealing with samples of people who have died of the disease that you're eventually studying and so it's impractical, it would certainly make sense to say that the risk to them of insurance and employment discrimination, of discovery of unwanted or uncertain information of psychosocial or emotional harm and their right not to know aren't risks to them because they're deceased.

And so some kind of a process that says, yes, in principle, we're looking at this, we see that there are risks, they are more than minimal risks, but as to this group that you cannot get consent from but whose tissues you want to use, those risks fall out and it moves to a lower category. So it's a somewhat more refined examination. As to other people in the sample group, yes, you're going to have to try to trace them down and get their consent. In other words, a process that is a little different where we're going to have to be recommending that there be potentially an alteration in the process and the IRB ask different questions.

Are we anticipating that out of a discussion like this, if that idea that the Chairman threw out, which is, well, that's only the current regulations, there could be other ones, are we going to have that in front of us as language?

DR. SHAPIRO: We could certainly put it in front of us if it seems like a helpful idea.

MR. CAPRON: It seemed helpful to me.

DR. SHAPIRO: Alta?

MS. CHARO: I want to make sure I understand the suggestion. And just by way of clarification, if the people whose tissues are being used have died, it doesn't matter what the level of risk is because they're no longer considered human subjects. The problem is that you don't usually know that they've died. You are faced with a collection of samples, you are told you have to get in touch with people, you send out a series of letters, a certain percentage comes back as undeliverable and you don't know why it's undeliverable, so you don't know which of those people are no longer human subjects and you can use their samples freely and which of them have simply

moved away. But more than six months ago and their mail is not being forwarded, having suffered that problem myself, a six and a half month sabbatical is very inconvenient.

But I want to make sure I understand more generally the example. The idea is we might be discussing a possibility in which researchers are encouraged to describe subpopulations within the samplesXthose for whom this is clearly minimal risk, and those for whom it is not yet clearly minimal risk. There's probably no reason why that can't be done at all underX

MR. CAPRON: It may even be a matter of making clear the way it could be done under current regulations. I just wanted us, to the extent that what I took away from the Mayo situation was the advantage of presumptively saying if the probability and the magnitude are such that this is "more than minimal risk," and let's start off assuming that most genetic research is, we get the IRB and the investigator looking at it, not just the investigator and not just to check off minimal risk, I don't have to do anything.

MS. CHARO: And, of course, in an ideal IRB, not the ones that you're worried about, it doesn't happen that way. But there already is a presumption of non-minimal risk in the sense that an investigator essentially has to petition for a minimal risk declaration by an IRB and has to prove that the protocol is eligible for it.

And if what's really being suggested is that that be somehow highlighted, emphasized, and that in the area of genetic researchXand I have a feeling now Steve Holtzman and Carol Greider are going to flip when they read the transcriptXin the area of genetic research there's such a public concern about it that one wants to strengthen that presumption and force an even stronger level of proof that it's really a benign kind of genetic research, that might be a very helpful way of flushing out this term.

MR. CAPRON: Right. I guess I would go back to the point that I mentioned a moment ago that you kind of dismissed, which is the difference not on the consent issue but on the expedited review. I think there is a huge difference between expedited review, which involves either the chair or the administrator checking off, yes, expedited review grantedXI'm always glad when I get expedited review, because it's easierXbut when you're dealing with these things, if our discussion, and this is not a regulatory change, but the discussion was the presumption should be at that point this should go before the whole IRB and get the normal process, and then coming out of that the recognition. But the conclusion can be as to certain parts of the population, or maybe the entire population you're looking at depending on who they are, this drops back down and you are allowed to have a process that does not involve individualized consent because it turned out that the risk is more minimal. That's I guess where I would put our discussion. And,

again, it may not be regulatory change, it may be change in the way the regulations are understood.

DR. COX: I like this discussion because I see it being a process discussion in that it doesn't lay the burden on any one individual or group of individuals to deal with these frontier issues. So the concept of the researcher having to petition because he or she believes something is minimal risk, goes to the IRB with an actual brief on it, the person has thought about it, the researcher has thought about it, then the IRB, even the chair of the IRB has that brief as the working point to say they either agree or disagree or need to get more information. So it's actually a substantive process that increases information about the frontier.

Now, you can tell this is like a scientist's way of thinking about things. There are other ways to do things in life. But as it gets more and more information, I think we will actually get smarter and smarter about what the right answers are. But if we don't get more and more information, if we just sort of lay it off on the one person or the other and then that person doesn't have any information to make the judgment either, I don't think we get any smarter. So the process I think could be a very good one and we lay that out.

DR. SHAPIRO: I think the notion that came up yesterday in another forum that really a lot of these procedures can be strengthened by having a higher quality process in which a lot of people are involved is interesting. It came up yesterday, at least I interpreted this coming up in that, in Alta's suggestion, or not suggestion but pointing out that there's a lot of initiative left to the investigator early on. That investigator has a lot of responsibility at the beginning in making various choices. It's something I think we should emphasize that's a little bit like the responsibility for the design of the whole thing, which is also a major responsibility of the investigator. And I think if somehow we can formulate the language as we go through these kinds of things to emphasize those aspects, it would be very healthy and will clarify a number of things that we try to work on language.

Alta?

MS. CHARO: I must say at that point just for the sake, in case he's reading the transcript, that Eric Cassell will be very happy to hear that, because I think that's his constant point about the research community's own education.

I would like to take up the other half of the equation that Alex was emphasizing earlier, if it's appropriate now, which is the nature of the harms and how one might view them. The usual way in which minimal risk is described in IRB review is by comparison to the risks of everyday life. And in the context of physically invasive research, that has been complicated enough, but people

have basically done it by having a sense of the likelihood that I'll have a puncture wound today versus getting an IV.

In theory, it should not be any more difficult to make the same kind of assessment. It will be just as muddy, no more muddy, for psychosocial, and yet I find myself finding it much more difficult. I think maybe it's because the subjective experience is even more varied in the area of psychosocial than it is in the area of physical invasiveness, even given the range of reactions to pain and such.

I'm not yet sure that this particular way of thinking about minimal risk is, in fact, useful in this context but am open to persuasion that it can be used as the kind of principle of measure. I was wondering if anybody here had thought this through better than I had?

DR. SHAPIRO: Alta, I'm not sure I understood the last part of what you said. Could I ask youX

MS. CHARO: Sure. I haven't been able to think of a way that I could use the experience of everyday life as my benchmark against which to think about the psychosocial harms associated with genetic research that may be on the association of dark hair with curls or could be on the association of some particular marker with a high probability of breast cancer. I was wondering if anybody here had been able to figure out a way to use this kind of everyday life experience as a benchmark?

DR. SHAPIRO: Alex?

MR. CAPRON: I agree with Alta, it's complicated. And I want to add an additional complication. I don't think that when we think of the physical risks of everyday life we think that most people are going to be subject to malpractice and get injured by their doctors in ways. But here, certainly one of the things that is most often cited is the breach of confidentiality.

I think we might want to say something quite directly that it cannot count towards one of the risks of everyday life that your physician or nurse or hospital is going to be very loose-lipped or very casual about your medical records and breach your confidentiality as a way of saying this happens in research, it happens all the time anyway. Because that enterprise is too closely connected to the research enterprise and you don't want to have people degrading the standards.

And this is not hypothetical. Certainly, in California one of the reasons a special statute was passed very explicitly about consent and about confidentiality of the HIV test results when the first antibody tests were developed was because everybody knew that ordinary medical records were simply not being adequately treated on the level of confidentiality.

And this was sensitive enough that they established requirements, which ought to apply to everything but it was sort of like that's a lost cause, that on this issue we're serious about it, you must tell people you're conducting a test, you can't just take their blood and then do a test on it, and you must keep the results confidential and only reveal them when they explicitly say yes, it's all right to tell so and so.

So I think we need to talk about that because certainly on this psychosocial level that's the thing that gets mentioned most often, that information. And you mentioned it under two headings; the kind of voyeurism or peeping Tom, just the nurse that lives down the block from you and she tells somebody so and so was in and got a test the other day, or the actual breach of confidentiality because the report is published in a way where your pedigree is obvious, that's obviously your family and now you're shown all these people with X's through them to indicate they have breast cancer or whatever and you don't want that out there. I think we need to address that.

I agree with you though that in many ways the other kinds of things are very hard. What is the risk that you'll be stigmatized? It doesn't seem as though that prejudicial reaction that people have in society ought to be carte blanche to say, well, so here's another stigma to get stuck on people. People have to deal with stigma, that's just life. So I agree with you, I think it's actually quite difficult.

DR. SHAPIRO: David?

DR. COX: So this sort of falls under the category we were talking about yesterday where should the IRB make judgments about something if it really can cause tremendous social mischief but is a high quality scientific question?

MR. CAPRON: I don't think this is the same thing, David.

DR. COX: But it's an analogy. It's a different issue. And the analogy as I see it is the following. It is that these are highly intertwined issues that can't have one institution or one body dealing with them all. And so the idea that you have subtle social prejudices and harms coming out of stigmatization, one of the ways of sort of dealing with that is with the privacy laws. And I'm saying I totally believe we should have those. But anybody that believes that we can solve the problem of discrimination and harms by writing laws, it's wrong. It doesn't mean that we shouldn't have the laws, but there have to be many layers and levels by which this gets dealt with.

Some of the them are going to be the IRB, some are other social institutions. So that you don't throw up your hands and say it happens so we can't write any laws. You don't write the laws and say that that's going to solve the problem. You acknowledge it's complex, we can deal with the practical things of privacy, but at the same time we point out that that's not enough and other social institutions have to pay attention to discrimination, whether it's on a person's skin color or whether it's on genetic information.

So I think it's by trying to make these things simple that we get into trouble, because they're not simple. They are going to be multifaceted checks and balances and we're not going to solve them all.

DR. SHAPIRO: Well, with respect to the question I thought you asked Alta, that is, whether one could use something like everyday, that it would seem somehow acceptable in another arena, my own judgment, and it's no more than a judgment, is that you can't. Not only for the reasons that Alex mentioned. But because even putting those issues aside, which are very important, it's really that you gave yourself the key explanation; namely, the variance is at least thought to be so much higher between individuals in that area that there's really no common way to think about it. Now, we may be fooling ourselves in the other area, maybe because of different reactions to pain and so on, as you said in your comments. So I don't think we can use that framework.

MS. CHARO: Well, if that's the case, and certainly where I was leaning, although, like I said, I was open to being persuaded it could be used. The alternative is to try to develop some kind of list, recognizing that it's highly imperfect, of red flags. That research that involves these kinds of things should be understood to probably be research that raises the possibility of a significant harm rather than an insignificant harm, and at this point, unless you can show that you've reduced the likelihood quite substantially, you really are not going to be allowed to call it minimal risk.

The list would, like I said, be highly imperfect but not at all non-obvious. It would be research that involves conditions that are life-threatening, disabling, or commonly understood to be socially embarrassing. It would include research that involves results that could generate a clinically ambiguous kind of information that puts people in an impossible position of having to figure out how to pursue their own care in light of truly intermediate insufficient findings. Conditions that regardless of the reality of them generate reactions of discrimination in the

employment or insurance context or social stigmatization. And that this be a kind of set of guidelines.

And that instead of trying to look at the overall risk by looking at the harm and the likelihood and comparing it to everyday life, in this particular area it may be necessary to break it down into its components a little bit more in a more reductionist fashion to come to some conclusion about eligibility for minimal risk.

DR. SHAPIRO: Yes. I think that sounds very helpful. I think that is the way we're going to have to go.

I think we've had a number of very interesting and helpful comments which will enable us to write some interesting proposals here for dealing with this particular aspect of it.

Why don't we go on then to the next issue, which is an issue I must say has me a little bit puzzled, but I hope I'll get some clarification here. That is the question of living relatives, what status they have. If I understand the situation, it is that the current regulations seems to indicate, at least some people think they indicate, that in fact we might need their consent because we're going to find out some things about them even if we're using a sample from a deceased relative. The question is, how do you deal with this issue of living relatives? Are they subjects or aren't they subjects in the research?

Now, I, very frankly, haven't thought of a good way to deal with this issue. It's just here to try to see if Commissioners feel that it is an important issue that we need to deal with, and, if so, how we should go about it. I think, and maybe Alta you could help me with this, I think currently people just treat them as not subjects. That is what's happening out there. And treating them as subjects seems mind-boggling to me. But yet I think I've learned that, in fact, the way the regulations are written that at least there's an argument to be made that they are, under existing regulations, subjects. The question is what do we want to say about this.

MS. CHARO: Your understanding of the regulations is right. The dead person is clearly not a human subject.

DR. SHAPIRO: Correct.

MS. CHARO: And the regulations are written in a generic way so that information about any identifiable living individual constitutes information about a human subject. But rarely does anybody in the research community take seriously the notion that these kin are, in fact, being transformed into human subjects. It's counter-intuitive to them because these kin are not the ones who are the primary subjects of study. They are incidental. And I don't have any idea how we

could limit this universe, since the study of any dead person is information about many, many, many other people in a quite indirect fashion.

MR. CAPRON: Maybe the probability arguments we were having a moment ago bear on here. It's certainly a lot more information about their first degree relatives than it is about a distant relative. So the probability of being harmed by that information, that you'll actually be able to say anything about that distant relative, is perhaps smaller. We may be able to employ some of the discussion we were just having. That's just a thought.

The notion that if my parents were deceased, their tissues were going to be looked at, both of them, to find genetic markers that would have direct implications for me at a 50 percent level or a 25 percent level, depending on what you're talking about, seems something in which I would have a rather great interest. But the notion that Great Aunt Matilda, the implication is much, much more remote.

And, of course, if my parents are willing to undergo the study, the fact that it is going to have implications for me doesn't allow me to stop the research. So we're dealing with a situation where we don't have that balance of consent. Just to add to the complication. I'm as much as subject, as it were, in the case where my parents consent as in the case where they can't consent because they're deceased.

DR. SHAPIRO: Bette?

MS. KRAMER: I was wondering, would this be embraced within the consideration of what's practicable?

MS. CHARO: It might come up there as well, but this actually cuts to an earlier decision point. The earlier decision point is are you doing research on a human subject. That's the second decision point. The first is are you doing research, then it's are you doing research on a human subject. If the answer is yes, then you head down to your nearest IRB and you start filing a lot of paperwork.

If we want to understand research on cadavers or samples from cadavers as research on a human subject because of its information yield on first degree relatives, we have in some ways a special case of the group effects from discussion yesterday. It's just one special case about the way in which research on one person can actually be of interest and significance to a larger number of people.

We also have the discussion we were having yesterday about the role of those secondary people in vetoing or giving consent. In your example, Alex, of research on the tissue of one or

both of your parents, it would not only be you, it would be all of your siblings, and if you're saying first degree relatives, it's all their siblings, and if they're still living, their parents who are interested in this.

MR. CAPRON: Exactly. Right.

MS. CHARO: And one possible conclusion is that since all of them are now being made into subjects of research by virtue of the research on just your parents' tissue, each of them individually in all three of those generations has a right to veto this research, because any one person denying consent shuts the research down. Which is a pretty significant finding. It may still be justifiable but it is the natural conclusion.

DR. SHAPIRO: I have to say, we have to think about this and talk about it more, it doesn't feel right to me. I understand the issue of probabilities in establishing risks, that risk itself is a product of two elements, one of which is probability of harm. But as I start thinking of treating first degree relatives as subjects, it sounds to me like an unmanageable problem. That's how it feels.

DR. COX: It's even more complicated because anybody that is involved with genetic counselling knows that for some people you tell them they have a 50 percent risk and they say, "Whew, I thought it was 100 percent." And then other people you tell them they have like a 1 in 1,000 risk and they break down in tears.

MS. CHARO: You been talking to my mother again?

[Laughter.]

DR. COX: No. So as a scientist, Alex, I agree with you that this makes sense. But from the point of view of how people perceive risks quantitatively in terms of whether they would want to keep something from happening, it becomes a very complicated issue.

MR. CAPRON: I was actually raising it from the other point of view, thinking of the more distant relative being someone for whom the claim is tenuous. In other words, because the probability falls off. I'm saying that if we start putting probability in here, we ought to

DR. COX: No, I understand. But that's these people that are the 1 in 1,000 and they say, well, that's still a gigantic risk to me and I don't want to deal with it. So I don't see how we can these discussions don't pass the red face test. But I'm trying to see if there is some way that we could incorporate this. And I don't see right now any mechanism. I'm struggling with a mechanism. Because if we could address it, it would be good. But I don't see how.

DR. SHAPIRO: Alta?

MS. CHARO: All right. Now to say this as somebody who is not yet a complete fan of the mechanism, but we chose it yesterday and I'm looking forward to seeing it. In the context of group harms yesterday, a mechanism that was chosen is as follows. Even when something is not required to go to the IRB because, in the example that Alex gave, you're using totally unidentifiable samples but it has the possibility of implications for an entire identifiable community, we were going to write something that urged PIs to go to their IRB anyway. Now, I've always been skeptical because it's hard enough to get them to go when they have to go, let alone when they don't have to go.

But given that we've chosen that mechanism, that sounds like one that would work here, if we could make it work at all. Which is, you're dealing with cadaver tissue, you're not clearly falling under the regulations in terms of the first degree or any degree kin as far as them being turned into subjects, but would you please go to the IRB anyway so that they can work with you on trying to minimize any kinds of harms that might flow to this kin group.

Indeed, there is a lot of stuff in the IRB guidebook already about the special problems of pedigree studies, the sort of obligations to go and ask for consent even where it's not required that you get consent just in order to make sure that this is done in the best possible manner. It goes back to Bernie's request for kind of a best standards kind of approach. And it may be that that's going to be the compromise. You can't make it a requirement but you can make it an aspirational standard.

DR. COX: I hadn't appreciated that. So if you think of it in the context of community, and it is a type of community, it certainly falls under that framework.

DR. SHAPIRO: So what you're saying, if I understand, or what you're suggesting here is they not be considered subjects because that would automatically require consent and so on in the case we're talking about, but that we develop some kind of another red flag or another issue that we want to point out for people to be conscious about and try to design their work to minimize any harms that might flow to this group even though we don't give them the status of subjects from the point of view of the regulations. I'd almost be satisfied with anything that didn't make them subjects. And that sounds like something to think about anyway.

MS. CHARO: At the same time, I'd also like to add that, and he's not in the audience today, I'd like to get the Director of OPRR to actually engage in a conversation, verbal or written,

with the Commission on this. Because one of the problems here has been the perceived absence of clarity in the interpretation of the definition of human subject. And if there is a good case to be made that these relatives should be understood to be human subjects and that there's a workable way to do that, I would love to know how that office has been in fact implementing that particular provision and take that into account as we move towards conclusions.

Right now, I feel like we're operating slightly in a vacuum. So if we can add that.

DR. SHAPIRO: We can certainly get that information. My preference right now, and I have to say I haven't thought enough about this, but my preference right now is that we should say something saying that they are not human subjects. And if it requires clarification of the regulations, then it requires clarification of the regulations. Then go on to say what we hope IRBs, investigators, and others might think about this because this is something which is a nontrivial issue.

MS. CHARO: That's right. In the end, we are not the authoritative interpreters of these regulations.

DR. SHAPIRO: Right. Correct.

MS. CHARO: There are many interpreters and the one that tends to be most authoritative is the agency that administers the regulations or that wrote the regulations.

MR. CAPRON: Well, on this subject, what our recommendation is is asking them to address it.

MS. CHARO: Right.

MR. CAPRON: And so we have to tell them in the process what we ideally would like to see them be doing.

MS. CHARO: Right. That's right. And I would love before we come to a firm conclusion to at least hear the other side, if there is another side to be made.

DR. SHAPIRO: We'll certainly do that.

David, then Arturo.

DR. COX: Why I'm so keen on this is it again comes back to taking the onus off the IRB and putting the onus on the investigator. So I think of this as an investigator and I say, all right, so I'm working with autopsy material and I have to think about is if this going to have any impact on the community of relatives. Why am I going to think about it? Because I want to make the argument that I'm doing my research in a way that it won't have that impact. So I think about it

because my motivation is to get that through so that I can do my research but that I'm not going to be able to do it unless I think it through clearly so that it just whizzes through the IRB.

Now what that means then is that there will be a clear brief for the IRB to either agree with it or not agree with it. So it's a process that puts the onus where it should be, which is on the researcher, but then it has the oversight where it should be, which is on the IRB.

DR. SHAPIRO: Okay. Any other comments?

Yes, Arturo, I'm sorry.

DR. BRITO: At the risk of going backwards a little bit, on Guidance 2 we talked about the implication of anyone other than the individual, the index subject. How does that differ from when the human research subject is deceased, a cadaver or what have you? I guess what we're worried about here is the implication of what this may have on a living relative.

DR. SHAPIRO: Right.

DR. BRITO: How do Guidance 2 and Guidance 4 truly differ? And is there a way to really just combine what we're talking about in Guidance 4 within Guidance 2, assuming we're not going to consider living relatives human research subjects?

DR. SHAPIRO: I think there may be, as we work through this, opportunities to combine some of these things. A number of the items here need to be combined and recombined to make coherent sense. And I was very conscious that that's a suggestion you made yesterday, I think. We certainly want to think about that carefully and see how when we actually articulate this. I think there are some differences but some commonalities, so they're not exactly the same. But I take your suggestion and we'll certainly think about that.

MR. CAPRON: I hope that as part of this process I think Alta has underlined a number of times the initial difficulty here that we're relying on investigators, against their own self-interest, coming forward and saying I'm willing to take the time before I do this research to sit down and discuss it with you, as David says, prepare a brief, and explain why I think I've done the right things. I could simply look at the existing regulations and say I don't have to do any of this.

One way that Arturo's point here I think ties in about combining them is, and Alta didn't say this, but one way of understanding this is that without saying they're subjects, we say they are enough like subjects that you need the IRB review to make sure that you've done all the things that David describes. And so, in a way, that's much clearer, Arturo, when you're thinking about family members than it is when you're thinking about this more amorphous group. But the argument there by analogy is that in a way they're sort of subjects, too, because you're really planning to reach conclusions, generalizations about this group, whether it's a Portuguese family

living in San Francisco with this interesting pattern where you're looking at the deceased relatives but making these implications about all the first degree relatives about them, or it's X, Y, Z, other community of this or that group.

So what we're saying here though has implications, in effect, for sort of a regulatory change. Which is, that they're a special category in the genetics area of saying that, because of this analogy, the subjects, even if you answer the question no, there are no subjects in the traditional sense because this is dead people's tissue, but will implications or conclusions be drawn with direct relevance to identifiable people, the answer is yes, then you have to go through a process which doesn't turn them into subjects but has the same effect of getting some IRB review. And that's awkward but I think it's worth thinking about because at least it says it's not just at the discretion of the investigator to be big-hearted about it and say, sure, I'll take the time and do this.

DR. SHAPIRO: David?

DR. COX: Yes. If we don't make it clear that investigators have to spend their time dealing with these issues, then some of them will but a lot of them won't, that's the situation that we have right now, even though the law says they have to deal with it right now. I actually am concerned that unless people have to come forward, and this is the point you were making, Harold, about having everything less than minimal risk, because what it does is it says that people have to address the issue. My argument against that was that you want people to be engaged. But I don't think that those have to be dichotomous, that's where I'm coming to now, because I don't like the idea of sticks by themselves, you have to really have people wanting to be engaged, but I'm becoming worried based on these comments that if you don't have any stick at all then people aren't going to even play. So there has to be some happy medium here.

DR. SHAPIRO: Right. All right. That's been a very helpful conversation the last fifteen minutes or so. I think we will be able, again, to articulate something quite interesting out of this for us to consider as we get through the next draft of this.

Let's just proceed along here. The way this memo is drawn up we're now at sort of Roman II, so to speak, and there are a bunch of things called recommendations that follow that. I think some of these are repetitive, things we already discussed and/or are made obsolete by things we've already discussed.

Recommendation one, which deals with encryption schemes, I think is, by and large, moot at this point. Something is identifiable or not, and that's what we decided on yesterday. Personally,

I don't think those encryption things are possible, but I'm not the expert here. But I just think it's moot; we don't need to spend any time discussing that today. We'll just put it aside for the moment. I could add a whole long list of these.

[Laughter.]

DR. SHAPIRO: But then recommendation two here really is what we've just been discussing. It is not a separate issue, at least as I understand it, Eric.

MS. CHARO: The answer to that one is no?

DR. SHAPIRO: Yes, subject to all the things that we've been talking about here and the processes around which we want to surround this to try to achieve the aims that we've just talked about in the last fifteen or twenty minutes. But that's just not a separate issue. It's something we've already dealt with.

Now what about recommendation three? Do you want to say anything about recommendation three here?

DR. MESLIN: Three and four, in fact, three, four, and five are variations on a theme and they were put there to try and distinguish different nuances of the same issue. All I think we want to mention in three is a concern about publication, which raises a particular type of risk. And in recommendation four, we are speaking about inadvertent identification and whether or not that should be drawn to the IRB's attention.

My view is that three and four can probably be folded together if the group feels that a guidance regarding publication of pedigrees would be of use. This is a moving target. There has been research very recently published on this by Jeff Botkin and others. So it may very well be that we can turn that into a guidance of sorts rather than a recommendation.

Please don't take the words recommendation versus guidance too literally in this memo. They are quite fungible.

MS. CHARO: The discussion yesterday, obviously, is richer in detail than the language that's here. So need we at this point in the transcript try to reiterate what was said yesterday, or simply say refer back?

DR. SHAPIRO: I think refer back if fine.

DR. MESLIN: I suggest that we fold it together. I think that will make it much easier.

DR. SHAPIRO: I think whether these come out as recommendations or guidances, whatever they come out as, these are not easy recommendations to write I think. I think there's a lot of problems in writing these and saying something we don't intend to say. It's a sensitive area.

DR. MESLIN: The only thing I would add is we discussed yesterday the possibility of writing a one-sentence finding or general conclusion that would precede the guidance statement. I know staff would be grateful if Commissioners might think about what that finding, that one sentence statement would be that would allow us to then say so it is our guidance that certain types of information should be provided.

I would be happy to work with any Commissioner who would like to do that. But that would be very helpful.

MS. CHARO: Yes. I know even in light of the complications of FACA and requests, et cetera, I would love to urge a return to the use of e-mail to allow for more interaction between meetings to get the text kind of refined.

DR. SHAPIRO: Yes, that's fine. FOIA is no problem in this area. No reason why.

Let me ask questions then about three and four. When I read it, my first reaction was one of being somewhat troubled by them. I understand the need to protect privacy of innocent people who are not participating in that. And if that's what's meant here, then I don't have any problem with it. If that's what's meant one way or another here, then I don't have any problem with it. And the question is, was anything else meant by this?

DR. MESLIN: No.

DR. SHAPIRO: In that case, whatever we say about this ought to be able to be said in a really compact form because I think it's pretty straightforward. And in what way would that differ from anything that's extant right now?

MS. CHARO: I'm sorry, we were on XI was dealing with another X

DR. SHAPIRO: Three and four in some combination. It would seem to me similar. It would need to be combined in some way.

DR. MESLIN: The only distinction is whether we feel it is important to make clear what is either ambiguous or silent in existing regulatory language regarding the ability of an IRB or others

to focus explicitly on potential harms to others. And we've listed the types of others and have put language that says there should be concern and sensitivity to this. But up until we say that the regulations should be changed that explicitly empowers IRBs to do this, then, no, there's nothing more involved than that.

DR. SHAPIRO: Putting IRBs or particular institutional arrangements aside here, who is it that is going to, if there is some responsibility here, you're trying to articulate a responsibility, who is it that has the responsibility and what's the nature of the enforcement action here that we're talking about? That's the part that's completely unclear to me.

MS. CHARO: Right. This is what was going on yesterday. As I understood the conversation yesterday, we were placing responsibility first on investigators to voluntarily present themselves to the IRB in situations where the regulations don't require it to ask for discussion, guidance, changes, et cetera. We were asking IRBs to take this request seriously and to develop expertise in how to minimize harms or how to look at the social implications of research, and if they are seemingly dangerous, how to review the scientific validity of the study even more closely. Because none of it was required. It was all voluntary.

Now that said, on a variety of these things it should be mentioned perhaps that IRBs are never forbidden to go beyond the federal regulations. They can always go beyond. They can do it on an ad hoc basis, or they can formalize it in the form of their Multiple Project Assurance with OPRR in which they promise to do it on a regular basis. If they do that, there is an enforcement mechanism because they are bound by that MPA and if they fail to comply with it they are subject to investigation and sanctions from OPRR, which may be a disincentive for them to formalize these supra-regulatory tasks. But those are ways in which this can be incorporated a little more formally.

The other thing that can be done is, as David and I were talking kind of on the side here, is to aim some of these things at the world of scientific journals and at NIH, NSF, and other granting agencies. Journals and granting agencies are also perfectly free to say that we will give preference to those papers or those research projects that meet an even higher standard from our point of view of the protection of human subjects. They can add that. So in the study section, they can not only ask whether the appropriate IRB review was done, but whether or not there are any residual problems. Study sections that I've been on have certainly gone beyond the IRB review on occasion and said this protocol is problematic.

DR. COX: And professional societies. Because this is then the carrot approach and not the stick approach. But if professional societies say these are very important issues to get more data on so we know what to do, and so we want the researchers to basically pay attention to this, it's not

being shoved down people's throats. On the other hand, I don't think it can be completely voluntary. But have different ways of enforcing this.

MS. CHARO: But it is true that in the end it is largely voluntary and it is circling around what Alex has called the "weak read" of IRBs. So that this is a bit of a house of cards.

DR. SHAPIRO: Okay. Well, in any case, we'll do our best there. We're going to combine these in some way to get it a little more effective. I still have some troubles, but I'll put those aside for now.

MR. CAPRON: One linguistic comment. The things under Roman I we were calling guidance, and here we're calling them recommendations. I realize that this is in some ways just a temporary memo and language was adopted for that reason. But things like this have a way of developing a life of their own. I see no reason to distinguish between recommendations that we make to the federal agencies and calling those recommendations one to whatever, and recommendations that we make for actual changes in the language of something, or IRBs, or whatever.

DR. SHAPIRO: Okay. Do you want to say anything further about recommendation five at all, Eric?

DR. MESLIN: That was a placeholder recommendation which is really folded under some others. Maybe Bernie wanted to say something.

DR. SHAPIRO: Bernie, I'm sorry.

DR. LO: I actually would like to say a little bit about five because I think it does get to this notion of group harm that we've been talking around. It seems to me there's a difference between the actual design of a study, going to a group that's been identified on ethnic or racial terms, often because they had volunteered for a previous databank, and using them mainly because they're convenient but the more you know the more interesting genes you find. That to me is different than you do a study where ethnicity or race is not a variable at the onset but when you finally do the analysis you find linkages or whatever.

It seems to me we ought to ask investigators to pay more attention to the former situation where it is part of the integral planning of the project. Again, I'm particularly concerned, I'm thinking about the news stories of concerns of Ashkenazi Jewish families in Baltimore who get used over and over again because there are lots of interesting markers and the samples are already collected and easy to get to. And yet they, at some point, maybe begin to have real concerns about the benefits being traded off against the sense that they have one serious marker gene after

another. And although all the studies when they're published say this does not mean that this group is particularly susceptible or the other groups may not have as high a prevalence, the point is we just keep going back to them primarily because it's convenient because the samples are there.

I think the problem there is I don't know how we can get beyond the considered implications and act prudently. But I think maybe some guidance there as to what do you do in that situation. You're going to do a study on that group most likely, how do you mitigate it? It seems to me there is a real role for having a real dialogue with the community and at least explaining to them why you're going back to that same group, providing a lot of community education as part of the price you pay for having a really nice database that someone collected for you twenty or twenty-five years ago.

All the questions we raised yesterday where the synagogue has turned over, they've moved, the initial congregation is dispersed. I think that's all true, but that you shouldn't use that to say now I don't have to do anything. I think you do the best you can to find people who could seriously feel that they're implicated by this design of the study. And, again, it's more in the nature of an exhortation we're talking about and all the comments people that we're saying about using the carrot approach. True. But if we could be more specific about what constitutes best practices in that situation, it might be helpful.

DR. MESLIN: Bernie, one of the reasons why I made the comment that I did was in talking about Guidance 2 yesterday, which was that something should be developed that directs IRBs to address the issue of group or community harm, that's what I was referring to by this recommendation. What we discussed yesterday was sort of concentric circles, individual, family, social group, non-descript group. If you feel that it would be helpful for us to actually stipulate now that that guidance should include a kind of consultation or engagement which we've been discussing, that can easily be added in as a specific suggestion for what thoseX

DR. LO: I was just saying that in this context I would like the implication here that some things you weren't planning at the beginning but in the course of doing your research you began to identify certain groups or families. And there are other studies where right from the onset you know the results are going to be attached to a certain readily identifiable group because that's the

way you designed it. That seems to me that latter situation ought to have more responsibility because it was much more foreseeable and sort of intentional.

MR. CAPRON: In many ways, I agree with you. But it would seem to me that if race or ethnicity is one of the factors which you are gathering in your database, we wouldn't want to have a situation set up in which we have a high hurdle for the first kind of study, the Baltimore study, and then people figure, well, I'm not going to do that but I'm going to gather the data, and I know I can always run the analyses and I suspect that I'm going to see some racial/ethnic, and I'll end up saying Jewish women not only have babies with Tay-Sachs, but they have breast cancer a lot, too, even though I didn't "design" it that way. That's not the right incentive to give.

DR. SHAPIRO: Alta?

MS. CHARO: Bernie, I think that it's possible that this set of concerns might be reflected again in the study that has been proposed on looking at the IRB system and human subjects protections generally. Because part of what has created this problem for us is the fact that the IRBs are not only under-staffed, overworked and under-rewarded within their institutions, it's that they are reflections of the professional expertise within the institutions, with very few exceptions, and that therefore they are in fact not a very diverse group of people and you don't have the kind of range of life experiences and sensitivities that you would have if you took a random group of twenty people off the street.

And so perhaps in that larger study one can address more widely some of the social costs that we are experiencing from having an IRB system that has been enfeebled by small size, overwork, et cetera, and the value of diversity in kind of preempting some of the problems. Most of the institutions, they don't have a lot of women, they don't have a lot of blacks, they don't have a lot of people who are disabled working there as professionals, relatively speaking, and so they don't show up on the IRBs either and their sensitivities don't show up on the IRBs in any particular way. So, it's all a part of a larger problem, and we can definitely make sure that it's highlighted.

DR. SHAPIRO: Okay. That's fine. Well, we'll certainly do so.

Let's go on and look at an issue which comes up as perhaps a little bit of a placeholder also, which is on the recommendation number six on page seven, which talks about waivers.

Alta?

MS. CHARO: This one actually got red pen on it from me, because I think it must be a typo. It recommends that when considering a waiver the investigator has to provide evidence it's not practicable. But that's already a requirement. So I figure that's got to be a typo. And, in fact,

what we're talking about is NBAC recommends that not practicable will be understood as the following. Is that okay?

DR. SHAPIRO: Yes. That's what I thought about it. That is either we have something to say here or we don't. If we want to say something, okay, if not we don't have to say anything.

MS. CHARO: And even before we get started on filling in what we think "not practicable" ought to mean, I'd like to add this to the other request about the meaning of human subject in a request to OPRR to simply alert us to any guidance they've ever issued or any contacts they've ever had with IRBs that have called them or written to them saying "What the heck do you mean by this?" so we can find out what precedence there are out there for interpretation of this term. It could be that I just missed it in the guidebook and there is an interpretation, but I didn't spot it.

DR. SHAPIRO: I didn't either.

MS. CHARO: And that would be useful information to supplement whatever we do here.

DR. SHAPIRO: We'll certainly do so. Alta wanted information on OPRR's dealing with the issue of human subjects and relatives.

MS. CHARO: Who have kin, living kin, right.

DR. SHAPIRO: What information they've put together.

DR. MESLIN: What you've just described is not a proposed recommendation. That's a request that we obtain that information to inform us?

MS. CHARO: It's a request for information. That's right, so we can work through what we think is a tentative recommendation today, but I would love to be able to test it against anything they provide.

DR. MESLIN: Yes. I mean, we have, for example, provided the Commissioners the two memos that OPRR provided guidance memos to NIGMS and to NHGRI of about XMelody Lynn knows the date, if she's in the audience she can confirm itXof probably a year ago which answered a number of these types of questions, not the specific one you're mentioning. But you would like to know whether there are other documents of that kind where OPRR has responded to questions of this sort.

MS. CHARO: On these two topics. Right. And if they've already been given to us, I apologize in advance. My filing skills are minimal.

DR. SHAPIRO: It's on these two particular issues as opposed to just other kinds. One dealing with the living kin, and one dealing with this issue of practicable, if there's ever been any tussling, conversations, working out of what on earth this means. David?

DR. COX: But I would just like to make a plea that as we ask HHS or OPRR or anybody for their interpretations of these, when nothing is forthcoming, that we make interpretations and that we aren't stymied by other people's lack of action.

DR. SHAPIRO: It's just to see if there might be some useful information.

Bernie?

DR. LO: I was going to jump to the next thing, of trying to flesh this one out.

DR. SHAPIRO: Yes. Let's go ahead.

DR. LO: This becomes a loophole; becomes a huge tunnel. Clearly, if someone is dead or moved away and you can't readily locate them, I think that would count. What bothers me is in most health care systems every year there is sort of a re-enrollment process where they check and make sure you still have insurance coverage and you've chosen them as the primary provider. It seems to me that in that situation where you're providing ongoing care, there is built-in periodic contact with the person. It seems to me at least the presumption or the strong presumption in that situation it's practical to contact a patient. Now, it may be very expensive from the point of view of the researcher who doesn't have a large grant. But I think we have to distinguish I can't do it because the person's not there or I can't locate them versus I can't do it because I just don't have enough 32 cent stamps and Xerox money.

DR. SHAPIRO: I think, Bernie, I think that point is well taken. But I think it is a critical issue whether economic barriers get sufficiently high to say that means impractical at some level. If it's only economics we're talking about and not logistics, that is, presumably with enough resources you can find a lot of people, even those who moved away and so on, you can trace them down. And so we might want to have some discussion of just what kind of economic burden do you have to exceed in order to sort of satisfy this hurdle.

Alex?

MR. CAPRON: We heard earlier on that there are situations in which health plans, for example, are cooperating with researchers on a prospective basis. And in a certain way we've separated the retrospective and the prospective, but today's prospective becomes tomorrow's retrospective. And it seemed to me that when we are talking about a health care organization that

is, in effect, setting itself up in a contractual relationship with a group of researchers, particularly when those researchers are private companies that see a product development coming out of this, that the notion that impracticality is a pretty thin excuse comes in here.

That is to say, it is not just on the reenrollment, but if you're putting people's tissues into a database which you then plan in effect to market, it seems to me reasonable to say you have some obligation to do the kinds of things that I think we heard the breast cancer group was doing, that of having a regular recontact of the people whether or not they're still in your health plan. But the every six months or every year, "We've got your tissues here. We want to stay in touch with you. Please confirm that this is your address. If this has been forwarded to you, please give us your new address. If we don't hear from you, that means we're taking your tissue out of the bank, which is a great cost to science and we really encourage you to continue to allow us to do the research." And whatever arrangements.

But it does seem to me we're talking about potential harms to people. We wouldn't care about this if there weren't some potential harms to people, and the ethics of protecting people against that harm unless they've consented to it. On the other hand, dollars and cents. And dollars and cents should be just as relevant in this aspect as they are to the fact you have to buy expensive reagents and hire Ph.D.s to do the research and so forth. No one says we ought to be able to do research by using slave labor or something. I think we ought to keep that in mind when people wring their hands and say, "But if you put up that rule and say that if you've sent a postcard and you've gotten no answer back, then that's enough. That it's impractical to re-contact the person because it would cost more to be more active and trace them down and do a little more digging. And if we don't do that, we lose the tissue." All right, well, we lose the tissue because you want to protect people against being used in situations where information is developed about them which could be harmful to them and they haven't consented.

And it's just a cost matter. So I think we have to elaborate on this practicality in some detail, and I'd set a fairly high level for impracticality before I would be comfortable.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I agree with Alex on this. I think the situation is exactly the same as that of longitudinal research where the burden is exactly the same. You have to recontact the persons who participated in the study and ask them to continue to participate. And it does cost money to follow them. There are some people who die and you have sample attrition. But it's just the same. I think we may be over-emphasizing this notion that it's impractical to continue to

contact people. And there are firms that specialize in doing just that for longitudinal studies; they find very clever ways to contact people and to get their continued enrollment in the study.

DR. SHAPIRO: Just to pursue this particular point. David, I know you. It's one thing to conduct a longitudinal study and an organization required to do that. It's another to come up with a problem and you want to go to a tissue bank, use some tissue or some other material of one kind or another, and then, not because you want to do a longitudinal study, because you want to do a study now on a particular issue, and then you're faced with the same problem of having to contact the people in order to protect them from harms.

And the question then is, I would think, that at some level economic burdens become high enough because they're a proxy for practical. That is that it's so hard to find these people and you have to put so much resources into it, there must be some burden whichX

MR. CAPRON: But the choice to use existing tissue samples rather than currently collected ones where the people are easily contacted is itself perhapsX

DR. SHAPIRO: Correct. That's a good point.

MR. CAPRON: This is an easily, readily available source. And we're not talking about a situation where you go to the tissue bank and say give me a bunch of anonymous samples, I don't need to know anything more about them. We're saying give me this, give me their medical records or heavily abstracted stuff from their medical records.

This is a choice. And if we're going to shrug and say, well, but it's just a matter of inconvenience to get that far and you could do it if you spent more money, or the way Diane says, you get the same firm to work and trace down this person and say are you willing to do this, if we're going to shrug it off, why are we worried about any of this? Why are we saying there's any concern? Just use the samples, don't worry about consent. And I don't think that's our attitude.

DR. SHAPIRO: Right. I agree.

Bernie?

DR. LO: I think we also have to look at the burdens relative to prospective benefits. So it seems to me, in addition to everything that's been said so far, it's not clear to me why for most studies you can't just use the samples for which you have recontacted and gotten consent. So that if you think there's an overwhelmingly important scientific reason why because those people may not be representative of all the samples, then you have to make that argument. But it seems to me, again, there's a counter. If you're so concerned about the sort of generalizability of a population, then you need to go back to a population drawn sample, not just all the people that happen to end up in your hospital.

So, I think in addition to what we've been saying about not allowing economics to sort of just run willy-nilly over concerns about privacy, I think also the argument on the other side that the benefits are overstated. I think we need to look very critically at arguments saying what the scientific loss would be if we restricted ourselves to samples where people have been contacted and get some sort of meaningful consent.

DR. SHAPIRO: Diane?

DR. SCOTT-JONES: I'd like to say that I also agree with what Bernie just said. I think there is always a conflict between the obligation to get informed consent and the possibility that you're reducing the generalizability of your sample because you're not including all of the persons. That's just something that we have to live with. And I agree with Bernie that we may be over-emphasizing that. This is always the problem of research and it is not particular to this kind of research. And that is, if we believe that research participation should be voluntary, then we have some loss on the scientific side that we learn to live with and we learn to manage it by other means.

DR. SHAPIRO: David?

DR. COX: So, Eric, this is one of those one-liners to put on the little card that you strap to people's chests, right? However, as much as I'm in favor of this, this discussion frequently gets extended in the following way, which is impractical. When you can't contact those people, you will extract all of their information out of the study so it's not there. That's not possible to do. So that you may not use the samples anymore, but that train left the station already in terms of how that sample information and data was in the study. And it is absolutely impractical, and I'm open to people showing me how this can be done, to take that information out of already analyzed data.

This is one of the reasons, and this will come up because people will try and obfuscate this basic principle, which is you go back and recontact and use the sample. But they say, well, but how can we ever extract that information out of our data in our study if it's already in there? The answer is, you don't. You just don't put it in anymore. But this is this whole business about giving people the right to withdraw from a study. So that they have the right to withdraw, but it has to be understood that after a certain amount of stuff is done, it really is impractical to take all of that information out of the study.

DR. SHAPIRO: Alta, then Trish.

MS. CHARO: First, I've got to tell you that we've run into exactly that situation on our IRB and I sympathize.

DR. COX: You can see it over and over again.

MS. CHARO: Right. I apologize for throwing a monkey wrench into what seems to be a developing consensus that money doesn't matter, money is no object, consent must be obtained at all cost. But I am not completely, maybe I'm misunderstanding, but what I'm hearing is that we should not allow people to say it's impractical to re-contact for consent simply because it's expensive. If I'm mishearing, that's great because then it's not so much of a monkey-wrench.

I am reminded of David's example about the kind of tiered research that might go on in which the first pass is simply to identify people that you might want to recruit for a more intensive look. So the example you gave was you might want to do a first pass looking for all people that have a hypothetical marker for a gene that is suspected to be associated with prostate cancer. And the goal is simply to identify the subset that have the marker, and then in fact to contact them and specifically ask whether or not they would be willing to be part of a study. And that first pass might be over many, many samples.

Now, in many circumstances, it might be true, that contact is feasible because they are members of health plans that have this kind of reenrollment process, et cetera. Not always, because a lot of the tissue collections that are described here in the early parts of the draft are not maintained by health plans. But it may be possible here. But the expense might be quite substantial. In light of the effect that has on your ability to get the research grants, which, of course, are limited by dollars, there are X number of dollars to go around and if you increase the cost of each one by virtue of requiring contact even for this kind of first pass, you reduce the overall number of grants available or you increase the R&D cost for a pharmaceutical company. You can speculate there is going to be some number of marginal research that won't get done. It will be that last few things.

I understand why this sounds really awful because it's the same argument about minimum wage and how there are marginal jobs that won't get filled because it costs too much. But I'm worried about this because there are, it seems to me, examples of exactly the kind of thing where expense seems to be a very legitimate concern but I don't have any idea of how to peg it. Is it percent of the overall cost of the research? Is it a certain absolute number of dollars? I have no idea how to implement this instinct that there really is an economic argument to be made that at a certain point it may be technically feasible but it is not practicable.

DR. SHAPIRO: David, then Bernie. Excuse me, Trish, you were on the list.

MS. BACKLAR: This is going on another path. I just wanted to go back to say what David said about when you have somebody, and it relates to what Diane said, if you have people in your research protocol and somebody drops out, you don't drop out the data that you have on them up

until that point. It doesn't matter when it's genetic research or it's on the kind of research that I do. So it's exactly the same situation.

DR. COX: But just to make that point, because otherwise it sandbags and it obfuscates this principle.

But Alta brings up a really important point, and this is being faced over and over again by the NIH. Alex said this well. This isn't all large epidemiological samples. These are samples that you will use over and over again that you get more and more information in. So the NIH right now in many different settings is trying to grapple with how do you deal with the expense and the coordination of getting high quality data.

And you know what they're doing? They're contracting it out. They pay for it. The expense doesn't go to the investigator, but it's viewed as this is part of the price of doing business. And it's not part of the funds that the investigators ask for in their grants. It gets contracted out. It is part of the research enterprise that for these subsets of patients and materials that are a national resource, you go back to those people.

That doesn't mean, though, that it's every large epidemiological study. So I think that the economics doesn't have to be at the individual investigator level.

DR. SHAPIRO: Bernie, and then Trish again.

DR. LO: Just to follow up on this topic, because I think it is really important and I think it does come up a lot with investigators and IRBs. I don't think that we were trying to say that economics never should be a factor. I'm just saying you have to really define what it means to say it's economically unfeasible.

MS. CHARO: My apologies for misstating what you said.

DR. LO: And I think also you just have to be really creative about how to address that. I think we should call for the NIH to fund center grants to set up the infrastructure. As David was saying, that's part of the cost of doing research. I agree with Alta that it's unfair to put the burden on the individual investigator. But the NIH is looking at prospective increases in budgets and this is one of the things that they may want to consider. To go back to Alta's example, losing by not restricting that first sweep to that subset of patients that you have been able to recontact through any of these other mechanisms, and is there you know a compelling scientific reason why you just won't be able to get that group. And then the next question is if you can't get it from your own database, why not go to one of these other large databases that has been collected by someone else that has set up infrastructure to be able to recontact people, or has had a tiered consent that we're going to talk about later, so that what we may want to do is to centralize a lot of this into a

relatively small number of very well maintained large databases that have the capacity for ongoing recontact. It's really important for a patient to know that their personal sample will be used for research. That's going to be impractical if it's at some outlying community hospital that doesn't do a whole lot of research. We shouldn't be misleading people to thinking their particular sample is really to be used. It will only be used if it somehow it has gotten its way into a database that someone is committed to keeping up. I think, again, I go back to the epidemiology. I mean if you're really wanting to get a representative sample, you've got to get a population-based sample. The samples I have lying around my hospital are biased samples of prostate cancer. And I'm kidding myself if I think that I'm gaining something by looking at those data, rather than a population.

DR. SHAPIRO: I know DianeXI want to call Diane in just a second. But just try to listen carefully to what's being said here. There is an issue of a loophole here which is gaping so large that we're not demanding. We're letting it through without sufficient oversight, in some sense. We're letting them use this excuse when, in fact, if you look at science requirements, they really don't deserve to be let through this loophole, and just become larger, and, therefore, not protective enough of those people whose tissue is being used.

And I think as an empirical matter, I think it's probably correct. And thenXand I thinkXso I think we all agree with that. I also think we agree that somewhere out there there is a ceiling where the economic stance for something, not just money, it stands for a whole series of difficulties, which we would declare impractical, but that's some high number, or, at least it's a threshold considerably above what's beenXwhat's currently in use, if I understand what people are saying. And then the question is just how do you deal with theXwhat's in between those two things and how do we articulate. Okay. I'm just trying to think out loud. I'm sorry.

DR. SCOTT-JONES: My pointXBernie started making, and that is that there is an infrastructure, the scientific endeavors, and David was referring to some of this, too, where people are now engaged in discussions of how to use data jointly, how to data share, how to do things to minimize the cost of research. So I think we need to make our recommendations in the context of what is going on right now in the scientific community and many people are discussing now how to minimize the cost of doing research through a number of means. So I think that you know we should put that in mind before we think that it's going to be too expensive to do the kind of things that we're talking about. Okay. Well, we're going toXalthough we're not through this, I think we're going to call the discussion on this particular report to a close now to get on to other things. We will continue this discussion by E-mail and other issues, that if we have time later today, we're going to pick up some of these. If we have time we can come back to some these issues, so it just depends on how much time we use on the other issues. There are still some very

important issues to be thought about here. So I haven't divided this between important and unimportant, but just to try to keep ourselves to some kind of reasonable schedule. So we may very well come back to this later on today, but if not we will do so well before the next meeting using one form of communication or another. I also want to mention something which didn't come up in yesterday's meeting directly, but it's really indirectly in some of the memos that we have received. Namely, there are increasing initiatives, and the level of state laws in this area. Do you know from the memos we receivedXand some of you are much more knowledgeable thanXor other reasons. Those will have to be acknowledged in some way and we'll have to couch our recommendation of the number of areas, given the background that states may choose more restrictively regulation on a whole number of these things, which, of course, they are perfectly free to do with these, as I understand it. We've not had a chance to discuss that, but that will also have to get worked into some of our material. Yes, Bernie.

DR. LO: If I could make a request of the staff with regard to that point? I think, as one of the people who doesn't know a whole lot about this, I think it is important to know what the pertinent state laws are. And so, I would actually like to see actual provisions of Florida and California. And it wasn't clear from this whether Delaware is a bill or a statute. I am actually much more interested in statutes that really are there, as opposed to bills which you know may or may not go anywhere. But the actual language and provisions would be really important, and maybe some comparison of theXI don't know whether it's three or four states that should have pertinent existing statutes.

DR. MESLIN: We can give it to all of the Commissioners. We have such a document available here today, and we can give one to you if that would be helpful.

MS. CHARO: Also, Bernie, just by way, I think you may have received a fax late last week of one memo from one of the staff people that actually did, at least in the fax that I got, have something like 20 pages worth of the actual provisions. So, if youXyou might find that you have some of it already. It's easy enough for them, sure, to get you another copy but.

DR. SHAPIRO: I've got the six page version.

DR. MESLIN: The lengthy text that Laurie provided was not faxed to everyone, but the cover memo itself was.

MS. CHARO: And theXwell, never mind. If you didn't get it. You didn't get it, right.

MR. CAPRON: One other thing, at some point we need to decide. One thing Laurie does in this memo is to say that if you see a pattern of state legislation or even a lot of legislative activity that isn't yet statutory, but it's still on the bill level and you make some conclusions about the area of public concernsXthis is the sociological use of the law, rather than a binding legally. And see I think that's a reasonable thing to do in the way of buttressing our concern.

DR. SHAPIRO: I agree. I agree with that. All right. We are due to take and will take now a break. We will try to reassemble at 10:30, because I know some of you need to check out, do other things, make phone calls, and so on. So, let's reassemble here at 10:30. Now, we'll turn our attention directly then to the what was known in shorthand as the capacity draft. So, thank you very much. We'll reassemble at 10:30.

DR. SHAPIRO: All right. I want to turn now to that part of our agenda that will deal with the draft we've all been studying regarding research involving subjects with mental disorders that may affect their decisionmaking capacity. And, again, I want to thank Jonathan for being here with us for this purpose, and for the help he's given us all along in this. And let me just say something about the agenda, then turn over the chair to Jim, who will take us through this discussion.

We will focus on this till 11:30, at which time we will take a pause for public comments. We will then immediately return to dealing with this report, and work on it through lunch. At one o'clock, Mary Claire King will be joining us and she will speak to us approximately in the neighborhood of a half an hour. And then, depending on how far we've gotten, we'll return to this or move on to other subjects. So, let me turn to Jim. Jim.

DR. CHILDRESS: Thanks, and let me just echo Harold's expression of appreciation to Jonathan for all of his work on this document. Also, other members of the staff and the Commissioners had a lot of input. And that's always been very, very valuable, and we're always amazed how much input Harold is able to provide on this for different drafts. We wonder when he sleeps. The schedule, as I understand itXand I'll get Eric Meslin to amplify this, would be that we do have the document from July 1 on the website. It's been sent out also for comments, and the staff will analyze the input and takeXwe'll take that into account, along with our own discussion today and social developments when we look at this again. The protocol review also is under way, and the analysis will be provided by staff. Staff will be working on the Maryland report. We have sent copies out before, and the final draft came out recently, and the interstate report, which we finished soon. And all of these will be things that will play a role in our preparation of the final draft. And then we would try to incorporateXdeal with those materials the best we can,

and based on staff analysis in September, try to develop a revised draft as soon as possible, and the hope is that we could sign off on this in November. Is that correct? I just wanted that to be before us, so that helps us clarify our marching orders for today and over the next several weeks. You have a memo prepared by staff on remaining issues. And I think this is a very helpful memo. There will be some other issues that Commissioners will want to raise for discussion. So, what I would propose is that we go through these issues, think about them in relation to the text, and then come back to a number of questions and comments, and proposals that they will have that go beyond the ones that are identified here. If that's satisfactory, then we'll just proceed that way. The first one shouldn't take very long, although saying that sometimes opens the door to X. The use of the words "subjects," that proposal poses no problem for people, I hope.

MR. CAPRON: Yes, it does. I believe we should continue to use the word "person." We are talking about people here, who may or may not become subjects of research. And I think the phrase, "subject," here is a way of classifying people already and deemphasizing them, their personhood. The choice is not between subjects and patients. Obviously, where that issue comes up, subjects is preferable to reminding people that although people are, perhaps, receiving medical care, they are, for the purpose of study, a subject. I would prefer staying with the word "persons."

DR. CHILDRESS: I think you've made a good case. I don't have strong feelings about it. Diane.

DR. SCOTT-JONES: I prefer using "persons" also, where appropriate. And I prefer using "participants," instead of subjects when we're talking about people actually involved in study.

MS. BACKLAR: I agree. But, also, I'm wondering in the title if we should not say, "Research Involving Persons with Mental Disorders that May Affect **Their** Decisionmaking Capacity."

DR. CHILDRESS: That we'll come to in a moment, as the second issue I think in the title itself. So let's do the studies part first, because I think that we do use language that may affect throughout. And sometimes we cannot get with their decisionmaking capacity; sometimes we don't. But in the title, if we're focusing on X and we'll come back in just a moment. So, let's do the subjects part first.

MS. CHARO: I may offer a compromise X at least accommodate this all. Until people have actually been enrolled, they are clearly persons. Sometimes they are patients, depending upon the phrasing. At the moment at which they are enrolled, they are subjects participating in research. Is that a way of getting everybody's points included?

DR. CHILDRESS: That is. But how will that help us with the title?

MS. CHARO: I'm sorry. I thought you said you were still working on subjects.

DR. CHILDRESS: Well, as it relates to the title part, as well.

MS. CHARO: Excuse me. I was a step behind you.

DR. CHILDRESS: But it's both. It's the title, the part having to do with subjects, but then it's also why we use it throughout. Larry.

DR. MIIKE: I would just go with "persons." If we're talking about subjects, we should be talking about human subjects versus animal subjects, versus other subjects. But "persons" would be the way to go.

DR. CHILDRESS: I hear a consensus that we go withXback to the original formulation of persons. And I think we'll need to look very carefully, actually, in the text. Because in some cases in the text, I think it will be more appropriateXto use subjects. And sometimes participants, Diane, will be more appropriate. But we also do have to tie in with the regulations. And so, we want to keep the subjects in mind forXin places where it would appropriate to do so. But with the staff alerted to this need to be flexible throughout, then will that be sufficient, Bernie?

MR. CAPRON: Well, to put a sense to what you're saying. Although the language of subjects is used in the regulations, some connotations are not ones we like, and participants may more sum up the sort of the ethical relationship. . . .

DR. CHILDRESS: Good. Duly noted. Any objection to that change in the title, and then careful attention to this throughout the text? Okay. The second part on how we think about may affect decisionmaking capacity. And, sometimes, we're talking about this generally, in terms of mental disorders, that affect decisionmaking capacity, or affecting decisionmaking capacity, where we want to indicate that sometimes, perhaps, even often there maybe that kind of effect, but leaving it open in particular cases.

MR. CAPRON: I thought she just wanted to put a pronoun in there?

MS. BACKLAR: I did. I just wanted to identify that this was their issue. They're a decisionmaking capacity, that mental disorders may affect them. I'm not saying that you said may effect them, but that's why I wanted to put their decision there. I want to make it very clear that it's going to effect them. That's all.

DR. CHILDRESS: Okay. Any objection? Sorry I misunderstood. Okay. Two categories of risk. We have discussed this before. Is Laurie available? Is she going to be?

DR. MESLIN: We've made an attempt. We're going to try again. We tried to get in touch with her. We haven't been able to.

DR. CHILDRESS: Why don't we just skip over this, and see if she can get involved with us, since this is something that she's been very interested in. Let's go to the dissent point, number three. And I'm missing some lines in my draft, so it's confusing.

MS. BACKLAR: If there was something at the bottom of the page that then went to the top of the next one.

DR. CHILDRESS: Right. So it's not clear, but that's the point. Is it the National Commission had a complete review on this, relating to overt objection. We've gone in the direction of no apparent dissent. And the question is we don't do we give enough justification for departing from the National Commission's standard, and are we satisfied with a departure.

DR. SCOTT-JONES: Jim, did you reference the pages where that is discussed?

MR. CAPRON: 111 is a discussion of the National Commission's view and following. And then our recommendations. We come to this statement, as well as in the special protections in research.

DR. CHILDRESS: Actually, I'm not sure. I think we could go ahead and discuss the topic, because the issue, whatever wording is there, is whether we want to depart from it in the direction that we have already taken, namely, no apparent dissent. Are you satisfied with our standard no apparent dissent?

DR. MIKE: That is stronger or?

DR. CHILDRESS: It will exclude a lot more people from the research.

DR. LO: I would like to see more explanation of what the differences mean. Because, frankly, I'm not clear what implications of changes there are. I think it would be nice to have a justification for why we're moving away from what up to now has been the accepted line on the subject. And we've made it pretty strong, in that, it does it is apparent dissent is in level with risks and of any level of benefit to the subject. So it's and apparent dissent can cover a variety of options resembling sort of waving one's hands, "no, no, no," would be quite sufficient to stop the research. So, this it's strong standard. Let me give it a try.

MR. CAPRON: I don't think we should have this discussion without Laurie. Because it seems to me again that she was bothered by that and talked about it, the notion that an incapable subject, not fully comprehending something that's being done, but it would say, "No, no, no." And if that was her view that you shouldn't necessarily halt the research, as I recall her discussion.

DR. CHILDRESS: Okay, I have several, Jonathan, Diane, Bernie, and then Trish.

DR. MORENO: Well, in response to Bernie's request for rationale. I think that the rationale would be that these are people, first of all, who are in a dependent relationship with the researchers and the institution. I think that the rationale would be that these are people who are in a dependent relationship with the institution and often the researchers, and that the image that they would be, in some fashion, forcibly required to go to a room and continue to be part of aXperhaps, an imaging study, or that they would be forced to accept an injection or the placement of a line, an intravenous line so repulsive that even if they didn't understand the underlying, perhaps, benignXand certainly benign motivation, that the atmosphere that would be created, and the statement would be made by such activity, would in the long run be a much greater harm than any expected benefit to science from this kind of participation.

DR. SHAPIRO: That was exactly the reason we used last time. WeXand I'm not speaking for Laurie, of course, who may have a different view. And that's a good point. We ought to check and see what her views on these are. But that wasXas I recall this discussion quite well. And that's exactly, at least speaking for myself, convinced me they didn't want to recommend anything which would force that scene. That's just my view.

DR. SCOTT-JONES: I agree with the position that we've taken. And I just wanted to point out that the National Commission's sentences reflect what's ordinarily done in research with children; that is, that if there is some direct benefit they can be forced, even though they don't assent. And I also looked at the document that we got from theXfrom Jack Schwartz regarding Maryland's recommendation. And I believe, if I'm interpreting correctly, they take the same position that we do regarding assent, that the potential research participant can, if they withhold assent, they cannot be enrolled in the research, and there is no provision made for an exception, and there is direct benefit. So, I think what they have decided is in keeping with the position that we've taken.

DR. LO: I just want to say, the other thing that I would say is that in clinical practice there are presumablyXthere is a known benefit, as opposed to potential direct benefit. It's very troubling for forced treatment on a non-assenting patient. And I think we cite the Canadian Task Force for that. But I think that's another reason I would put in in support of the position.

MS. BACKLAR: I'm just back this up. I just can only imagine being ushered in to have an MRI, for instance, if you wereXand you maybe were afraid, and nobody was going to listen to you. That's all. I just you knowXjust have a visual image of how that would effect the subject.

MR. CAPRON: Well, I justXthis is a recommendation. It appears on page 162. And what we're really talking about is where in Chapter 5, and how explicitly we provide the rationale. As I understand it, there reallyXthere are two issues, which we've collapsed a little bit in this

discussion. One is the issue of whether you need to doXthere is a difference between any objection and no overt objection. And the other is what is the status of the individual? Because the National Commission certainly looked at capability of assent, depending upon the person's ability to appreciate what was involved in the research, and, so forth, even if they didn't have the ability, the full ability, to do legally binding consent, as I understand it. And so, we're really taking a stricter view on both of those points. Is that correct? And I think we need to explain the justification quite fully. I agree with the conclusion, but it does mean that we need to say that since we're not talking about consent, this is an issue which can be revisited with the individual after further discussion, or at a time when the person is calmer, and so forth. Because we don'tXif someone saysXwhen you participate in a research and someone says, "No, I will not." The idea of constantly going back to them and battering them, as it were, badgering them, rather, for it is wrong. But on the other hand, if consent has been given, and then at that moment the persons says, "No, no, no, I don't want them doing that, too, right now." You sort of say, "Okay. We're dealing with a situation where they're fearful. We can sit down. We can go through whatever methods work, if any do, in taking a person, and givingXraising their level of comfort with this, and then saying, now, can we do it?" And they don't object now, or they continue to, whatever the outcome is.

But it seems to me we need to indicate, this isn't sort of a cut-off of the research forever. It's just that it would be wrong to force a screaming person into a tube to do something you know is benign, but they don't find it benign.

DR. CHILDRESS: So you would agree with the line ofX

MR. CAPRON: I agree.

DR. CHILDRESS: Because if you're dealing with someone who really doesn't have the ability to give assent, what you're doing is you're placing theirXthe interaction, quite correctly, takes predominance, even though it's like a two-year-old child or something, in terms of their ability to actually make an intelligent decision about this. And we're just saying it's still wrong to do it to them at this moment. So, we'll add that, presumably, in the discussion, although we're talking about the National Commission's view, but also at the point in our framework and special protections.

MR. CAPRON: Well, I'm not clear about that. It would seem to me that when we get to the recommendationXare you saying at 162, where we give the recommendation? Because I thought that the way those recommendations usuallyX

DR. CHILDRESS: No, I said the framework of special protections, which is the chapter within which the recommendations fall. And it would seem to me that that would be an

appropriate place for it. Because there we have a more extensive discussion of what we ended up with in the recommendations themselves. It's really 149, following. And that a bit of it's already there, but needs to be I think fleshed out along the lines that have just been indicated. Is everyone in agreement with the twoXthe direction that several mentioned? One comment. On 162, are we going to have trouble when we qualify the word "dissent" by a parent? That seems pretty big standard.

DR. MIIKE: But that's the Commission talked about overt. We're talking basically about dissent. But if we see an apparent dissent, thatXit should be a lot more in the opposite direction.

DR. CHILDRESS: Any form of resistance. For example, going to an MRI. So, it isXit's much broader. We capture a lot more people that way.

DR. MIIKE: Well, I'm just a little worried of how full and apparent as the qualifier of what he said.

DR. CHILDRESS: And we've had some discussion about it. Jonathan, do you want to say anything about this?

DR. MORENO: To use the phrase "apparent dissent" places a much heavier burden on the member of the research team to show that there is no apparent; that there is no reason to suspect that this person doesn't want to continue or start the study. If one were to say, "no dissent," then clearly one could construe that in a much stricter fashion. Dissent means for us such and such. It means calling one's lawyer, insisting that the one be able to rip up the original consent form, setting chapter and verse of the regulations, and so forth.

DR. MIIKE: Instead of apparent, could we say expression of dissent? An apparent, one gets to be very subject, in terms of what oneXan expression can be an expression, verbal, nonverbal, etc. Anyway just consider that. To me apparent is so vague, that it's just wide open.

MS. LEVINSON: But maybe one would want to put in "expression," and then parentheses, verbal or nonverbal. It makes it more specific.

DR. CHILDRESS: Harold has mentioned that indication is a possibility, no indication of dissent, which would be another way to go.

MS. CHARO: It strikes me that the discussion is, in a sense, really about the deeper issue that troubles us I think, which is that what you'd like is to honor all authentic dissent, and in this and every otherXtransient thing. And the fear is really that if there is any discretion in the interpretation of the expression indication, whatever, of dissent, that there will be a tendency to

interpret away many expressions as nonauthentic. And that returns us over and over again to the degree of confidence we have in the research community in this particular area. And so, although I know you can use the indication or expression, or whatever. Actually, Larry, I found "apparent" to be a word that seemed to reduce the discretion of the research community as much as possible at the cost of excluding many people who were not authentically dissenting. It was an extremely protective standard. And so, really, in some ways, whether you pick that word or not, the question is do you want to have this extremely protective standard, or do you want to have more discretion and interpretation on the part of the researchers?

MS. BACKLAR: I am trying to think of the kinds of people who might have great difficulty in expressing something, somebody with dementia. I mean I'm listening to what you're saying, and I'm very concerned about the discretion of the researcher, with somebody who has dementia or Alzheimer's. I'm less worried about some other situations; people with schizophrenia in this particular situation, or people with bipolar disorders, and, so forth, that I'm very concerned about that group of people who may not have a very clear way of expressing their fears, except that you can certainly see it. So, and indeed that's what you're seeing may need to be retained.

DR. LO: I think that we should try to hear what you're trying to do this morning. It would be very helpful I think if we gave some examples of the kind of things that counted as expressions of dissent, or indications of dissent or apparent dissent. Because the way I lost my page here, I think it is. It's very theoretical and abstract, sort of a philosophical discussion. I think the IRBs and investigators really help. What are we talking about here? A person says, "No, I don't want it." Okay. That's fairly clear. Folds the arm, so you can't do the I.V. I think that's you shouldn't sort of force the arm. I think some examples of what we mean would help flesh this out. It's a said kind of a de facto standard.

DR. CHILDRESS: And I think that a good place to do that is 149 and 50, where we do get into a discussion of the rationale for this position. Okay. Other points to be made?

MR. CAPRON: I just want to state that I understand what Larry was saying about the use of the word "apparent." But the more I hear the conversation going on, I really think it is important to keep it somewhat well, it somewhat may be left open to interpretation, because it does put the onus on the researcher. And I would be more comfortable with leaving it as, "any apparent dissent," than even putting indication in dissent. Because then the researcher can say, "Well, they didn't say they didn't want to do this," or they can interpret it and say, "Well, they're not you know they're mentally ill, they don't know what they're talking about," or something like

that. And in the practical day-to-day research, I can see how this would be left open to more interpretation. I just like using the word "any apparent dissent." So, I'm in favor of leaving it as it is.

DR. CHILDRESS: Well, there was no apparent dissent, an indication, an expression, and, obviously, the need to amplify this, in terms of examples. I don't know whether you want to push it to a resolution of the word today, or whether we actually would prefer to have examples, and then sort of see what we think makes the most sense, in terms of that.

MS. BACKLAR: Make sure that we indicate both verbal and nonverbal.

DR. CHILDRESS: Right. I think the feeling of the Commission is really pretty straightforward here; that we do want to be restrictive. We have to give some examples to give it some light, as Bernie as suggested. But let's not worry today about preparing for a syndication versus something else, whatever we settle on there will be. If we have good examples, it will be true and clear.

MS. CHARO: I just want to respond to the possibility that this may be excessively protectionist, regarding the participant's rights. And it clearly states that halting the research intervention with the subject at that time, so it doesn't mean that the person discontinues participation entirely, just at that time.

DR. SHAPIRO: And Alex's elaboration of that I thought was very helpful in getting in something we really need to include.

DR. CHILDRESS: Okay. Is that? If there is no apparent dissent, we'll move on to the next. Okay. Independent and professional support for subjects and surrogates. This is a question, in part, and this actually comes up in some areas, too, that when you look very carefully out in the framework of special protections, and in the recommendations, were sometimes not clear that we are actually applying certain things only to greater than minimal risk research. And I think one way we can clarify this is actually to have appropriate statements in the framework of special protections about what we're doing with minimal risk research. So, we don't really. As I look back over this, we don't really say that. We do have a little box on the chart, if you're. If you look at our chart. And, Bernie, I do find the chart useful. This is on page 173. We do have. If you look over the next to the last line, vertical line, that's where there is minimal risk research. And we say a no apparent dissent is required. But it might be a lot better if we actually spelled that out in the text, as to exactly what we're doing with minimal risk research. And I think that that will help people interpret our document. But that having been said, what do we need to say about independent professional support and the categories for which we are applying it? The recommendation here is that we limit that to only greater than minimal risk research. But then, you have a lot of discretion

of IRBs, in terms of ~~X~~I mean the scope of the involvement of such persons. So, let's open that to discussion. Jonathan, anything you want to add?

DR. MORENO: It seems to me that its use is limited to the greater than minimal risk research. I think I feel pretty comfortable with that. Involvement in this particular group we're talking about; allowing the IRBs, of course, to acquire it if they choose to. In any other research project they're dealing with, if it somehow seems appropriate to them in the situation.

DR. CHILDRESS: I also think the issue here is, even in saying it, the independent professional should be involved for both subjects and surrogates, as appropriate. The question of what that involvement details, what's the scope of it? What's ~~X~~what exactly that would include? It's something, perhaps, we ought to discuss very clearly. Perhaps, there is something we want to leave open to IRBs will it determine.

MS. BACKLAR: But what is the section where we describe? I thought that you just ~~X~~that it is starting to make sense in this particular draft.

DR. CHILDRESS: Where we dissent, those page numbers are accurate. And first of all, on 134, we have the extensive discussion of independent pressures for ~~X~~

DR. MORENO: And then the recommendation on 156. And then there is ~~X~~probably is also a section in the special protections as well. I don't see it just now. On page 156, there is a paragraph that gives it during the course of the study. Maybe I'd just add that in thinking, trying to think this through, Trish, I found it difficult to express in detail for a vast range of studies and circumstances, exactly what role the individual would have. I think we have to work, to some degree, at least, on the confidence in people's professionalism; that once ~~X~~that the positions that I know, once one of them would be identified for this role, they would take it very seriously. And they would see that they're on the line, as well as the investigators and officers that are involved in the institution with the research, so that one would think that they would be quite responsible in their execution of this role. And I don't think that it's possible to go much further than that, frankly.

MS. BACKLAR: I actually thought on page 134, the top of 135, I thought it was ~~X~~and then when you referred to the British Law Commission, I think that's very well done, and probably as good as you can.

DR. MORENO: Not that I'm not willing to hear your suggestions. Of course, I'd be delighted to hear suggestions to elaborate this.

DR. LO: I wanted to go back to the flow chart on 173, because I keep in my mind coming back to it to try and pull this all together. And I guess one thing that isn't clear to me is. It's not clear to me why we choose the bottom lines as we do, rather than other bottom lines. So, I think it makes sense to say that subjects cannot do informed consent. They need more protection than when they can, if it's you know greater minimal risk and no direct potential benefit. But why we put two things in the box, rather than three, or why those two, we don't really go through. And I think it would be helpful to get IRBs and investigators to use this, not just why we think there should be more protection, but why those specific protections are called issues and not others. So, I think that's what I'd like to see more of throughout you know this draft, just to make it more useful. And then I had some other questions about the way the outline runs in 173. Are subjects likely to be capable of giving full consent? I'm not sure that's the operational question. Isn't it whether they are capable? Because if they're likely to be capable, but in fact not really capable, then this particular situation doesn't make much sense to talk about getting informed consent. So, I was confused about that.

DR. MORENO: The problem we run into here, Bernie, is that the state in which the IRB is making these judgments, the specific likely participants may not be known. And so, to a great extent, at least, this, in the initial stage of reviewing the proposal, the IRB members have to make a judgment based on what is known about the population from which participants are going to be drawn. This is a real problem. This has been a terrible problem.

DR. LO: But then what happens? It's something of a protocol to say I do this. I get IRB approval, then I go on this subject that she is not capable, according to the guidelines I spelled out in section 1B of my protocol with whatever independent monitoring. Then what do I do with that?

DR. MORENO: Right, the investigator, the onus is on the investigator to make it clear what arrangements are going to be made under those circumstances. But shouldn't we, by the extent of our logic, say you can't use that subject if they can't give an informed consent?

DR. LO: I think that actually and this comes up in some other issues of what we talked about today, too, that we're sometimes confused I think of what the IRB has to consider in thinking about the group and what a particular individual may be whether a particular individual may be enrolled or not, and the kinds of qualities or limitations.

DR. CHILDRESS: I would agree with your direction here.

DR. LO: Look at the protocol and make sure there is an adequate branch in the protocol of individual subjects or persons to decide what happens if in fact they aren't capable.

DR. SHAPIRO: My understanding of the process, I have notXI think maybe that some elaboration of this is really a very good idea, is that if you go down that route and you're wrong, they can't give informed consent. Then it's over.

DR. CHILDRESS: I think that needs clarification, but I think the point he's suggesting is the one that I think is found in the text, but the other elements are present, too. We need to just clarify that.

DR. MORENO: Well, in some defense of the explanation that's in the current draft, we do make it clear if you look at the boxes at the bottom of 173, where informed consent is required, or where it is an alternative. So I do think that we do explain, if not perhaps in sufficient enough length, we do indicate in the draft where it is required and where people would simply have to be thrown out as candidates for participation if they didn't have capacity consent. But we need to revisit that and make it clear perhaps earlier.

DR. CHILDRESS: I agree, affirming Bernie's point though about beneath, or, perhaps, more elaboration, the reasons for choosing some of the particular requirements for each of these boxes. Okay. Other points about independent protectional support, as we move from that to a more general consideration about the way in which we argue for different requirements for different boxes. Do you know the points? I take it then that there is agreement that the scope which would need to be determined by our leads, and that's something that has to be worked out in relation to particular protocols. It's the scope of the involvement. Okay? Okay. Another issue has to do with consent monitor, and this is addressed on page 148.

TheXwhy this recommendation is being made here is a staff-prepared memo, is that we really need to distinguish why we do not in the current text in that one particular paragraph on lines 10 to 14. There is a concrete proposal for the way that we write that. Any objection to that? Okay, good. Now we move intoX

DR. LO: Who are you expecting to pay for this consent monitoring? Page 148 suggests that an IRB member, or an Ethics Committee member is going to do it. This is a lot of work. And you know are we expecting investigators to compensate people for this? That should beXI don't knowXa fundable part of your grant. Because I'm afraid that if we say something that's really impractical, people are going to say, what is this guy thinking?

DR. MORENO: There does seem to be, Bernie, at least one institution that operates through overhead. It pays the salary out of their research nurse, who goes around following a consent process two or three days later, and essentially reinterviews the subjects in that room. That is one option. Other institutions may choose to do it differently.

MS. CHARO: Bernie, I wonder if it would be sufficient if we simply take note of the fact that it has to be paid for by somebody, and that institutions may vary. Those that do a lot of this research may have an institutional response; others may leave it up to the PI to incorporate that in the cost of the grant, and not for us to try to decide who pays for it.

DR. KING: As a researcher in the field, could I ask that whenever your recommendations will lead to substantial additional expense, that you please note that in your view these are expenses that NIH needs to consider supporting for those of us that writeXthat support all of us off of IR-1's, so that we can put in our human subject sections of our grants, in order to be able to follow NBAC's recommendation that such and such, we have added a 20 percent type of position for the research, or 20 percent type of position for a genetics counselor. Otherwise, study sections who do not include, typically, large numbers of people working with you and subjects in the field well funded and will be stuck.

DR. CHILDRESS: And also, that it probably can't come out of indirect under current interpretation.

DR. KING: It wouldn't come out of the indirect anywhere.

DR. CHILDRESS: You know let's see. If I'm not mistaken, we are offeringXcorrect me if I'm wrong. This is only under the heading of guidance for IRBs, and not in terms the requirement, right? That changes a bit, in terms of the kind of discretions. Am I right about that? Okay.

DR. SHAPIRO: The point is well taken. There are a number of recommendations here and in other reports, which we discussed earlier this morning, which are in that character. But by recommending simply as guidance, then for IRBs we are allowed a lot more room, where they are considered a variety of factors, including the cost elements.

DR. CHILDRESS: Okay. Anything else? Okay. Let's turn then to the point raised on 161, 162, the recommendation to, which is also discussed in different ways on 170 and 149. And this seems to me to be another place where we may be jumping back and forth between the group and the individual. Because there are two points that we're concerned with; one is that we not exploit a particular group or class of potential subjects. And that's the reason we are requiring that the research can be done with another group or class, so be done. And there never is the issue of consent for particular individuals and what surrounds that. But we do have this specific point here, and a question being raised about whether the recommendation we have would prevent

individuals who have mental disorders and who can consent from participating in research studies and directly relating mental disorder and an example was given.

DR. SHAPIRO: I guess I'm not sure that what we recommendXI guess I'm not sure if we would exclude that. I think it wouldXI think it allows that. Well, at the very least, we could articulate exactly what it is we'd want to say here.

DR. CHILDRESS: And make sure thatXand then satisfy ourselves this report says or doesn't say it. But I guess we'd have to hear what people think we all want to be the result. Right now, it's the result of one person's interpretation and just to get the discussion going. Diane.

DR. SCOTT-JONES: As I reflect on the pages 161 and 162, it does not seem to me that what precludes the study that's given in the example on page 2 of the memo, that is, that there would be a genetic study examining the relationship between cardiovascular disease and Alzheimer's disease. What we have already written says thatXonly says that you wouldXI'm sorryXthat you would exclude the participant if the research could be done with other subjects. And that clearly isn't the case with the example. You couldn't study the relationship between cardiovascular disease and Alzheimer's disease without using Alzheimer's patients. So, it seems that we have already taken care of this in what we've written.

DR. CHILDRESS: That's my sense also. Other thoughts? Okay. Just to make sure, let's assume that is right and we just want to make sure Commissioners feel that's the right position to be in. I'm satisfied with that position, certainly, but I want to make others are, as well. Okay. Further discussion? Larry.

DR. MIIKE: But are we talking about research that's unrelated totally to their mental incapacity? So the example that Diane gave is one that related to the group of people in capacity. So, I think we need to make it clear. ThisX

DR. SHAPIRO: What do you propose then?

DR. MIIKE: A clarification.

DR. CHILDRESS: Okay. You have language to suggest, or just recommending, as we've been recommending IRBs just do it?

DR. SHAPIRO: Well, I understood Larry to say that there isXthat maybe the use of an example here, which might involve this population, you want an example where they weren't involved in something that was specifically related to a mental disorder. Is that right?

DR. MIIKE: As long as they have the capacity to consent.

DR. SHAPIRO: Right. Okay. Diane, did you want to say something further about that?

DR. SCOTT-JONES: I just wasn't sure what Larry was saying. That isn't already covered. I'm not sure what your comments are.

DR. MIIKE: Well, the way that it says, subjects with mental disorder, anyXif we're talking about research, involving subject with mental disorders that may affect decisionmaking. That's the all-encompassing. It talks about any research. It's not limited to research that is related to their mental disorder. So I'm saying that if you read this and I, as a person covered by this, developed cancer and suffered a particular cancer that is of interest to researchers and they had the capacity to say yes, this would say they can't participate in that protocol, and I don't think that's what it means. As long as they have the capacity to consent to that. That's what you're getting at, right?

DR. CHILDRESS: This is moving between the group and individual in class.

DR. SHAPIRO: I need some clarification here myself, and I apologize. Maybe I'm just confusing a few things. One of the decisions we made early on was that this population should not be used if it wasn't necessary. If the research could be carried on with other populations perfectly well, then that's what people should do. We have that recommendations somewhere here. And now we have an example, an interesting example, which Larry brings up. Namely, what if we want to do genetic studies of one kind or another that are unrelated to the disorder that these people have? Which means they don't need these people to carry on the study. But the question is do we still want them to be able to participate? Because the issue that your question raises in my mind. . . .

DR. MIIKE: Well, I think I was going on the assumption that the earlier discussions were something like Phase I trial, where you're talking about the physiology of a particular medication, where this is a totally different issue.

DR. SHAPIRO: Correct. I agree with that. And I think that if we're going toXif that's what we want, I don't have myself any objection to it, to have a capacity consent, just as you've said.

DR. CHILDRESS: We need to look at 145 and 146 before this is discussed and the framework of discussion reflections. We've just been just looking at the recommendation. And, in particular, look at 146. And I think there is some problem in that firstXI think the first part of the sentence doesn't work well. We need to probably work it out. But it says that, "An individual with impaired decisionmaking classes on 15, 14, may have a life-threatening condition for which there is no satisfactory treatment. When the intervention is designed to potentially cure a life-threatening condition, then under current regulations these individuals may obtain investigational treatment outside the closed study on compassionate grounds as a matter of justice, etc." I don't think that fully addresses your concern, Larry, but this is at least one place in the text where they're trying to talk about something close to it. Eric?

DR. MESLIN: It may help just to clarify one point. Perhaps, the case example is not the best example. The reason that it was put in was to try and ensure that we would not be discriminating those individuals, who, by dint of having a mental disorder, that perhaps coincidentally can be mapped on to another physiologic disease. They might be able to participate in that research. Do we want to discriminate against them just because they have a mental disorder? Larry's question is really asks whether the consent issue renders that movement you can consent, and the fact that you have a mental disorder shouldn't disqualify you from consenting to any kind of research that comes along down the pike. It only becomes a problem when there is some impairment to your capacity.

DR. CHILDRESS: Again, I think we're just not clear in the document about the effort to avoid exploitation of a group or class. And the issue of particular individual consent. And I'm not sure I have a good way to get those two together. But I don't use them unless the research is necessary, never to avoid exploitation of this population as a group. Then for particular individuals of consent, why shouldn't they be allowed to enter other kinds of protocols that are not directed at them as a group? And that seems to me to be the way to think about it. For that direction, if it's a protocol in cancer research, and this particular individual who has a mental disorder that may affect his or her decisionmaking capacity, could consent to that, then that person should we should be moved to protect. Does that make sense?

DR. SCOTT-JONES: I think is covered very well in the Belmont Report. It says explicitly when research is proposed that involves risks and does not include a therapeutic component, other less-burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. I think it includes the therapeutic component, which is captured in the example on page 146. And it was excluded I think Larry's example, a researcher is studying cancer and could use any person as the participant. There is no need to use persons who have Alzheimer's to be in that research, even if they can consent. That's different from when there is a therapeutic component, as in the example on page 146.

MS. BACKLAR: The kind of person I'm thinking of protecting, who would want to be in such a protocol, would be for instance somebody, a very high functioning person with a bipolar disorder, that you wouldn't want to stop them from being in another kind of protocol that has nothing to do with bipolar disease.

DR. KING: I would point out a practical case from our experience, in which in large kindreds with inherited susceptibility to breast cancer, there are from time-to-time people with bipolar disorder, or schizophrenia, or Alzheimer's, and those persons sometimes wish to participate in these studies. They're not treatment trials. They're research projects. But if the person is capable ofXif it is possible to obtain legitimate consent from the person we certainly wouldn't want to exclude them. So, it isn't only treatment. I think that's the point.

DR. SHAPIRO: All right. At this moment, we have three or four people signed up for public comments today. I just want to remind everyone that the rules of the Commission are five minutes, in order to give everyone a chance to say what they'd like before the Commission. Anybody, of course, who would like to give us written material is always welcome and it will be distributed to the entire Commission. So, let me just proceed immediately to those people here for public comments. Let me turn to Dr. Ted Falk, first.

DR. FALK: Thank you. Mr. Chairman and members of the Commission, I wanted to welcome you all to Oregon, the bioethics state. If you didn't see today's newspaper, the headline on it is, "Fitz Harbor Defends Suicide Law." And this is just really typical. For the last decade, I think probably once a week there is a front page article in the *Oregonian* about some bioethic issue. So, you've made an excellent choice of a place to conduct this meeting. I do have some written remarks, which I distributed to you, and they're short. But in lieu of the five minute rule, I will not even read through these. I have really only two points that I wanted to make, one about the report on mentally disordered subjects, and then a little discussion about Oregon's law of genetic privacy. On the report about mentally disordered subjects, I wanted to point out something to you, which is perhaps already crushingly obvious to you from your own work. But, of course, I didn't participate in the discussions, so I don't know about this. But, really, within your report on the mentally disordered subjects is the seed of a very powerful critique of the existing IRB system, very much along the lines of the recent OIG Reports. And so, I am hoping that you will extend your work on the rather special problems involving mental disorder subjects to return to a much more general features. Because as I read through your draft report, I actually found relatively little that I thought was all that specific to that population. Many of the points that were being made are general laws in the IRB process. And so, I'm hoping that you will be able to return to that in a future agenda item. And I gave a few bullet points in my testimony to illustrate why I think that's so. Turning now to the matter of genetic information, I don't know exactly where you're going with your report. But what I thought it might be useful for me to do would be to tell you a couple of things about Oregon's genetic privacy law. I was part of the group that wrote that law in 1985. And I've attached to my testimony a copy of the statute. And it's basically a law which establishes consent rights for individuals whose genetic information or DNA materials are going to be

obtained, retained, or in the case of information, disposed. And what Trish Backlar, particularly, suggested would be useful for me to say a couple of words about is the property clause. Because this is something that's been very controversial in Oregon. Whether or not you agree with it, I at least wanted you to know that there was a rationale for it, and it was something that a great deal of thought was given to. The property clause, which is set forth in the statutes, but I've just cluttered itXthe roman part in the memo declares in statute that, "An individual's genetic information and DNA sample are the property of the individual." The thing goes on to say, and most people don't read on, to say that, "The property clause is not to be used in determining whether an individual is entitled to compensation or royalties." So that was not the purpose of the property clause. What I suggest in my testimony was the purpose. It's a sort of metaphor, and you might ask why do you go to the trouble of enacting a statute or metaphor. And that is in response we are very rapidly changing biological fields. You want to have a coherent principle for dealing with a situation, which, at the time, a legislature is dealing with that, at one moment you have an only very imperfect glimpse of, especially in a very rapidly changing biological area, plus in a legal field in which there are practically no known issues about violation of genetic privacy that one points to. And by appealing to a word like "property," you establish a framework for evaluation of cases as they come up. And, of course, there may be very little genetic privacy law, but there is a great deal of property law. And so, what this law accomplishes suggests to a decisionmaker that the relationship of the individual to their DNA sample, or to their genetic information, is like the relationship of an individual to their property. It doesn't go beyond that. But that actually would be a big help to someone. They'd at least know which section of the law library to go to for analogies if they wanted to analyze a particular case. So, that was really the purpose of the property clause. Another approach that might be taken, and which is often taken in federal legislation, and which I feel is kind of unfortunate, to try to map out an extremely detailed scheme of rights and remedies. We actually looked at a very well written model statute, which attempted to do that. It's very difficult to do that in a fast changing area where the biological knowledge itself is so new. And, therefore, the understanding of the legal rights and relationships is so imperfect. And so, I guess I think there is something intelligent about trying to write a statute in what I call constitutional fashion, where you, a person, have a concept to deal with for future development, rather than trying to write every detail into the law as it exists. That's what I wanted to say to you, and if you have any questions, I'll be happy to respond.

DR. SHAPIRO: Thank you very much for being here. Alta.

MS. CHARO: Yes, thank you, Dr. Falk. And thank you for providing a copy of the statute. I was just last night asking somebody if I could see it. If I'm reading it correctly, and I ask you that as a question, this statute would preclude what is permitted under the federal regulations; that is, the use of stored samples, where their use represents a minimal risk to the source of the sample,

and where contact to obtain permission is considered impractical. This statute, as I'm reading it, it would preclude that, assuming that the samples are identifiable through coding or whatever. Am I reading it correctly?

DR. FALK: Well, first of all your attention to an exception which is built in, and I do mention this in my testimony, and then you can track through the statute. There is an exception for anonymous research. The sample is not identifiable as belonging to a particular individual. And I think we assume that reverse DNA engineering would not mean that a subject was identifiable.

MS. CHARO: Right, but the more common situation, the one that we've been struggling with here, is where a coding system has been used, so that it's not obvious what the person's name and address is, but the code can be broken. And that would appear under your definitions, if I'm reading them correctly, to meet the standard for identifiable. So, this seems to be a quite typical scenario, look one state to the south in California, you've got people that are working coded samples. They're using the codes in order to allow for periodic updating for the medical records that are being abstracted. And it's been determined by the IRB at UCSF, this is minimal risk and it's impractical to re-contact people for consent. And so, under the federal regulations the research is permitted to go forward. Do I understand correctly that in Oregon that research could not go forward because of the statute?

DR. FALK: I think you'd have to deal with some legal technicalities about effective dates, about when the sample is collected and so forth, because I don't think the statute probably has a retroactive effect on samples that have been collected prior to the enactment of the law. But with that caveat, I would agree with your interpretation.

MS. CHARO: So, I'm sorry. I'm just trying to get toXthe law was enacted a couple of years ago. I'm curious. What has been the experience now in Oregon? How much have you been following the experience in the research community, as to the effect it's had on what can and cannot be done andX

DR. FALK: Well, I know a lot of people are anxious about what cannot be done, although probably should have asked Dr. Kolar at the reception last night, but I do not believe that biomedical research in Oregon has ground to a halt. And whether people are puzzling over what this law means, I don't know. And I actually cannot tell you how it's being applied in the field in Oregon. But I think that your interpretation is correct; that there would not be, on the fact of the statute, any sort of exception for minimal risk research, as opposed to substantial risk. That's

correct. And, of course, the federal law doesn't have any preemptive effect. I agree with that. And I guess I would put back to you that I'm not sure that there is anything wrong with that result.

MS. CHARO: I'm not sure. I just want to know, but we can't answer it.

DR. FALK: I think it was the drafters of this statute, that I was a part of, felt that the use of stored sample bank was entirely too casual, that Xand an individual had a right to consent before their information will be put into historical sample bank. That's correct.

DR. LO: I want to again thank you for preparing all of this for us, which I think is very helpful. We probably don't have enough time to do it now, but if you could also provide some sort of information of specific examples of how the property clause in the statute has helped? And what are the sorts of situations in which that sort of guidepost has been, or is thought to be, useful for winding one's way through disputes? That would be helpful, as well.

DR. FALK: There is actually a sort of coalition at OHSU that whose job it is to monitor this statute, and furnish advice, and I'll suggest to them that they see if there is any further information they could furnish on that.

DR. SHAPIRO: That would be very helpful. We'd appreciate that very much, if that's not too much effort. Any other questions?

DR. FALK: Thank you very much.

DR. SHAPIRO: Thank you very much. We very much appreciate you being here today. Is Dr. Sid Glasser here? Thank you. Dr. Glasser is from San Francisco.

DR. GLASSER: Okay. Thank you for the opportunity to speak here. First, several people have given public testimony at earlier sessions on being preyed upon by government agencies or their contractors. Some of what has been relayed may seem fanciful and unbelievable. It's not the inability to correctly interpret the means by which such abuses have been carried out that's important, but that they have been subject to psychological and other tests of a sadistic nature without their approval. Understanding may be lacking, but the reality of the abuse is real. I'm here today Xexcuse me. One more private citizen, whose life has been Xwhose life has been severely damaged by the domestic covert activities of the U.S. government. Next, intrusion on the privacy and intended abuse of ordinary citizens have used means which are essentially those mentioned previously, subliminal for the individual signals, drugging, microwaves, etc. An indication of the indifference of government is suggested by the two House bills, H.R. 3946, of 104th Congress, which was shelved, and a modified bill, H.R. Bill 3946, of the 105th Congress. The former is for the protection, or was for the protection of humans from government-sponsored research or abuse, and means for compensation. The new bill, which is the modified version, protects only

animals. The statement of each bill is enclosed with the other materials. Number two, protection of humans from exposure to behavior control methods. (A) The agencies and the contractors we're dealing with are distinctly different from those discussed heretofore. We are dealing with agencies who have never had much constraint placed on any of their activities. Traditionally, Congress has been loath to study the details of their operation. Results and deniability have been the only goals bringing them advancement. History has proved again and again the need for tight oversight control. Next, few programs such as psychological warfare evolve and seldom end. The one in which I had been a participant started in 1952 for me, and became more expensive as applications were conjured up. They appeared from years of no restriction to those of improvingXfor improved technology, and limited controls. And, finally, toXwhen the President says to stop, "We're working on it, just give us a little more time." Finally, the intelligence agencies are trained to be deceitful. They are essentially on their own among the public. They get higher ratings when reporting having pressed the right button without revealing exactly what citizens they choose to bother. Okay. Constraining the agencies. The robust discussions at previous meetings have some good ideas relevant to constraints. There should be a ban on invasion of privacy, including eavesdropping for test profiling, or related reasons, and/or the use of private citizens without their written consent, no exceptions, just plain and simple. Now, one idea which may have been missed, probably was from the past transcripts, is having an Office of Consumer Affairs.

That is a citizen's police review board, Office of Citizens Spared, or complaints and retribution or compensation, whatever you want to call it. Any citizen who has some concern goes to the citizen's council, which then has the agency in question respond directly to the complaint. And the resolution watched over by calling in experts, such as yourselves. If we're going to have a future of ongoing, closer government surveillance, which certainly looks like the case, then we need such a council for it. And this idea is likely to be more effective and necessary than some of the earlier ones given, because of all of the attending intramural and intermural bureaucratic turf battles. Okay. I have one last thing to say. The rest is several references which sum up my own ordeal, and that of some of the other thousand pledge victims, which are mostly connected through the Internet. Many individuals and organizations assisting one another, as is telebiostimulation, the woman spoke last time, and those listed in the packet given you today. Now, the rest are references, dementia in family, which covers a lot, and subliminal stimulation. There is one that I'd like to point out, which is a little different. It's called the Control of Candy Jones, being a book written by Donald Bain, who is a friend of the family. Candy Jones was a famous model. She offered office space to an FBI agent and some other individual, ended up being drugged and involved in some sort of spy-related episodes over a couple of years. Now, when the doctor in charge was told to end it, end all of the experiments, or whatever, he then tried to have her

commit suicide through drugging and hypnosis. Anyway, the rest are references that have been distributed. Thank you.

DR. SHAPIRO: Thank you very much, both for the material you provided, and for the trouble you've taken to come up and speak to us here in Portland. We very much appreciate it. Any questions from members of the Commission? Once again, thank you very much. Next, is Ms. Karen Hansen. Karen Hansen here is representing Public Responsibility in Medicine and Research, which is to speak to us on the issue of the Inspector General's Report on the IRB. Thank you very much for being here.

MS. HANSEN: Yes, I have a letter that I'd like to share, that was written by public responsibility in medicine and research. "Dear Chairman Shapiro and Distinguished Members of NBAC: The House Committee on Government Reform and Oversight recently held a hearing on Institutional Review Boards, using the Inspector General's Report as a base. It is imperative that others associated with IRBs comment both on the misinterpretations of this report in the national media, and the worthwhile substance of the OIG report itself. PRIM&R, Public Responsibility in Medicine and Research, has been active in the education and promulgation of policy for IRBs for the past 25 years.

The problems enunciated in the OIG report are those that PRIM&R has described many times in regularly scheduled conferences, and has even proposed solutions. With all of the negative remarks in the press directed to the unsatisfactory manner in which we in the IRB community protect human subjects of research, it is imperative to remember that the OIG report looked for but found no widespread or substantial violation of subject/patients' rights. What it did find, however, was the potential for problems to both the changes in the system to protect human subjects, and to lack of ongoing assessment of outcomes by that system of protection. One problem noted was that the meaningful work of IRBs is being subsumed with ever increasing amounts of paperwork, most having little to do with actually protecting subjects. At a time of exponential growth of biomedical research, as well as seeing increasing complexity of that biomedical research, IRBs have been stressed by inadequate resources. It is also increasingly difficult to recruit senior medical faculty to IRB membership. The demands on their time have also increased, and there is little recognition of the significant amount of time that is necessary to devote to this work. PRIM&R welcomes to OIG report for two reasons: First, it significantly documents this lack of resources; second, the report acts as a wake-up call to institutions, sponsors, and our regulators about the potential for problems and the system of protection. Without assessment of outcomes, we cannot be certain how well the entire system of protection is working. One type of outcome assessment is performance-based evaluation. It is possible and probable that

with a concentrated effort on the part of regulators working together with IRBs, we can develop performance-based evaluations for IRBs. NIH has called a panel together, which meets the end of this month, to deal with this very issue. There is no one who will deny the variability of IRB review. Performance-based evaluation should be a considerable aid to all IRBs, as they seek improvement. IRBs cannot function effectively, efficiently, nor provide the appropriate educational opportunities for investigators without sufficient staff and administrative support. We must find better mechanisms to fund our IRBs, than the traditional indirect cost method. All regulators need to reconsider much of their paperwork requirement, scale them back, and make them more meaningful. Regulators and institutional administrators must also provide the resources for the development of educational programs for investigators, IRB members, and potential subjects, in order to make the mandates given to IRBs take their proper form. Until all of the players in the research enterprise are sensitive to the fundamental ethical principles when involving human beings in research, we have not accomplished much more than paper checks and balances. Education will play a significant role in helping to internalize those ethical principles. In summary, we must make sure that we understand the nature of all of the major problems and come up with solutions that do not have perverse, unintended consequences. The next PRIM&R meeting about IRBs in November 1998 will devote considerable time to the OIG's report and its implications.

PRIM&R hopes that NBAC will help the process of full identification of problems, and development of truly effective solutions. Sincerely, Sanford Trodoch, M.D., President, Board of Directors, Public Responsibility in Medicine and Research. Thank you.

MALE VOICE: Thank you. And, once again, thank you very much for being here. Let me see if there are any questions from members of the Commission. Alta, then Bernie.

MS. CHARO: You spoke about one specific suggestion with regard to improving the quality of the IRBs, and that's the performance standard. It's kind of a CLIA model, based on the laboratory certification model we have. There are two other cogs in the system, and I wonder if your organization has thought about some very concrete suggestions. One is with regard to individual investigators, with whom everything really starts, since they are the ones who have to approach the IRBs. IRBs can't review things that are not brought to their attention. Have you thought about specific ways in which to enhance the understanding of their obligations under the regulations and the way in which they need to interact with the IRBs? The second, you mentioned the problem of the paper flow to track the activities of the IRB. I think everybody is sympathetic with that, and I wonder if your organization had any specific suggestions about where that could be, either cut back or altered in a way to make the process more streamlined.

MS. HANSEN: Since I'm not on the Board of Directors of PRIM&R, any comments that I might make really represent my own, and can't fully represent PRIM&R. So, first of all, though, as far as investigator obligations, I think a lot of that, through the training programs, both that the NIH has in regional workshops with OPRR and FDA, as well as what PRIM&R and ARENA both offer, as far as educational outreach. There is always a continued emphasis, unless you really get in touch with our investigators, what kind of training programs do you have. And I know, for example, this coming November at the ARENA program that we're planning, there is again a whole panel that's devoted to education. And I think that is where the emphasis lies in really getting the word out to investigators, and making sure they understand what anonymous means, or what, for example, coded information means. And when it comes to the paper flow, and I take it that you're talking about increasedXthe increased paperwork and how might we gear back a little bit. Just, again, this is personally, I think in the area of annual progress reports and review, that there are situations potentially where some of the volume of activity for the full IRB can be presented in more of an expedited review fashion, based on the status of the research at the time of annual review by the IRB. So, there are some areas where things could be cut back. And, again, I think, too, that with multi-site trials, where there are so many adverse events report, that if there was really terrific collation of offense reports, so that they came to the IRB Board Review in a meaningful fashion on an annual basis. And, certainly, at times, immediately if there is an immediate adverse event to report.

But in the annual assessment process again, where we look at studies every year, it would be really helpful to have some collated, really useful information that enables the IRB then to do their job of reassessing risks and benefits of a study. So, those are two suggestions I have. And those are my personal suggestions.

DR. LO: Thank you for coming and presenting to us. I have a question and a request. The question has to do with finances and dollars. We have spent some time this morning trying to figure out how much recommendations cost. And I was wondering if your organization has figures on how much wouldXhow much additional extra support it would take for a good-sized IRB to do all of the things that have been suggested over and beyond the term of funding. And my request is that if you could convey back to PRIM&R, and I guess the individual members that weXI think we would very much like their input on the drafts of these two reports that have been up on the Web in one case, and going up on the Web. We are making a lot of recommendations that call on IRBs to take an even greater role in areas that up to now they really have not played as large a role. Whether this seems practical, feasible, desirable, etc., from the point of view of members of IRBs, I think would be very, very helpful, too.

MS. HANSEN: I don't know exactly what's in the pipeline with PRIM&R. But I do know that there is a lot of attention currently being taken to assess what's the level of salary support for people that are running IRBs, and they're doing salary surveys, and, so on. And along with that I think we'll be sure to mention back to the PRIM&R Board, as well as the ARENA Council that this is an area of interest that will be real useful, both to the NBAC, as well as the IRB community.

DR. SHAPIRO: You should alsoXand we'll turn to Bette in a momentXbut point out that we are looking at the broader review of federal oversight, a report that we issue next year, in which we'll be directly dealing with these issues. We are indirectly dealing with some of them in the two reports that areXwill be issued hopefully soon. And so, we do have some time, and any feedback you could give us in that area would be very much appreciated. Bette, I'm sorry.

MS. KRAMER: Thank you very much for your presentation. I'm curious: does your organization, or is anybody tabulating the numbers, the percentages of IRB members who actually avail themselves of these educational programs? I gather these programs are not compulsory for IRB members.

MS. HANSEN: The educational conferences that PRIM&R and ARENA put on are not compulsory. It's primary if the institution is going to support attendance of their members, chairs, and administrators to attend them. They're open to the public, as well.

MS. CHARO: One of the areas in which I've heard and noticed a lot of complaints is in the area of collaborative research with multiple IRB reviews from multiple institutions. It's not simply that you need to have five different reviews, it's that the five reviews rarely come out exactly the same, so that they then all need to be coordinated. And so, in the end, five investigators at institutions may wind up with easily 15 to 25 interactions with their IRBs while they make things uniform. The current regulations, however, seem to require this, because they require local IRB review for each investigator. Has PRIM&R as an organization ever had an occasion to look closely at this phenomenon and investigate the advantages of local IRB review and measure them against the burdens that this lack of centrality has caused? And have any suggestions ever emerged?

MS. HANSEN: Timely question, they're actually having a conference on central IRB process. That will be late October, and they are having a workshop to evaluate central IRB process. And I have not received the agenda outline yet, so I can't comment on it any further. But if you were interested, certainly we could arrange to have NBAC provided with the information about that conference, because it sounds like that might be useful.

MS. CHARO: It would be very useful. Thank you very much for the offering.

DR. SHAPIRO: It would be helpful, and I do want to send a little gratitude, for not only your presence, but the work that this group has done over a long period of time now. I might point out to the Commission there is a Web page for this organization's support, which will probably give us a clue to a lot of these resources and we ought to take advantage of them. Thank you very much. Thank you very much. Okay. Let me see. I have one other person, whom I'm not sure is here. Is Ms. Sarah Hardstat here? If not, then let me suggest that we decided yesterday, we would work through lunch. But let's take a ten-minute break now, and then reassemble. There will be some provision for getting our lunches in front of us, and then we'll begin work. Thank you very much.

[OFF THE RECORD.]